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U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)
CENTER FOR BIOLOGIC EVALUATION AND RESEARCH (CBER)

Public Meeting:
Promoting the Use of Complex Innovative Designs
in Clinical Trials

Tuesday, March 20, 2018

8:35 a.m.

FDA White Oak Campus
10903 New Hampshire Avenue
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1 P R O C E E D I N G S

2 DR. PRICE: Good morning. We're going to go
3 ahead and get started, realizing that there are many
4 attendees that are trying to get through the lobby
5 security right now. But we'll go ahead and get
6 started, realizing that in the afternoon we'll have to
7 keep a check on the weather.

8 So we'll -- I'll ask Dr. Aloka Chakravarty,
9 who's the acting director of the Office of
10 Biostatistics in CDER to begin with welcoming remarks.

11 WELCOME, OPENING REMARKS AND INTRODUCTIONS

12 DR. CHAKRAVARTY: Good morning, everyone. I'm
13 Aloka Chakravarty, acting director of the Office of
14 Biostatistics, CDER, FDA.

15 Welcome to the FDA public workshop, public
16 meeting on promoting the use of complex innovative
17 designs in clinical trials, which is being convened by
18 the Center for Drug Evaluation and Research, and the
19 Center for Biologics Evaluation and Research.

20 We're pleased to be joined for these
21 discussions by leading experts across government,
22 academia, industry, and care delivery for a productive

1 exchange on the issues on-hand.

2 Our purpose today is to facilitate discussion
3 and information sharing about the use of complex
4 innovative designs in drug development and regulatory
5 decision-making.

6 This meeting fulfills obligations under both
7 21st Century Cures Act and PDUFA-VI to convene a public
8 meeting to discuss various complex adaptive, Bayesian
9 and other novel clinical trial designs with particular
10 focus on clinical trial designs for which simulations
11 are necessary to valid operating characteristics.

12 We have seen examples of innovative designs at
13 various stages of development. But its use can be
14 improved by consistent acceptance in regulatory
15 decision process of such designs and clarity may be
16 needed to -- how to proceed with such a design.

17 Today's meeting is meant to be the beginning
18 of an ongoing effort to discuss and explore the use of
19 complex innovative designs in drugs and biologics. And
20 it will be a chance for the leading experts to discuss
21 their experiences with these techniques and to provide
22 input as FDA develops a pilot program for complex

1 innovative designs.

2 Throughout the day, we encourage meeting
3 participants to consider opportunities for increased
4 collaboration, both across industry and with agency to
5 support these efforts.

6 In a few moments, we will hear from the
7 speakers about their thoughts on complex innovative
8 designs and where they'll see potential for additional
9 work.

10 We will be specifically talking about four
11 topics: a session on complex adaptive clinical trial
12 designs, a session focused on other innovative designs
13 including external or historical control subjects,
14 Bayesian designs and master protocols, a session
15 looking at clinical trial simulation for confirmatory
16 trial design and planning and a session where
17 stakeholders share their thoughts about the upcoming
18 pilot program for complex innovative design.

19 Before we get started, a few housekeeping
20 notes. As you'll note in the agenda, each session will
21 begin with 15-minute presentations, followed by panel
22 discussion. We also have time set aside for broader

1 discussion with audience participants.

2 For those in attendance, we have microphones
3 setup in the room, in the aisle, for you to use during
4 the question-and-answer during the day. Formal
5 comments can be sent to the open docket. The link is
6 listed on the agenda.

7 I want to remind everyone that this is a
8 public meeting, and the event is being broadcast
9 online. So everything you say will be part of the
10 record. For those in the room today, if you need to
11 purchase a lunch, please be sure to order and pay for
12 it at the Sodexo kiosk before the end of the first
13 break.

14 Finally, a reminder that although this meeting
15 is being convened by the FDA, it's not a federal
16 advisory committee. The meeting will be a success if
17 there is a robust discussion of ideas and open
18 discussion.

19 So with that, I would like to thank all the
20 panelists and the audience for participation, and we
21 welcome and look forward to an active discussion.
22 Thank you.

1 DR. PRICE: Thank you, Dr. Chakravarty.
2 Before we being our first presentation, I would like to
3 thank all of our panelists for traveling near and far
4 to be with us today. We look forward to a very
5 interesting and robust discussion.

6 I would ask that you each introduce yourself,
7 giving your name and affiliation, and we have further
8 information at the desk about your actual biography.
9 So I'll start with Ivan.

10 DR. CHAN: Hi. My name's Ivan Chan. I work
11 at AbbVie.

12 DR. LEWIS: My name is Roger Lewis. I'm the
13 chair of emergency medicine at Harbor-UCLA Medical
14 Center, and the senior medical scientist at Barry
15 Consultants.

16 DR. ZHONG: My name is John Zhong and I'm from
17 Biogen.

18 DR. LEE: Hi. My name is Jack Lee. I'm from
19 University of Texas, MD Anderson Cancer Center. I'm a
20 professor of biostatistics and associate vice president
21 of -- president of quantitative sciences.

22 DR. MARCHENKO: I'm Olga Marchenko from Bayer.

1 DR. PRICE: Hi. I'm Karen Price from Eli
2 Lilly and Company.

3 DR. HARRELL: I'm Frank Harrell. I'm with the
4 Office of Biostatistics, FDA, CDER and with Vanderbilt
5 University, Department of Biostatistics.

6 DR. TOERNER: Hi. I'm Joe Toerner. I'm at
7 FDA, CDER, in the Division of Anti-Infective Products.

8 DR. SCOTT: I'm John Scott. I'm in the Office
9 of Biostatistics and Epidemiology in FDA, CDER.

10 MS. BENT: I'm Robyn Bent. I'm in the Office
11 of Biostatistics CDER.

12 DR. PRICE: I am Dionne Price. I am the
13 acting deputy director of the Office of Biostatistics,
14 CDER.

15 DR. LEVIN: HI. Greg Levin, statistician.
16 Office of Biostatistics, CDER.

17 DR. CHOW: This is Shein Chow from the Office
18 of Biostatistics, CDER.

19 DR. LAVANGE: Good morning. I'm Lisa LaVange.
20 I'm associate chair and professor in biostatistics at
21 University of North Carolina, Chapel Hill.

22 DR. ASHBY: Hello. I'm Deborah Ashby from

1 Imperial College London, statistician.

2 DR. BRETZ: Frank Bretz, Novartis.

3 DR. EMERSON: Scott Emerson, professor
4 emeritus, biostatistics, University of Washington,
5 Seattle.

6 MS. LIEBERMAN: Good morning. I'm Gracie
7 Lieberman from Genentech.

8 DR. BERRY: Scott Berry, biostatistician,
9 Berry Consultants.

10 DR. MEHTA: Good morning. I'm Cyrus Mehta,
11 president and cofounder of Cytel Corporation and
12 adjunct professor of biostatistics at Harvard
13 University.

14 DR. PRICE: And if I could ask my colleague,
15 Lauren Sucher, to stand in the audience. She is our
16 representative from the press office today. Thank you.
17 And one minor correction: The bios are online.
18 They're not outside on the table.

19 So without further ado, our first presenter,
20 Dr. Greg Levin, will begin.

21 SESSION I: GENERAL CONSIDERATIONS FOR COMPLEX ADAPTIVE
22 CLINICAL TRIAL DESIGNS TO SUPPORT THE EFFECTIVENESS AND

1 SAFETY OF DRUGS OR BIOLOGICS

2 PRESENTATION

3 DR. LEVIN: Hi. Good morning. I'm going to
4 provide a brief presentation to introduce and hopefully
5 stimulate a good discussion in session one.

6 Session one focuses on general considerations
7 for complex adaptive designs. The primary focus of
8 this session is on adaptive designs that will be used
9 to support the effectiveness and safety of a drug or
10 biologic, although we expect that some of the
11 considerations discussed will also be useful for early
12 phase exploratory trials.

13 I'm going to provide a brief overview of
14 adaptive clinical trial designs, including a definition
15 to outline the scope of today's discussion. And then
16 I'm going to discuss some important considerations for
17 adaptive designs that I expect will be discussed in the
18 session this morning, and I'll conclude by briefly
19 going through the questions that we're going to ask the
20 panel to discuss this morning.

21 So our definition -- our working definition of
22 an adaptive design for today's discussion is a clinical

1 trial design that allows for prospectively planned
2 modifications to one or more aspects of the design,
3 based on accumulating data from subjects in the study.

4 Importantly, there are two scenarios that are
5 therefore not within the scope of today's discussion.
6 The first is when there are unplanned changes based on
7 comparative interim results. For example, dropping of
8 a dose because of unexpected toxicity.

9 The second is when there is information from
10 sources external to the study. For example, results
11 from a different study of a different drug that might
12 motivate changes to the ongoing study in the form of a
13 protocol amendment.

14 These are important scenarios that come up
15 that could warrant another discussion. But today's
16 session is focusing on adaptive designs that are
17 prospectively planned.

18 One way to classify adaptive designs is by the
19 type of adaptation that is being made at an interim
20 analysis. For example, there can be adaptations based
21 on baseline characteristics, such as a covariate
22 adaptive design that attempts to reduce imbalance

1 between treatment arms.

2 There can be adaptations based on pooled
3 outcome data, often called blinded adaptations. For
4 example, to modify the sample size at an interim
5 analysis based on pooled blinded estimates of the
6 variants or the event rate, or there can be adaptations
7 based on comparative interim results, often called
8 unblended adaptations, such as group sequential designs
9 that allow stopping for efficacy or futility, or
10 designs that allow adaptations to the sample size, to
11 the patient population, to the treatment arms included
12 in the trial, et cetera.

13 Another way to classify adaptive designs is
14 according to whether there are adaptations to
15 statistical aspects of the design, such as the sample
16 size, or whether there are adaptations to scientific
17 aspects of the design, such as the patient population,
18 the treatment arms in the trial, the endpoints.

19 When there are adaptations to scientific
20 aspects of the design, the primary estimand, i.e., the
21 primary measure of drug effect that we are trying to
22 estimate in the clinical trial, will change

1 accordingly.

2 One of the motivations for adaptation is that
3 in some cases, an adaptive design can provide
4 advantages in statistical efficiency over a non-
5 adaptive design, such as a greater chance of detecting
6 a drug effect at a given expected sample size.

7 In some cases an adaptive design can also
8 provide ethical advantages. For example, the
9 opportunity to stop a trial for futility or efficacy
10 can help ensure that patients inside the trial are not
11 exposed to unnecessary risks, and that patients outside
12 the trial are provided promising therapeutic
13 alternatives as soon as possible.

14 And in some cases, adaptive designs can also
15 provide advantages in the understanding of drug
16 effects, such as an improved estimation of the dose
17 response relationship.

18 On the other hand, there are some limitations
19 and challenges of adaptive designs. There are
20 methodology challenges in ensuring the control of the
21 chance of erroneous conclusions and ensuring the
22 reliability of treatment effect estimates. There can

1 be added operational challenges in maintaining
2 confidentiality to comparative interim results and
3 ensuring trial integrity, and there can be potential
4 challenges in interpretability and generalizability due
5 to changes in the estimand of interest during the
6 trial.

7 In some cases, adaptive designs can be quite
8 complex in that they may include multiple types of
9 adaptations such as an interim analysis that allows
10 adaptations to both the treatment arms in the trial and
11 the sample size that will be accrued before the next
12 analysis.

13 They could include adaptations to scientific
14 aspects of the design, and many often involve
15 simulations to evaluate operating characteristics at
16 the planning stage.

17 A couple examples of adaptive designs that
18 have been carried out that have some complex
19 adaptations involved include PREVAIL II, which was a
20 trial to evaluate ZMapp for Ebolavirus disease, and
21 included frequent interim analyses with decision rules
22 based on Bayesian posterior probabilities and allowed

1 the opportunity to add experimental agents as treatment
2 arms during the trial if they became available.

3 And another example is I-Spy 2, which was a
4 Phase II trial to screen breast cancer treatments and
5 included potential adaptations to the sample size, the
6 randomization ratio, and the treatment arms.

7 This slide lists a number of important
8 considerations for adaptive designs that I expect will
9 be discussed in the panel discussion this morning. I'm
10 going to go into these in a little more detail on the
11 coming slides.

12 The first is the control of a chance of
13 erroneous conclusions. We also have the extent of
14 reliability of estimation of treatment effects, the
15 extent of pre-specification of details of design, the
16 maintenance of confidentiality to comparative interim
17 results and the extent of documentation, both prior to
18 and during the trial.

19 One important consideration is the extent to
20 which the chance of erroneous conclusions is controlled
21 in the trial, and this includes the control of
22 incorrect conclusion -- the chance of incorrect

1 conclusions of safety or effectiveness, of incorrect
2 conclusions of a lack of safety or effectiveness and of
3 incorrect benefit-risk evaluations due to misleading
4 estimates.

5 One important component of the evaluation of
6 effectiveness is typically the test of a null
7 hypothesis in a clinical trial. And it is well-known
8 that the use of adaptations in a trial can inflate this
9 type one error probability without appropriate use of
10 adaptive testing methods that have been supported by
11 theory or comprehensive simulation.

12 Another important consideration is the
13 reliability of treatment effect estimates. The
14 availability of accurate and precise estimates help
15 facilitate a reliable benefit-risk evaluation and
16 appropriate labeling and reporting of results to enable
17 evidence-based medicine.

18 Adaptations can induce bias in estimates, and
19 some methods have been developed to have more desirable
20 properties. An important topic for today's discussion
21 is the extent to which this bias should be evaluated
22 and the extent to which methods, where available,

1 should be used for reporting.

2 Another important consideration is the extent
3 of pre-specification. This can vary and could include
4 things such as the anticipated number and timing of
5 interim analyses, the type of adaptation, the
6 statistical methods for interim and final analyses and
7 the algorithm governing the adaptation decision.

8 Possible motivation for pre-specification
9 include that it facilitates the use of appropriate
10 inferential methods for many types of adaptations. It
11 can help increase confidence that adaptations are not
12 based on accumulating knowledge in an unplanned way,
13 and it can help motivate careful planning and
14 monitoring.

15 As I mentioned previously, the scope of
16 today's discussion is on prospectively planned adaptive
17 designs. But one important topic within that scope is
18 the extent to which that should all be flushed out and
19 documented at the design stage.

20 Another important consideration is the
21 preservation of trial integrity. It is recommended in
22 ICH E9 guidance that access to comparative interim

1 results in all trials is limited to individuals
2 independent of personnel conducting or managing the
3 trial. And there are some added logistical challenges
4 in maintaining confidentiality to interim results when
5 you have an adaptive design.

6 Special considerations include whether there's
7 use of a dedicated adaptation committee or whether the
8 DMC is instead tasked with implementing the adaptive
9 design, the use of confidentiality agreements,
10 firewalls, data access plans and whether steps are
11 taken to minimize knowledge that can be inferred
12 through the adaptive decisions.

13 The documentation for an adaptive design can
14 also be more comprehensive than is typical, and may
15 include things such as the rationale for the design,
16 the evaluation of important operating characteristics,
17 the adaptation, monitoring and data access plans and,
18 in some cases, a comprehensive simulation report.

19 There are also a number of other
20 considerations that I have listed here, but am not
21 going to go through in too much detail, but that may
22 come up during the discussion this morning: the use of

1 simulations in planning and the role of Bayesian
2 adaptive designs are parts of sessions that will come
3 later today and will generate a lot of discussion.

4 There are some special considerations for
5 adaptations in time-to-event settings, such as the role
6 of nuisance parameters, such as the enrollment rate or
7 the censoring distribution in trial planning.

8 There are special considerations for
9 adaptations based on potential surrogate or
10 intermediate endpoints, such as the modeling of the
11 relationship and the assumptions about the relationship
12 between the intermediate endpoint and the clinical
13 outcome of interest.

14 And the final consideration that I'll mention
15 is the importance of the evaluation of safety in
16 adaptive clinical trials. For example, there may be a
17 minimum number of patients or a minimum duration of
18 follow-up that is expected for a reliable safety
19 evaluation, and this can certainly impact the nature
20 and timing of interim analyses that will be appropriate
21 in an adaptive design.

22 With that, I'm going to briefly read through

1 the three questions that we're going to ask the panel
2 to discuss this morning. The first question is the
3 following: What are the two to three most important
4 principals for sharing the appropriate and effective
5 use of complex adaptive designs.

6 Our second question for discussion is the
7 following: Discuss the extent to which complex adaptive
8 designs should be pre-specified. For example, discuss
9 the importance of pre-specifications of the specific
10 algorithm that will be used to determine adaptive
11 decision-making.

12 And finally, bias and treatment effect
13 estimation is currently less well studied than type one
14 error probability control in the context of complex
15 adaptive designs. How important is the evaluation of
16 the properties of point and interval estimates? Should
17 adjusted estimates be included in labeling and
18 reporting of results?

19 That concludes my presentation. I'm really
20 looking forward to just a great discussion this
21 morning. I'm going to turn the microphone over to our
22 two primary discussants for session one, who are going

1 to provide reaction to my presentation and any
2 introductory comments to get the discussion started.
3 So I think we'll start with Dr. Bretz, who has a slide
4 here to present to you all.

5 DISCUSSION

6 DR. BRETZ: Good. Okay. Good morning, and
7 thanks to the organizers for inviting me to this very
8 important panel. And congratulations to Greg for this
9 very comprehensive overview.

10 I would like just to add one perspective
11 before we go into the actual discussions, with respect
12 to the three questions that Greg had posed, and my
13 comment is about the usability of adaptive clinical
14 trials and that it really depends on the specific
15 application.

16 And in order to illustrate my point, I wanted
17 to bring one analogy. Since I'm based in Switzerland,
18 I thought I'd introduce the Swiss Army knife. And
19 think about you have a very well-defined task about
20 cutting a piece of paper. And, if you'd please click
21 once, then which of the tools you would like to use?
22 And probably everybody would use a simple scissor

1 because it is the optimal tool for a very specific
2 task, namely to cut the piece of paper.

3 Now if you'd click once more please, you may
4 recognize this is a Swiss Army knife, which is a
5 versatile tool that combines several individual
6 functions within a single unit, one for every
7 perceivable need. So these knives are often used in
8 the general -- as a general phrase to -- as an analogy
9 or as a metaphor for usefulness and adaptability.

10 And the point I'm trying to make is that with
11 a Swiss Army knife, you can still cut a piece of paper.
12 You see the little scissor toward the bottom right.
13 However, the scissor is not optimal because it's small
14 in size, but you can still do a reasonable job.

15 Now, if you think about doing some other task,
16 you can still use the Swiss Army knife reasonably well,
17 so that if you really don't know what -- you want to do
18 it in advance or you only have a rough idea, then you
19 can do multiple things with this tool, and then the
20 Swiss Army knife is probably a good tool to use.

21 However, you can also overdo the things, and
22 if you click once more, you see the picture of a real

1 knife that you can actually buy. It has about 200
2 functions, one for any need that you can imagine, and
3 it weighs about two pounds.

4 Now, imagine there is somewhere among these
5 200 functions, there is also a little knife. Now,
6 imagine you really want to cut the piece of paper with
7 this little knife. You can imagine that this becomes
8 complex. It becomes really difficult.

9 So while this tool really looks very, very
10 impressive and probably -- well, it's expensive, but
11 still you would like to have it. Once you have it, I
12 can tell you I tried to cut a piece of paper and it
13 doesn't work very well. So you can spend a lot of
14 money, but in the end, you just put it into the shelf.

15 So be careful. And that's my real point, is
16 that in applying adaptive design, do please consider
17 also simple tools, such as a scissor, as they're very
18 appropriate in many cases. But definitely avoid the
19 so-called giant Swiss Army knives in clinical trial
20 practice, I guess. So thank you.

21 DR. EMERSON: So first, thanks for presenting
22 the issues. There's a couple points that I just want

1 to make for emphasis on the things. I guess the -- I
2 always put it under a category of it's very important
3 as we talk about any clinical trial design is what's
4 the burden of proof.

5 And very often I find the biggest mistake is
6 trying to use one clinical trial to answer every
7 question, when you could more efficiently answer all
8 the different questions of safety, efficacy and
9 effectiveness, perhaps by focusing on some different
10 trials.

11 I also like to always think about, you know,
12 what do we need at the end and then, what we need at
13 the end is we need an indication for the drug, which
14 involves what's the disease, the definition of the
15 disease that we're using, what's the population that we
16 think we'll use it in, what's the exact treatment that
17 we think we would have, which is a complete treatment
18 regimen and then, what's the outcome we're looking for?

19 And any of those that change, you've really
20 changed the indication. But at the end of the day, we
21 also need to write a label. And what do we need on the
22 label that the physicians can use this treatment,

1 recognizing that the clinical trial always has a
2 comparator that is generally not the comparator that
3 the physicians are considering.

4 That is to say, they're not always just
5 considering this drug versus placebo. They're
6 considering this drug versus another drug or another
7 sort of treatment, whatever the standard of care is.
8 And so, being able to write a label so that people can
9 understand what's there is very important.

10 And then the last part, I am, you know, merely
11 closet Bayesian. But it's the Bayesian questions that
12 are the most important. We want the treatment that is
13 approved to be one that we think there's a high
14 probability that it works. And so, always thinking
15 back to the fact that as we start on drug development,
16 the vast majority of drugs that we think work don't.

17 And so, it's very important to remember that
18 as we go through this process, confirmation is very,
19 very important because the positive predictive value
20 after a Phase II study is necessarily much less than
21 one after a Phase III study.

22 And the problems that we have as we come to

1 adaptation, if you start off with a drug that truly
2 works at the level that you think in your Phase III
3 protocol, all Phase III studies would be positive,
4 right? I mean if you really -- if you have 90 percent
5 power, 90 percent of Phase III studies would work, and
6 they don't. And that's just because the prior
7 probability is less than a hundred percent.

8 And so, just making certain that we focus, as
9 we talk about adaptation, of what of these adaptations
10 are very, very appropriate at the early stage, and a
11 huge improvement.

12 And I like the Swiss Army knife analogy. I
13 often remark to my hiking companions that what if you
14 really know that the only tool you need is a corkscrew.
15 Do I approve you bringing just the corkscrew on the
16 hike? And no, I want the Swiss Army knife. I want it
17 to have a few more tools, but not too much.

18 And my point would be even at the confirmatory
19 Phase III study, limited flexibility is still within
20 the confirmatory aspect. But it's going to be very
21 important to talk about what's the prior knowledge that
22 you have that you're contributing the confirmation to.

1 DR. PRICE: So thank you both for those, for
2 your reactions to the presentation. I will ask Dr.
3 Meurer -- and I apologize if I'm mispronouncing your
4 last name -- to please introduce yourself, just giving
5 your affiliation. And if we have any other panelists
6 that may have joined us, feel free to come up to the
7 panel.

8 DR. MEURER: That was an excellent
9 pronunciation. I'm William Meurer. I'm an associate
10 professor of emergency medicine and neurology at the
11 University of Michigan.

12 DR. PRICE: Thank you. And Dr. Goodman, as
13 you are getting settled, if you'd like to introduce
14 yourself as well?

15 DR. GOODMAN: Sure. Thanks. I've been here
16 listening, so I missed it. Steve Goodman. I'm a
17 professor of medicine and epidemiology at
18 Stanford.

19 DISCUSSION

20 DR. PRICE: Thank you. So we are going to
21 move into our first discussion. We plan to do this by
22 -- this is not an AC. It's a scientific discussion.

1 But we're going to use a similar method. If you could
2 just kind of raise your hand, Robyn and I will look,
3 and we will acknowledge. We will keep a running list
4 of those people that would like to answer a question.

5 So we're going to start now. Again, the first
6 question is what are the two to three most important
7 principles for ensuring the appropriate and effective
8 use of complex adaptive designs. And I see Dr. Mehta.

9 DR. MEHTA: I think there are three really
10 important issues that must be addressed in adaptive
11 designs. The first I think most important is not to
12 disturb the equipoise of the investigators because they
13 -- as long as they feel comfortable randomizing
14 patients, they will participate. But in an interactive
15 design, changes are made in a midcourse. And so, there
16 has to be a lot of care not to disturb equipoise.

17 My second important point is to keep the
18 interim data very secure and auditable so that you know
19 at the end of the trial, if there is to be a final
20 analysis, it should be possible to actually document in
21 an auditable matter what was the state of the data at
22 the interim analysis because the data from the interim

1 analysis will be combined with the data from the second
2 stage.

3 And the third point is perhaps, everyone would
4 agree, that you must simulate the operating
5 characteristics of the design.

6 DR. PRICE: Dr. Lewis?

7 DR. LEWIS: Thank you, Cyrus. I think one of
8 the first comments, which has already been partially
9 alluded to, is that we need to be very careful to match
10 the adaptive design to the true threats to trial
11 success, where success is defined by getting the right
12 answer, whatever that turns out to be.

13 I consider a trial to have failed if, at the
14 end of the day, you don't have a clear and correct
15 answer to the primary question that motivated that
16 trial.

17 I think there's a tendency to go the other
18 direction, which is try to pretend that the real
19 questions are the ones for which you have a solution as
20 opposed to letting the true threats to the success
21 drive the selection of the design.

22 The second point I'd make is that the design

1 choices that we make, that affect the balance of
2 various complex goals -- and I'm thinking of things
3 like bias and variance tradeoffs, the dual purpose of
4 controlling error rates, traditional type one/type two
5 error rates versus bias correction -- really should be
6 guided by what we anticipate to be the actual use of
7 the result of the trial, either to drive regulatory
8 decision-making or clinical decisions at the bedside.

9 And as a practicing clinician, it's my
10 observation that clinicians tend to use the overall
11 qualitative result of trials in making treatment
12 decisions. They very rarely look in any detail at the
13 precise estimate of the treatment effect and that, at
14 least in that context, the overall error rate is a much
15 more important in consideration than the accuracy or
16 lack of bias in estimates of treatment effect.

17 And then, if I will, I'd just say in terms of
18 the equipoise comment, which I wasn't going to comment
19 on until you brought it up, Alex London at Pittsburgh
20 has written some really nice philosophical work on the
21 concept of equipoise as it applies to adaptive trials
22 that use response adaptive randomization. So I just

1 want to make sure that people know that there's a
2 really good resource on that particular topic.

3 DR. LEE: Okay. I just want to add a little
4 bit on what's been said. I think that we all want to
5 make the correct -- quote, unquote, "correct" or
6 "accurate" decision. And from FDA's point of view, FDA
7 would like to approve safe and efficacious treatment.

8 And regarding the inference, I think as a
9 statistician, we all know that they are two main
10 different ways of making inference into the inference
11 framework, you know, the frequentists and the Bayesian.

12 I'd like to say that in the past, these two
13 approaches has been very competitive. They fight with
14 each other. Currently, it's more competitive, okay?
15 And we are here today to talk about complex, novel
16 design. And again, you can look at from the Bayesian
17 point of view or frequentist point of view.

18 And I think the future, I think it would be
19 more collaborative in the sense that type one -- yes,
20 type one/type two error rate are important, but not the
21 only thing. We will also need to look at the posterior
22 probability of how effective a treatment is, okay?

1 So I think from the inferential point of view,
2 it's not just a traditional point estimate or
3 confidence interval estimate, you know? Yes, that's
4 important, but also we need to look at what's the
5 probability of success in a sense, right?

6 And I want to say a little bit more on this.
7 That is, I think, you know, Steve worked a lot -- Steve
8 Goodman, on these compared two different philosophy or
9 the framework.

10 But one really limited approach in frequentist
11 approach is this non-significant hypothesis testing,
12 you know? That's kind of a -- you know, it has its
13 role, but it's a very limited role. So let me just
14 point that out, and I think we can have more
15 discussion.

16 But through all this, I think three things are
17 very important. One is education. Okay. The second
18 one is innovation. The third one is implementation,
19 okay? So I think we really need to do better in all
20 three aspects.

21 DR. PRICE: So we have Dr. Ashby, followed by
22 Dr. Marchenko, followed by Dr. Goodman.

1 DR. ASHBY: Thank you. Firstly, thank you for
2 very clear presentations. I mean, to me the single
3 most important thing is that you need to think really
4 carefully what you're trying to do. Now, that's true
5 for any study. And the whole debate on estimands
6 actually says to me that you have to think really
7 clearly what the purpose of the trial is.

8 But when you begin to think adapting, you have
9 to think why are you adapting because that drives the
10 design. It drives all of your decisions. So just in a
11 dose response trial, are you trying to hone in on the
12 best dose to take forward to the next stage or are you
13 trying to learn about the dose-response curve because
14 that will, to some extent, influence what the best
15 adaptation algorithm is.

16 Secondly, it is plan, plan, plan, and again
17 that's true for all trials. But for adaptive studies,
18 you're generally doing it because you want to be really
19 efficient. You've got one shot at it. And so the
20 simulation, the discussions, maybe the rehearsals, you
21 know, the decision-making processes can't overemphasize
22 it.

1 My third point is really more of a question
2 because I think when we're flipping around between some
3 things which are really kind of more appropriate to
4 early stage studies and some which are more
5 confirmatory studies. So the third question we've got
6 about what you put in the labeling would be very
7 appropriate if you're doing some adaptation in a
8 confirmatory study.

9 Actually, it seems to be almost irrelevant if
10 you're doing an adaptation of dose on a first-in-demand
11 study with a limited endpoint. And I just wonder
12 whether just passing out some of those general
13 considerations might actually help clarify the debate.

14 DR. LEVIN: Yeah. This is Greg Levin. Yeah.
15 Thanks for that point. I mean, I'd say that our
16 primary focus, what we're hoping is that we primarily
17 focus the discussion on trials that would be intended
18 to support determination of safety and effectiveness,
19 so at the confirmatory stage.

20 But we expect that many of those
21 considerations, like getting the question right and
22 planning also have a role in early phase exploratory

1 trials. But that is our primary focus, and that is why
2 that very question is focusing, for example, on
3 reporting results.

4 DR. ASHBY: Okay. That's very helpful.

5 DR. MARCHENKO: Okay. Yeah. I just wanted to
6 add a little bit. I think I'm a big proponent of
7 adaptive designs. And I think even if in the end we
8 don't use adaptive designs, they allow us to
9 understand, or at least evaluate it, quantify some
10 uncertainties and then definitely help with planning
11 better designs.

12 But I do want to tell -- or at least remind
13 everyone that, in the end, what we want to do, we want
14 to improve patient care. So we shouldn't just think in
15 terms of specific adaptive designs for specific trial.
16 We need to think in terms of programs and go even
17 further because I did have an experience previously
18 when the program went very quickly through Phase I, II,
19 III and got approved. But then payers did not actually
20 want to pay for the drug.

21 And in the end, we didn't improve patient care
22 because we didn't have enough information on specific

1 endpoint of interest, like overall survival. So we do
2 need to think in terms of progress rather than
3 individual trials.

4 DR. PRICE: If I could ask if you're not
5 speaking, please turn your mic off. That may help with
6 some of the projection of sound problems that we're
7 having towards the back of the room. So if you're not
8 speaking, if you could turn -- push the red button.
9 Turn your mic off. Thank you.

10 DR. GOODMAN: So, oh, that sounds loud enough.
11 I missed the introduction unfortunately. So I don't
12 know if there's like a dividing line between complex
13 and adaptive. I hope there is because there's simple
14 adaptive, too. We should not have complex inalterably
15 next to adaptive because current trials are adaptive,
16 just having samples -- you know, stopping rules is
17 adaptive. So there are all sorts of things that --
18 forms of adaptation, stopping for futility in one arm,
19 that we do all the time.

20 So let's not always say complex adaptive.
21 Complex is a choice and, as has already been made
22 clear, many of these trials, particularly in the

1 confirmatory phase, don't have to be that complex. We
2 might adapt on one thing or two things, and usually
3 we're adapting for one of two reasons, either ethics,
4 or efficacy -- or efficiency.

5 And the efficiency is either that we don't
6 experiment in areas where we don't -- where the
7 conclusion is clear, or we're borrowing strength
8 internally from things that are mutually informative.
9 We don't want to ignore that,

10 So in the confirmatory stage, usually the
11 dimensions of adaptation are much more limited. So
12 let's say adaptive, and then only invoke complex -- and
13 I love Dr. Bretz's -- the Swiss knife analogy. That is
14 a very appropriate.

15 On the issue of equipoise, we have to be
16 pretty careful here. You know, there's individual
17 investigator equipoise. And then, there's sort of
18 population equipoise, which is really the most
19 important thing. That was the innovation that Friedman
20 brought to the concept, which was it's disagreement in
21 the treating community and not just in the individual
22 investigator. It's epistemic. It's ethically

1 important.

2 And we always have to think about whether the
3 trial will be convincing to that community. If it's
4 not, then it doesn't matter what the investigators
5 think. So we always are shielding investigators to the
6 extent that we can from the ongoing results.

7 And this is a technical complexity, but the
8 overriding issue is always how convincing is it going
9 to be to the community? And often, if -- literally
10 everybody knew what the DSMB knew or what -- their
11 equipoise would be disturbed in a trial. That's almost
12 always the case.

13 But it's not the case that those same results
14 at a distance will be so convincing to the community.
15 So you can disturb the investigator equipoise and not
16 disturb -- and still be in an ethically tenable
17 situation. I just want to say that, which is not to
18 say that this issue of not letting the adaptations be
19 informative is not an issue. It is, but it's not that
20 fragile.

21 And the last thing I'll say is very often the
22 adaptation is done on safety. I'm sorry, on advocacy.

1 But the clinical decisions have -- and I agree with
2 Roger's point that the physicians are not that
3 sensitive to the size of the effect. But what we're
4 all sensitive to, and they are actually sensitive
5 whether they explicitly put it this way, is the effect
6 in comparison to the safety.

7 And the safety often does not come into their
8 randomization -- into the adaptation. So it might, it
9 might not. So we always have to keep in mind that, in
10 the end, the therapeutic decision is going to be based
11 on some sense of what we're buying for the degree of
12 safety risk. And the safety risk may or may not have
13 anything to do with the adaptation.

14 If it is going to be a critical factor, then
15 it should be brought in if they're on equivalent time
16 scales. But the challenge, of course, is adaptation
17 has to -- you have to adapt on the basis of accruing
18 information and safety may be on a totally different
19 timescale than the efficacy information, and it can go
20 in both directions.

21 So it may not be possible to adapt on safety,
22 and yet that might be the determining factor at the end

1 of the day. So we have to always keep in -- understand
2 where we're getting the complexity from, which is very
3 typically from the -- on the efficacy side, but know
4 that the therapeutic balance is being judged with
5 another parameter that may or may not be incorporated
6 into the design.

7 DR. PRICE: Dr. Chan?

8 DR. CHAN: All right.

9 DR. PRICE: And please cut your mic off, Dr.
10 Goodman?

11 DR. GOODMAN: Oh.

12 DR. PRICE: Thank you.

13 DR. CHAN: Okay. Thank you. Just wanted to
14 add a couple points, and obviously I really liked the
15 example of being sort of practical and not too
16 complicated if it's really not needed.

17 For example, in many of the trials we conduct
18 nowadays, we try to use just a simple futility rules as
19 limiting -- or synthesize re-estimation. It's a very
20 simple tool. And those typically could address maybe
21 70, 80 percent of the adaptation that we do to try to
22 help us to be more efficient in running our clinical

1 trials. So that's number one.

2 Number two is based on the questions that was
3 asked. I think a couple of the principles, one is that
4 definitely we want to try to see if there's a sound
5 statistical principle that's behind the adaptation
6 rules, and that would be the best.

7 And if we get too complicated, the designs, a
8 lot of times we may not have the theoretical results
9 and then we have to rely on comprehensive simulations,
10 look at different scenarios.

11 So having those sort of really workout is
12 critical to ensure that people will be convinced about
13 the adaptive designs that we put in place and review us
14 in the scientific community and even ultimately when we
15 try to report the results in the label and to the
16 physicians, how you characterize the trials and how you
17 adjust the potential bias due to the adaptation. Those
18 are really critical elements that we need to spell out
19 in the protocol.

20 And so, and I know that there's a second
21 question that I'll touch on a little bit. It's the
22 pre-specification is extremely important interface so

1 that we can have perhaps an independent committee to
2 review the interim data and to help the sponsors or the
3 institutions to make adaptation. So the rules of
4 adaptation and what's the implication, those I think
5 need to be very clearly laid out in the protocol. So
6 I'd leave it at that, those two additional comments.

7 DR. PRICE: We have a list. This is great.
8 So I'm going to say who we've seen. Dr. Lieberman, Dr.
9 Harrell, Dr. Toerner, Dr. Chau, Dr. Zhong, Dr. Price,
10 Dr. Emerson, Dr. Barry.

11 So we will try to get through as many as we
12 can, realizing we want to get feedback on questions two
13 and three as well. And I can -- I can say those again
14 slower. So we're going to move to Dr. Lieberman now.

15 DR. LIEBERMAN: Okay. Okay. Thank you. Just
16 a quick comment. So we talk about the need to pre-
17 specify, but I think we have to think about it. Are
18 there pre-specifications and the adaptation that would
19 eventually un-blind the team to the interim results?

20 Because even if it's a different group doing
21 the interim analysis, the implementations of the
22 adaptations will be implemented by the team. And if

1 it's really pre-specified and very detailed, all of a
2 sudden we say, oh, this is where we're going if we're
3 doing this adaptation. So I think there has to be some
4 thought about that. Thank you.

5 DR. PRICE: Dr. Harrell?

6 DR. HARRELL: Yeah, and I have two points.
7 First point is whenever someone uses the phrase
8 operating characteristics, I hope what's not in
9 everyone's mind is just frequent, just operating
10 characteristics.

11 Type one and type two errors are actually not
12 even errors. It's not even the right term for them.
13 They're probabilities of assertions. And so, what we
14 need, at least as important as those, is the
15 probability that the posterior probability will be
16 definitive at some point, either definitive for
17 futility or efficacy or harm. And we need to calculate
18 the probability of inefficacy, which is a lot different
19 from the idea type one and type two errors.

20 Second point is what I think is fundamental to
21 any sort of clinical trial, but especially when you're
22 using response adaptive clinical trials, is to have a

1 precise high-resolution response variable.

2 So I've seen investigator after investigator
3 struggle to -- in a uncommon disease, to get 60
4 patients in a study, and then do a responder analysis
5 which makes the sample size effectively 30 or 20. And
6 so, to collect 60 and analyze the information as if it
7 was 30 patients is really statistical malpractice in my
8 view.

9 And so the choice of the response variable is
10 all important. You have to be able to adapt on the
11 basis of high information. And that usually calls for
12 a continuous variable or something that's ordinal with
13 lots and lots of categories and the measurements are
14 reliable.

15 So a variable like bone mineral density is a
16 high-resolution, high accuracy variable that you can
17 learn from very quickly, just as an example.

18 So the net effect of not doing that is that
19 people are learning about things in adaptive clinical
20 trials where the signal is very strong in a binary
21 response situation. So the signal has to be very
22 strong. In many cases, it has to be super clinical.

1 It's more than a clinically interesting or clinically
2 useful effect. So just remember whenever you're using
3 a binary variable, the chance of missing a real
4 clinically meaningful effect is really huge and the
5 adaptation may not be very reliable.

6 DR. TOERNER: Yeah. Thanks for the discussion
7 so far. As deputy director for safety in the Division
8 of Anti-Infective Products, I think the most important
9 principle is safety. And Dr. Goodman and others,
10 thanks for introducing the topic of safety.

11 But I wanted to highlight what Dr. Ashby had
12 talked about in the context of first in-human adaptive
13 trial designs, and we're seeing this in our pre-IND
14 consultation program where sponsors are increasingly
15 interested in a seamless Phase I to Phase II
16 development program within the context of one study.

17 And Dr. Emerson, in contrast to, you know,
18 efficiency in having multiple trials, we're hearing the
19 opposite, that it's more efficient to have one Phase
20 I/Phase II trial design.

21 But when companies describe this to us,
22 invariably the Phase II portion in patients with the

1 disease for which the drug is intended to treat,
2 there's a question mark about the dose and duration of
3 therapy because that's derived from the Phase I studies
4 of multiple -- of single ascending dose and multiple
5 ascending dose in healthy volunteers.

6 So we would view that second portion to fall
7 within a category that we would characterize as
8 insufficient evidence to support safety of patients
9 enrolling in the trial. So we actually would consider
10 that to be a clinical hold, where we just don't have
11 information to support safety and efficacy.

12 And so, while we have no trouble at all
13 embracing a seamless Phase I development program of
14 single ascending dose to multiple ascending dose, where
15 you have pre-specified stopping criteria based upon the
16 observations of adverse events, that type of adaptive
17 trial design is acceptable.

18 We do have a significant concern when moving
19 into patients with the disease for which the drug is
20 treating where we don't have enough information yet on
21 the dose, duration of therapy and observations of
22 safety in the Phase I portion of the drug development

1 program.

2 DR. PRICE: I'm going to take moderator's
3 prerogative. Dr. Goodman, did you want to respond to
4 Dr. Toerner?

5 DR. GOODMAN: Well, I'd be -- yes.

6 DR. PRICE: Okay.

7 DR. GOODMAN: This may be more of a question.
8 Are you saying that the Phase I portion in this
9 continuous, seamless elusion is going to be shorter
10 than if they conducted two separate trials? Is that
11 why you're not informed? Is that the concern?

12 DR. TOERNER: The concept that's being
13 presented to us is a more streamlined and faster
14 development reaching Phase III drug development.

15 So that's the concept that's being presented
16 to us, that's it's more straightforward to have IRB
17 approval, for example, for one trial, instead of having
18 multiple trials in order to reach Phase III
19 development.

20 But what we're saying is we don't have
21 information to support dose and duration of therapy for
22 patients with the disease in a Phase II evaluation. So

1 that's the concern we have with an adaptive trial
2 design, moving from Phase I in healthy volunteers into
3 Phase II in patients.

4 DR. GOODMAN: Phase I in healthy volunteers,
5 not Phase I in patients. That's the critical
6 difference, right? That's why you're objecting to the
7 transition?

8 DR. TOERNER: That's correct.

9 DR. GOODMAN: Oh, I see.

10 DR. TOERNRE: In our world, Phase I is
11 conducted in healthy volunteers. We are gathering
12 pharmacokinetic and safety information --

13 DR. GOODMAN: I see.

14 DR. TOERNER: -- on the drug itself before you
15 move into Phase II in patients.

16 DR. GOODMAN: I call that phase zero. So we
17 have a phase shift here.

18 DR. CHOW: It seems to me I guess we are
19 already beyond that question. Number one, I think that
20 I would like to take this opportunity to share with you
21 some of my experience on the adaptive trial design.
22 I'm not speaking for the FDA. I mean, this is just my

1 personal experience before I joined the FDA.

2 At Duke University, basically my experience
3 that we pretty much followed the following steps for
4 the clinical trial studies that have been utilizing the
5 adaptive trial design.

6 The step one is that we will first ask the PI,
7 the principal investigator, of the commission to come
8 up with a so-called wish list. In other words I think
9 that we would ask commission exactly what's on your
10 mind. What do you want to do?

11 I mean, usually I think that basically my
12 experience in communicating with the commission, they
13 have some hidden agenda. They would like to answer all
14 of the questions, and then with limited data, some more
15 clinical trials, something like that.

16 So really, this is a way of forcing them to
17 come up with some kind of a wish list, exactly, I mean,
18 what's on their mind. And then after that, the step
19 two, based on that wish list, then we can determine
20 what kind of adaptations should be pre-specified. I
21 mean, the list is very important because, I mean, based
22 on this one, we cannot propose some kind of very

1 complicated adaptive trial design with some pre-
2 specified adaptation, also as Greg mentioned in his
3 talk.

4 And the step number three, and then after all
5 this is all said and done, I think that we will develop
6 the plan for assurance of the data quality because I
7 think that analysis based on the clinical data
8 collected from the complex adaptive trial design is
9 already important.

10 After all this is done, I think that step
11 number four, because I think usually with a lot of the
12 adaptation, we may not have the statistical methodology
13 fully developed in order to reflect the last
14 adaptation. So I think that we would conduct the
15 clinical trial simulation to evaluate the operating --
16 I mean, the characteristics, as Dr. Harrell mentioned.
17 This is under the condition that if the statistical --
18 I mean, the methods of full data analysis are not fully
19 established.

20 This is pretty much what's my experience for
21 the clinical trial study utilizing the adaptive trial
22 design. Along this line, I think that I would go back

1 to the question number one. Pretty much I think in my
2 opinion there are three principles, I think, for the
3 adaptive trial design.

4 Principle number is that I think, in my
5 personal opinion, the principle investigator should be
6 in the driver seat, not a statistician.

7 But I think in the past maybe 10 years, I
8 think that my experience working with a commission,
9 usually I think the statisticians are all in the
10 driver's seat to tell the commission what can be done,
11 what is things that can be done, what cannot be done or
12 something like that.

13 So I think that the first principle I would
14 like to offer is the PI should be in the driver's seat,
15 not the biostatistician.

16 The second principle has to relate to the
17 quality and the validity and the integrity of the
18 adaptive trial design. The principle number three, I
19 think that this is extremely important, in my opinion.
20 We never misuse and abuse adaptive trial design. In
21 the past many, many years, I've seen this. I think
22 people at least misused and also abused adaptive trial

1 design. We have to avoid that from happening. Thank
2 you.

3 DR. PRICE: So before moving onto two, we'll
4 cover Dr. Zhong. You're next. Dr. Price, Dr. Emerson
5 and then Dr. Barry, and we'll move on to question two
6 and three, which we might have touched on already a
7 bit.

8 DR. ZHONG: I really like idea that a Swiss
9 knife, don't make the adaptive too complicated and to
10 be practical. And I also like Dr. Chow's comment on
11 the scientific validity and on what you have in
12 decision-making to guide the decision rule on adaptive
13 design and that's very important.

14 But I would like to just comment on Dr. Chow
15 about who's in the driver seat. I think that for
16 adaptive design, it's not who's on the driver's seat,
17 it's the complete collaboration. It should be
18 statisticians, the scientists at the company, as well
19 as the PI and the independent data committee.

20 So this is complete collaboration. It require
21 education, right? And it's not just let the PI to join
22 it. I'm a statistician by training. And I would like

1 to allow my counterparts -- allow to collaborate,
2 understand what the adaptation is, what the purpose is.

3 So I think we're not in the driver's seat.
4 But we all should be in the driver's seat. It's not
5 just one person in driver's seat. It's we all should
6 be in the driver's seat, right? So I think it's very
7 critical.

8 Now, to get back to the questions and
9 discussion, I think the decision rule is very
10 important. We have to set up a decision rule. Some is
11 critical. It used to be pre-specified, and some may
12 not be able to pre-specify. We may discuss that later,
13 but I'm not going to talk about it now. But please be
14 acceptable to some unplanned adaptation that will not
15 jeopardize integrity of study. I think it is
16 important.

17 And the education part is also very important
18 because -- I mean, even with one SI, right, sometimes
19 it is a lot of emotional factor there. People outside
20 the statistical community do not quite understand what
21 the decision rule means.

22 And a lot of emotional factors there, and the

1 company could make an undesired decision when they
2 emotionally look at the data and went to regulatory and
3 said, okay, we have a fantastic drug, give us approval.
4 Or they could, I mean, prematurely terminate the trial.
5 So we really have to educate all the stakeholders in
6 this process.

7 And I would like to add a couple comments on
8 Dr. Mehta and Dr. Goodman's comments. Regarding the
9 safety in adaptation, in my experience I believe we can
10 build the safety criteria into adaptation. I just
11 speak for myself. So that's number one.

12 And number two, in terms of whether or not --
13 I mean, it can relate to who drives what? I mean, the
14 PIs -- like that's not -- don't make a comment. Don't
15 interrupt when the PIs get comfortable. I think that
16 it kind of depends. I mean, if we educate the PIs well
17 -- I mean, reasonable investigators well, then we are
18 on this common page. And even though they are very
19 comfortable, which they know the patient n, but
20 remember one thing. I mean, our drug development is to
21 improve their care and health, the care of the
22 patients, provide the care options, treatment options

1 to the patients as soon as possible. And therefore, I
2 mean we have a common goal there. And if we educate
3 the PIs well, even though they can enroll tons of
4 patients in, but we are kind of obligated to the
5 public, that we may want to think about adaptation to
6 allow us the opportunity to bring the drug to the
7 patients. I will stop here.

8 DR. CHOW: Dr. Zhong, I would like to clarify
9 one thing. It's what I mean that I think we are in the
10 driver's seat, I mean it's the project lead.
11 Definitely this is teamwork. I mean, the commission,
12 without the statisticians, they wouldn't be able to do
13 it. So I mean, this is definitely teamwork. So the
14 driver's seat, that means the project lead. Thank you.

15 DR. K. PRICE: Great. Thank you. As it turns
16 out, I'll be restating or reemphasizing a few points
17 that I think have already been mentioned.

18 But a couple of the things I think are really
19 important to ensure that the appropriate and effective
20 use of these designs and one of those is that there
21 should be the holistic planning of the drug development
22 -- of the development of the drug. So it should be the

1 exception that we arrive in the confirmatory setting
2 and go, oh, oops, we need to do some adaptation here.
3 These things should be thought about well in advance
4 and part of the drug program.

5 And as part of that, thinking about what other
6 studies might need to be accompanying it, if the
7 adaptations that would be necessary would require some
8 longitudinal modeling or we've talked about natural
9 history studies or other things that might need to be
10 happening in the meantime prior to the confirmatory
11 portion of an adaptive design, those should be part of
12 this holistic drug development paradigm so that we are
13 most effective in that confirmatory setting.

14 The other point I wanted to emphasize is it is
15 in fact a very cross-functional and cross-stakeholder
16 activity. So those points have been mentioned. But
17 it's very important we keep in mind that through the
18 pilot program, and as we are proposing these designs
19 and having conversations with FDA and industry and
20 others, that there are cross-functional representatives
21 as part of those discussions and that we are able to
22 bring to bear patient perspectives and other

1 stakeholders' perspectives, and then thirdly, that as
2 has been mentioned, I think to ensure these are most
3 appropriate and effective is keeping the patient first,
4 and what information do they need to make well-informed
5 decisions about whether or not to take a specific
6 therapy. Thank you.

7 DR. PRICE: Dr. Emerson?

8 DR. EMERSON: So just a couple of comments,
9 just to focus on what we're talking about. Clinical
10 trial development has always been a sequential adaptive
11 process. What we're trying to do is speed it up now.
12 We're trying not to go through wildly separating times
13 of Phase II, Phase III.

14 However, that is largely the sponsor's view,
15 not public health's view in the sense that we have lots
16 of treatments being tried and if you study one and then
17 there's the white space that's dreaded, you go on to
18 study something else at the same time. And trying to
19 optimize that is a very important thing.

20 So I understand Dr. Toerner's point. The
21 sponsors all want to hurry it up, but I'm saying, you
22 know, we don't necessarily want to help them without

1 being certain that we're doing the same things that we
2 could do, which is how many people review Phase II
3 results as they then decide to put patients on Phase
4 III currently? And are we trying to shift it that only
5 three people know those results, rather than it's been
6 published in the literature and people have thought
7 about it and it's reviewing the thing?

8 There's no question that going through 70
9 different IRBs is a slow process, and don't want to
10 unnecessarily go through that. But we need to make
11 certain that we're keeping the population preeminent in
12 my mind, not just the patients who are on the clinical
13 trial, but how fast we can adapt things.

14 And then I will note -- and speaking to your
15 question of we can't pre-specify everything. And the
16 FDA is of course well-aware of that because they all
17 the time reduce, restrict indications at the end, you
18 know, that they -- without gathering more data on that,
19 they suddenly say, well, we don't feel comfortable in
20 the really light patients or the really old patients,
21 or people with renal failure, and you have to do
22 something.

1 And of course that I justify with saying it's
2 the game theory, you know. The sponsor has more of an
3 interest in getting this drug approved, whereas the FDA
4 sometimes steps back and says we'd rather go with
5 errors of omission rather than commission sometimes.
6 And so, again, it's how can we -- vast improvements can
7 be made. We just don't want to throw out everything.

8 DR. BERRY: So I struggle with -- and maybe
9 it's why I live along this, that -- let's not be too
10 complex. I mean that statement is a tautology. Too
11 complex is too complex. The question is what's the
12 right complexity.

13 Many of our adaptive designs, for example,
14 Scott, are you need to slow down. We need more
15 exposure. We don't know the answer. And it's getting
16 it just right, what's the right sample size, what's the
17 right time, what's the right complexity.

18 While you may do just futility, there are
19 situations where much more complexity is the right
20 answer for the particular situation. So I think it
21 does go back to Dr. Ashby's point, that what are the
22 right questions for the population, for this drug, for

1 the whole class? What is the right design that fits
2 this?

3 In order to answer that, it's about simulation
4 and pre-specification. The Swiss Army knife is nice.
5 But I take it as a incredibly different point that I
6 think it was presented. That's for somebody who hasn't
7 pre-specified what tools I actually need. I bring
8 everything with because I don't really know what I'm
9 doing and I might need 200 different things.

10 If I know I need a screwdriver and I need a
11 scissors and a toothpick because I've pre-specified and
12 that's the right complexity for this, we're going to
13 run better trials. We're going to get better answers.

14 And I think that's part of what we're here
15 today, is in situations where the trial needs more
16 complexity than we're used to, how do we do that well?
17 And I think that's critical, is the pre-specification,
18 simulation and understanding the questions and the
19 threats to those questions that Roger brought up.

20 DR. PRICE: Thank you, Dr. Berry. That's a
21 very nice segue into question number two, which deals
22 with pre-specification. So we will ask you to formally

1 discuss the extent to which complex adaptive design
2 should be pre-specified. And I see Dr. Mehta, followed
3 by Dr. Lewis.

4 DR. MEHTA: I think that what's important to
5 pre-specify in an adaptive trial is the method that
6 you're going to use at the end of the trial for a final
7 analysis. As an example, if you're going to drop a
8 dose or increase the sample size, you specify in the
9 statistical analysis plan that I'm going to use this
10 type of method, control of error rate or combination or
11 closed test. This is what I'm going to use at the time
12 of the final analysis. That's all you need to specify.

13 At the time of the interim analysis, the
14 actual decisions rule that you use to drop the dose or
15 to increase the sample size, there can be flexibility
16 in that. That will not affect the type one error, as
17 long as you have specified the manner in which you will
18 conduct the final analysis at the end.

19 I know that the regulatory agency wants you to
20 also specify the decision rule that you will use. All
21 I'm saying is that may not be the optimal thing to do
22 because you might see things -- the DMC might see

1 things that make it a better idea to adapt in a
2 different way. And as long as you keep the principle
3 of how you're going to do the final analysis properly
4 locked up, then I think that should be allowed.

5 DR. PRICE: Dr. Lewis?

6 DR. LEWIS: So I now regret putting myself
7 right after you because I'm going to unfortunately
8 contradict you. So in my view, the discussion that we
9 are going to have about simulation is critically
10 important because simulation often yields tremendous
11 insights into the strengths and the liabilities of a
12 proposed trial design.

13 And I find that people's intuition about the
14 way a trial design may misbehave is actually not very
15 good. And sometimes, in fact if you simulate
16 traditional group sequential designs with some things
17 like biased coin randomization, you can actually get
18 operating characteristics, with apologies to Dr.
19 Harrell, that are actually quite different than you
20 were promised when you were taught these techniques
21 early in your training.

22 So I think that simulation is a key thing we

1 need to be able to do well if we're going to be honest
2 with ourselves about whether we under the behavior of
3 the trials we're proposing.

4 To simulate, you have to pre-specify. So if
5 you're one who's going to simulate, you have to be able
6 to write code that simulates the trial. You can't
7 simulate the trial without pre-specification. That
8 pre-specification should enable simulation that
9 includes realistic effects that may affect performance,
10 such as time to information, missing data patterns and
11 the like.

12 So in my view, for the context of this
13 discussion which is complex, adaptive designs, my
14 understanding, that simulation is necessary almost
15 always. It's eye-opening when you do it on designs you
16 thought you understood, but you were wrong, and to
17 simulate, you must pre-specify. Thank you.

18 DR. PRICE: Dr. Bretz? And if I could remind
19 everyone to please turn your mic off when not speaking.
20 Thank you.

21 DR. BRETZ: Actually I think I can agree to
22 both statements, in the sense that I would also like to

1 make the point that we should avoid pre-specifying
2 specific algorithms and put them upfront in the study
3 protocol.

4 We need to specify the type of adaptations,
5 the methodology we're using to integrate the data and
6 for the fine analysis. But that's probably about it,
7 because at interim analysis we would like the decision-
8 makers to be able to integrate the data they see and
9 possibly move away from any pre-specified algorithms.

10 This does not exclude the need for running
11 simulations and understanding the operating
12 characteristics for some foreseeable outcomes at the
13 interim analysis. So I would certainly like to
14 advocate, if the teams come to me and ask for advice.
15 I always tell them, so what is the interim decision you
16 want to make and please think in advance what exactly.

17 So for example, in a treatment selection
18 design, you tell me, yeah, we want to select the best
19 dose. So what do you mean by the best dose? You have
20 to tell that to me, right, because the DMC or whoever
21 the decision-maker is will have to make the decisions.

22 And if it's an independent DMC, quite likely

1 they will have to make the decisions on our behalf, on
2 the responder's behalf. So more importantly, we will
3 have to understand the operating characteristics. At
4 the same time -- and this will have to be communicated
5 with DMC.

6 But at the same time, it allows the DMC to
7 have the flexibility if unforeseen safety patterns come
8 up, that they can read the balance, efficacy and safety
9 and, you know, make the right decision, so to speak.
10 So in that sense, I think I can agree to both of the
11 previous panelists.

12 DR. PRICE: Dr. Meurer, followed by Dr. Ashby.

13 DR. MEURER: When I was first looking at this
14 question, I thought that answer was quite simple, in
15 short, which would be discuss the extent to which
16 complex adaptive design should be pre-specified. And I
17 would say fully.

18 There is nuance to this. But I think, you
19 know, going to the last point, yes, data and safety --
20 an external data and safety monitoring board does have
21 rights and obligations. But I guess the roadmap for
22 the complex adaptive trial and the algorithms that are

1 pre-specified, I would sort of challenge, you know -- I
2 think one of the things before was like we need to, you
3 know, sort of respect the PIs. You know, I'm a PI.
4 I'm a clinician. I'm kind of dumb. I mean, like I
5 don't know the -- you know, and I think this --

6 DR. BERRY: You're so hard on yourself.

7 DR. MEURER: But I think that if we have a
8 dumb question, we need to be told we have a dumb
9 question. And if we have a dumb way of framing things,
10 and that, you know, we have a lot of other concerns
11 that aren't encapsulated in our primary endpoint, then
12 maybe we need to have some other endpoints so that we
13 can properly value those things in terms of whether
14 they're important safety outcomes or not.

15 So and I think, you know, potentially if this
16 was something like, you know, the consort statement, it
17 would probably have similar things, like at least for a
18 fixed design in terms of making sure all of those at
19 least interim stopping rules are very pre-specified.

20 So I think pre-specification is important for
21 the transparency and the, you know, reproducibility of
22 the research. But that's not to say that data

1 monitoring committees shouldn't have rights as well to
2 perhaps do things that are pre-specified. But I think
3 that's different from the performance of the design and
4 the protocol as intended.

5 DR. ASHBY: Thank you. I mean, William just
6 used the word that, to me, is the absolutely guiding
7 principle here, which is transparency. That's what I'm
8 most concerned about. And so, in that context, I would
9 be very much in favor of trying to pre-specify the
10 algorithm. I think that has benefits when one's
11 working up the trial because it's only when you
12 actually pre-specify it that you really have those
13 conversations about what is the PI trying to do, what's
14 the overriding goal, how are the statisticians
15 interpreting that, if you've got patient input.

16 I've had some very good input from those in
17 some of these discussions. It may well be when the
18 trial is live that some other characteristics happen as
19 well, and so that may change it. But it should be
20 completely transparent what was pre-specified, what
21 were the additional factors and why. And certainly --
22 and I've spent my time on UK advisory committees,

1 European advisory committees. What you want to know at
2 that stage is what was pre-specified, what else
3 happened and why? But it's got to be completely
4 transparent. And if you get that right, I think the
5 rest falls into place.

6 DR. PRICE: Dr. Lewis, did you have your hand
7 up? And then we'll go to Dr. Goodman.

8 DR. LEWIS: So this is a discussion that's
9 interesting that I was having yesterday at the Wellcome
10 Trust. We were discussing E6 and some issues that have
11 to do with protocol amendments.

12 And I think the concept of what is and is not
13 a protocol amendment is helpful in clarifying the
14 discussion. When I state that a trial design should be
15 pre-specified, in my mind that is the trial as you
16 intend to conduct it if nothing unexpected happens.
17 And that ought to be pre-specified, and it ought -- you
18 ought to be able to simulate it.

19 If something comes up and the DMC sees a
20 safety signal that was unanticipated, there was
21 external information, which I know was excluded from
22 this discussion, and they, in their infinite wisdom --

1 I use that term guardedly. I'm on many DMCs -- chooses
2 to drop a dose or change an allocation regimen, that's
3 a protocol amendment. That's a change from what you
4 pre-specified. And it needs to be reviewed through the
5 appropriate mechanisms assure that that amendment, that
6 un-pre-specified change is appropriate from scientific,
7 ethical and regulatory points of view.

8 So I think that we need to be very careful
9 about being clear when we talk about things that you
10 might do partway through a trial to distinguish those
11 things that are pre-specified and are not protocol
12 amendments versus those things that are post hoc
13 unanticipated changes that are maybe appropriate, but
14 need to be clearly identified as such.

15 DR. PRICE: Dr. Goodman?

16 DR. GOODMAN: Thanks. That was -- that
17 eliminated 90 percent of what I had to say, and said a
18 lot of things I wouldn't have thought of saying.

19 The only thing I will add is that it's also
20 possible to explore through the initial simulations the
21 effect of deviations from the written protocol and
22 that's as important. So you can say, well, what

1 happens if we don't adapt on, you know, the
2 randomization or what happens if the surrogate is not
3 informative about the final endpoint.

4 I mean, all of the sensitivity to the
5 assumptions can be explored. And in fact, many of the
6 operating characteristics, however we define them,
7 frequentist or Bayesian, are pretty resistant to, you
8 know, commonsense modifications as you go along,
9 whether they be unintended or even in response to
10 things that you should've predicted.

11 So I think it's very important to build into
12 the pre-specification what happens if we're wrong and
13 if we made different choices. And even you can do that
14 to some extent ahead of time and find out that, you
15 know, things won't change that much. And if they are
16 exquisitely sensitive, you need to know that.

17 DR. PRICE: Dr. Chan, Dr. Meurer and then we
18 will move to question three very quickly before opening
19 up for public questions and answers.

20 DR. CHAN: Okay. Thank you. Just a couple
21 things to add. I think -- and I fully support sort of
22 in terms of, in the complex design, do we really need

1 to pre-specify the general algorithms as a guideline
2 for the DSMB or independent review body to understand
3 how the potential implications. And a lot of times
4 when we work with our DMCs, we try to mark up different
5 scenarios of what would've happened if the trial go
6 this way or that way, according to how the adaptation
7 rules were written.

8 And then when -- and the DMC will make their
9 recommendation. But there are certain aspects that the
10 sponsor would have some additional information outside
11 from the protocol that could help the sponsors make a
12 decision after taking the recommendation from the DMC.

13 So this is really critical, as much as
14 possible, to let the DMC through the DMC charter or the
15 strategic analysis plan specific to the adaptation
16 rules.

17 So then -- and that goes with something that
18 we haven't really talk about, is the communication
19 aspect under Greg, in his slides, talked about the
20 importance of how you're going to maintain the
21 integrity and communication and firewall, who actually
22 have access to the blinded -- un-blinded data and who's

1 the DMC communicating to the sponsor's personnel. So
2 those need to be sort of also pre-specified to really
3 ensure acceptance of the adaptive trials in the
4 scientific community.

5 DR. PRICE: Dr. Meurer?

6 DR. MEURER: One other thing that I forgot to
7 mention, one thing that one has to be careful about --
8 and again, I am a fan of transparency and openness.
9 But at times, you may need to not have your enrolling
10 investigators in say like an un-blinded study with
11 multiple arms, there may be some details of the
12 algorithm that need to be held back from them so that
13 they're not reading too much into they have three
14 people in a row in one treatment.

15 Not that they should read too much into that,
16 but that could be the transmission of information about
17 the algorithm, in terms of like if it's response
18 adaptive randomizations. That could lead to
19 operational biases and that should all be pre-
20 specified. But it may not need to be public. And we
21 do have one example of a trial where we know that
22 response adaptive randomization is occurring. But the

1 enrolling investigators don't know the precise ratio
2 that it can go to. But obviously the un-blinded
3 statistician knows that and has codified that prior to
4 the initiation in the study.

5 DR. PRICE: Thank you. So we were overly
6 ambitious in our questions, which is a good thing,
7 which means we've had a lot of discussion, and it's
8 been very informative.

9 We're going to be a little bit adaptive.
10 We're going to go to question three, but we're only
11 going to take two responses -- whoever feels most --
12 oh, wow. This is not going to work. I saw Dr. Harrell
13 and Dr. Emerson. So they'll respond to question three.

14 We'll then move to public questions and
15 answers. And we have a lot more discussion, so I'm
16 sure you will have opportunities to speak as the day
17 goes on.

18 So question three: Bias and treatment effect
19 estimation is currently less well-studied than type one
20 error probability control in the context of complex
21 adaptive designs. How important is the evaluation of
22 the properties appointed in interval estimates? And

1 should adjusted estimates be included in labeling and
2 reporting of results? So Dr. Harrell first, followed
3 by Dr. Emerson.

4 DR. HARRELL: I want to just steal a moment to
5 celebrate two things. The first is I've been on a lot
6 of panels without enough gender diversity, and this is
7 not one of them.

8 And the second thing to celebrate is we have
9 sitting, side-by-side each other, the incoming
10 president of the Royal Statistical Society and the
11 incoming president of the American Statistical
12 Association. That's pretty darn cool.

13 So my comment about this question is that when
14 you use a priority distribution for adapting or for
15 stopping or for your final evidence for efficacy and
16 you use that same priority distribution at getting the
17 posterior mean, the posterior mean will give you the
18 right calibration for early stopping then other
19 adaptation.

20 So we know that if you stop early for
21 extremely high efficacy, the mean would be biased. The
22 posterior mean will pull that to exactly the right

1 thing.

2 So if you don't use Bayesian methods, Scott
3 Emerson has the best software for helping you derive
4 the incredibly complex sampling distributions if you're
5 doing a complex design or just doing group sequential
6 designs. It's very complex and it's hard to deal with,
7 unlike the Bayesian posterior mean.

8 DR. PRICE: Dr. Emerson?

9 DR. EMERSON: So I would not say what Frank
10 just said about me. But the thing that I would say is
11 I do think, thinking about the Bayesian properties is
12 very, very important. But I don't believe you ever get
13 the right thing unless you take the population of
14 priors. And so getting a population of priors is very,
15 very important, and I think that's an important thing
16 to look at.

17 I think it is very important to do this bias
18 adjustment. But very few people do it. And I have
19 some guesses as to why it's not done that much. One
20 aspect is probably the regression to the mean of only
21 reporting these estimates when the drug is approved
22 swamps everything else.

1 And so, you know, there is this idea. But I
2 will just note that if you look at the medical
3 literature, there is some resistance of people to take
4 any sequential results. There's some papers out saying
5 if you stop early in a clinical trial, you get reversal
6 of your results more often than not.

7 And I think that's wrong. I think that if you
8 control for the P value that is stated, the sequential
9 trials with properly adjusted P values do better than a
10 fixed-sample study with just a P value, but just
11 realize that there is that aspect.

12 And then the last comment I'd make is interval
13 estimates are of course very, very important if you're
14 going to go with the frequentist paradigm and you're
15 interested in non-inferiority and things like that.
16 And they should be proper intervals.

17 But in the -- probably including it in the
18 labeling, I'm going to make the rash statement that
19 this would make a material difference really only with
20 hazard ratios because almost anything else you did,
21 you'd give the raw data, and people would do their own
22 simple analyses using fixed-sample results. So if you

1 just give me the proportion of, you know, people who
2 had response, people are going to quote those response
3 rates and not do the adjustment. And I'm not going to
4 be in favor of withholding the raw data in this case.
5 So there's going to be a problem.

6 DR. PRICE: We will open the floor up now for
7 public questions and answers, or questions. I'm not
8 sure about the answers. Could I ask you to please give
9 your name and affiliation?

10 AUDIENCE Q&A

11 QUESTION: This is Qing Liu. I used to be at
12 DBI, FDA a while. And now, I'm working for Amicus
13 Therapeutics on rare disease.

14 Now I have three points to make. The first
15 one I think goes with any other designs with which we
16 follow the KISS principle, K-I-S-S -- keep it as simple
17 as possible.

18 We need to understand actually what it is
19 actually we're doing, you know, why do we need adaptive
20 design? Can we find any other approaches to solve the
21 problem? We have to focus on the ball, think about the
22 problem we're solving and then find a solution to the

1 problem. Maybe adaptive design is one of the approach
2 to solve the problem. So that's my number one.

3 Number two, actually this is a responding to
4 many of the comments and discussions that we -- you
5 know, any time we have a novel design, adaptive design,
6 we need to really have a inferential foundation to the
7 design.

8 By that, I mean, for example, estimation. The
9 estimation problem has been solved for simple two stage
10 adaptive design in 2002 in the JASA paper me, Mike
11 Proschan and Gordon Pledger. And that procedure has
12 been actually applied to many different other
13 situations. Now, so that's regarding estimation.

14 Now, I read many papers by Scott Emerson, and
15 he actually showed in one paper that, you know, there's
16 really not a whole lot of difference from Bayesian and
17 the frequentist. I mean, if you have a Bayesian
18 design, you can actually, you know, do some
19 transformation and convert to a frequentist design and
20 vice-versa.

21 So that doesn't really actually help anything.
22 And I hate to say, actually, you know, Thomas behind me

1 from John Hopkins University, the wording for -- the
2 problem, the fundamental problem in an empiricist
3 approach. For example, if I have a sample size of
4 three, I can do a T test, and I'm going to have alpha
5 value of 0.025, right? One-sided.

6 What about actually I increase the sample size
7 to 1 million? I can still do an alpha test, 0.025. So
8 the problem is if you think about science, the larger
9 the study -- assuming there's no other bias -- and
10 then, the probability of making any error should be
11 goes to zero.

12 So having said that, the right foundation for
13 clinical trial and the interest in general also for
14 adaptive design is really an evidential approach that
15 can actually include frequentist, Bayesian as well as
16 Richard Royall's law of likelihood as a special case.
17 That's has been actually developed, and I've yet
18 actually, you know, to make more public presentations.

19 Now, the last point I want to make is actually
20 integrity. And this is based on a real-world evidence,
21 meaning a real-world experience, is that, you know, we
22 talk about integrity, openness, transparency in terms

1 of the process, I mean, set up the DSMB and the data
2 and everything else.

3 So what about actually one of the biases is
4 actually reporting bias. So remember, actually,
5 adaptive design can be a two-edged sword. So you
6 increase the sample size. You can drive the overall
7 statistical significance. But also it gives you the
8 ability to find out, ah-hah, there is a treatment by
9 subgroup interaction where the subgroup is actually
10 meaningfully pre-specified.

11 Now, here is a question, that when this study
12 is reported, it's submitted to regulatory agency, I
13 mean -- well, because this treatment by subgroup
14 interaction is not actually pre-specified in the ISAP,
15 in the agreed framework with the FDA, does the company
16 has the responsibility to say actually in fact we find
17 something else? And also, does the FDA should go
18 further to understand you know, well, I mean, there's
19 something else negative about this drug, even though
20 the overall statistical significance is reached.

21 Now, the next question is that when the
22 company publish the result in medical journal, should

1 company disclose the fact that there is a treatment by
2 subgroup interaction. In fact, none of the group -- it
3 doesn't seem to be there is any substantial evidence
4 for efficacy. That's it.

5 DR. PRICE: Thank you for the comments. I
6 think in the essence of time, we'll move to the next
7 person at the mic. Thank you.

8 QUESTION: Hi. Tom Louis, Johns Hopkins. A
9 couple, just two brief points, one on the monitoring
10 plan. I think we have to look at it relative to
11 history. I mean, O'Brien-Fleming monitoring with
12 nothing else. It's still advisory. I mean, it's not
13 as through you're locked in.

14 I think of all these as an aid to navigation,
15 if I can use a nautical analogy, and that we should
16 study them and explore and be very detailed, as much as
17 possible, knowing that it's always just a navigational
18 aid.

19 And then, another point having to do with
20 that, screen, as much as I'd like to reduce the
21 prominence of P values, I'd really like to route the
22 word bias. It has such emotional resonance. I'm all

1 in favor of good estimates. I like mean squared error
2 small estimates.

3 Any of you who have ever fit a regression
4 equation and have stopped short of saturating the
5 model, heaven forbid, are fitting a biased model. So
6 let's get away from that emotionally laden word and
7 talk about estimates that are good either with mean
8 squared error or something else that doesn't just focus
9 on that one piece. Thank you.

10 DR. PRICE: Thank you, Dr. Louis. And the
11 speaker at the second mic?

12 QUESTION: Yeah. Hi. I'm Russell Ray (ph),
13 from Ocuvia (ph). I have a question. These designs
14 tend to be a little bit more fragile than the fixed
15 designs. For instance, if you have a treatment by
16 region interaction, that could affect your operating
17 characteristics, even in simple cases of a sample size
18 re-estimation.

19 Is there any thoughts of how we can account
20 for that and how much we have to investigate those sort
21 of issues that might cause the outbreak characteristics
22 to not be what we want it to be?

1 DR. PRICE: Dr. Berry has a response.

2 DR. BERRY: Sure. So first of all, I think
3 the whole idea of the adaptive design it's much less
4 fragile than the fixed design. Running a sample size
5 to a fixed number, getting to the end and saying, oh,
6 shoot, I got the wrong sample size. I had these
7 issues, is much more fragile than something that can
8 recognize it.

9 So there are threats to the trial sample size,
10 the conclusions and it might be these various nuisance
11 aspects of it. And as you simulate the trial and you
12 simulate these different effects, you can see that, oh,
13 no, if I do this sample size re-estimation and I
14 actually have a large treatment effect, my sample size
15 grows enormously because it misestimates the nuisance
16 parameter and you can see that as simulated.

17 So this incredibly thorough simulation and the
18 threats to failure typically bring about adaptive
19 things and better adaptive things to prevent exactly
20 that for the whole purpose of it being much less
21 fragile than just going to a number and getting to the
22 end.

1 DR. PRICE: Thank you. And our final comment
2 or question before heading to break?

3 QUESTION: Hi. My name is Smita Asare. I'm
4 the executive director of the I-SPY trials operations.
5 And a couple of answers that I can give you for some of
6 your questions, one other thing is in adaptive trials,
7 which is unusual or different from your regular trials,
8 is that the data has to be available now because you
9 are real-time assessing.

10 And I think a lot of people forget that data
11 is hard to get in a clinical trial, and you always have
12 to be thinking about your inputs and having a lot of
13 control about those inputs.

14 In the I-SPY trial, we do a lot with MRIs,
15 pathology. We have real-time data inputs with
16 recruitment and one of the points I would like to say
17 is recruitment has an effect also on your algorithm.

18 If your recruitment is slow and you don't get
19 to those certain endpoints, it can have a big impact on
20 your randomization algorithm. So things to think about
21 is data, data collection, quality, review. We have
22 remote monitoring on all of those data elements, the

1 number of the inputs and of course time.

2 So your simulations are great. It's just that
3 they also have to account for reality of the patients
4 coming into the trial. Thank you.

5 DR. BEITZ: Can I make one comment?

6 DR. PRICE: A final comment before we head to
7 break.

8 DR. BEITZ: What I find is that some companies
9 come in and they don't really have a stat analysis plan
10 at the time their protocol is in. And for the sake of
11 doing an adaptive design, I would argue that you really
12 need to see the stat analysis plan to make sense of the
13 whole picture. That's my little punchline.

14 MS. BENT: Okay. Thank you. So we're going
15 to move to break now. We'll be back at 10:30. And for
16 those of you who have not ordered a lunch, please order
17 a lunch from the Sodexo kiosk if you're going to need
18 one because they need to prepare for that. Thank you.

19 (Whereupon, the foregoing went off the record
20 at 10:15 a.m., and went back on the record at
21 10:37 a.m.)

22 DR. PRICE: We will go ahead and get started

1 with session two. The format for session two will be
2 the same as that of session one. However, the FDA
3 panelists will be rotating out throughout the day. So
4 I would ask my two colleagues to introduce themselves
5 prior to Dr. LaVange beginning.

6 DR. SRIDHARA: Hi. I'm Raji Sridhara. I'm
7 the division director of Division of Biometrics V. My
8 division covers all of oncology hematology products.
9 Thank you.

10 DR. BEITZ: My name is Julie Beitz. I'm a
11 director of Office of Drug Evaluation III in FDA, CDER.

12 DR. PRICE: And our second presenter of the
13 day really needs no introduction, but I'll give her a
14 brief one.

15 Dr. LaVange is professor and associate chair
16 of the Department of Biostatistics in the Gillings
17 School of Public Health at the University of North
18 Carolina at Chapel Hill.

19 Many of you are well aware that prior to 2018,
20 Dr. LaVange was the director of the Office of
21 Biostatistics in CDER, and as Dr. Harrell mentioned,
22 she is our 2018 president of the American Statistical

1 Association.

2 So Dr. LaVange, without further ado?

3 SESSION II: GENERAL CONSIDERATIONS FOR OTHER INNOVATIVE
4 DESIGNS INCLUDING EXTERNAL/HISTORICAL CONTROL SUBJECTS,
5 BAYESIAN DESIGNS AND MASTER PROTOCOLS
6 PRESENTATION

7 DR. LAVANGE: Thank you very much. And I am
8 so excited to be back on campus in spite of having to
9 go through security -- worse than the airport. No, and
10 I'm very excited that this meeting is taking place.
11 How do I start the slides? We can get the slides
12 going. There we go, okay.

13 This meeting is the culmination of a couple
14 years of negotiation and work with our pharma and bio
15 colleagues, and under the Prescription Drug User Fee
16 Act, number VI.

17 There is a project -- the complex innovative
18 designs project, was part of the PDUFA VI negotiations.
19 It was a project that was proposed both by the FDA and
20 by the pharmaceutical biotechnology colleagues on the
21 other side of the table.

22 There was a great meeting of the minds. A

1 couple people here today, Gracie Lieberman, one, was
2 part of that background negotiation. And it -- the
3 PDUFA VI project also overlapped very nicely with the
4 commitment under the 21st Century Cures Act, which was
5 passed by Congress.

6 And the two together, both called for a public
7 meeting to discuss complex innovative or novel trial
8 designs. And this meeting is in fulfillment of that.
9 In addition, they both called for guidance work, and
10 I'll say something about that in a minute as well.

11 Partially to respond to Steve asking why we're
12 dropping the word complex in, in front of adaptive, the
13 project is actually complex innovative design, of which
14 complex adaptive designs, but other designs as well are
15 considered a part.

16 And for purposes of the PDUFA negotiation, we
17 defined fairly simply that anything that required
18 simulations basically was complex. Anything that
19 didn't have a simple analytical derivation for
20 hypothesis testing or some other way of making
21 inference. Now that's obviously a simplistic
22 definition, but it, you know, helped further their

1 negotiations.

2 And in addition to the public meeting which
3 we're having today, the guidance commitments, there's
4 also a pilot program which you'll hear about this
5 afternoon, which is a very exciting part of the
6 program.

7 So as mentioned, the complex innovative
8 designs, we broke into two buckets, one, adaptive
9 designs that may be complex. Not all adaptive designs
10 are, as was pointed out, because they're either
11 adapting on multiple factors or they require
12 simulations to determine their operating
13 characteristics, which as Frank Harrell pointed out,
14 could mean a number of things, not just type one error.

15 And there could be other reasons why the
16 adaptive designs are complex, but certainly all
17 adaptive designs are not complex.

18 The session we just had this morning, I
19 consider that a warmup session, not very controversial.
20 Everybody was very polite. So with this session, we'll
21 get into the more controversial topics, and I'm
22 expecting a lively discussion. I'll be disappointed if

1 we don't have one.

2 I will just say one thing about the complex
3 adaptive designs. The FDA CDER and CBER issued a
4 guidance in 2010 on adaptive designs, in partial
5 fulfillment of both the PDUFA VI and 21st Century Cures
6 Act. The adaptive design guidance has been revised
7 instead of being finalized in its current form. It was
8 revised to make it a little bit more clear what was
9 expected of sponsors when they had a complex design.

10 And this was done by putting the principles to
11 guide any adaptive design into the guidance rather than
12 talking about this design's okay. This design's not
13 okay. And that guidance is in clearance. Greg Levin
14 presented on it this morning. He's one of the primary
15 authors of it, as is John Scott, who is in -- will be
16 presenting this afternoon on simulations.

17 So this session is on other designs. They may
18 or may not be adaptive, but they're complex for another
19 reason. And there are lots of different types of
20 complex designs that we consider under this rubric of
21 complex innovative designs.

22 They might be complex because they're

1 leveraging external data sources for one reason or
2 another. Could be a control group, could be a natural
3 history study to inform your analytic model. They
4 might be complex because they want to use another
5 criteria, or they use another criteria for decision-
6 making.

7 They might base interim adaptive decisions on
8 probabilities of future success with another endpoint,
9 for example. Or they might be complex because they
10 involve collaborative efforts, novel ways of sharing
11 data in something that might be called a master
12 protocol.

13 So I'll just roughly touch on each of these
14 three types to get the conversation started. But they
15 -- this is not in any way meant to be an exhaustive
16 list of complex designs. There's many other ways you
17 can go into complex designs.

18 And also, just the purpose of this discussion
19 is to advise the FDA, to let the FDA hear from
20 sponsors, academics, other government regulators about
21 the different ways to approach complex designs, not
22 necessarily to endorse or not endorse any of the

1 examples that I'm about to use.

2 So why would you even need to innovate? Well,
3 you might want to innovate because you've got a very
4 restricted population size.

5 We had a meeting yesterday on rare diseases,
6 another public meeting which was just a terrific
7 meeting where people talked about ways that we can
8 facilitate and accelerate drug development in even
9 very, very rare diseases where patients are such a
10 scare commodity, or a scare resource.

11 You might need to innovate because you want to
12 try to improve the decision-making during a trial to
13 get an answer sooner or to quit the trial sooner if
14 things are not looking good, and do this in a
15 complicated way by predicting probabilities of success,
16 for example. You might want to innovate because you
17 want to optimize product development by getting
18 sponsors to put their data together.

19 But -- and this is consistent with what Roger
20 Lewis said in the first session, that the real reason
21 to innovate is to make sure you get the answer to the
22 question you're seeking. It's pretty -- it's not

1 desirable ever to finish a trial and not have an
2 answer.

3 And then why the need for FDA guidance? Well,
4 the idea of adding to the guidance is to better
5 understand if CDER and CBER, CBER being a sign-on to
6 our 2010 guidance, whether CDER or CBER accept
7 innovative designs, what innovative designs are
8 accepted, how do they base that acceptance to better
9 understand if you are running a complex design, how you
10 submit that design, if it involves simulations, how you
11 interact with the agency, what about the simulations
12 needs to be submitted to the agency. That's the topic
13 of session three.

14 And then finally, to try and ensure
15 consistency of the advice that's given by FDA and the
16 acceptance by FDA of complex trials across the
17 therapeutic area, something that FDA is sometimes
18 criticized for.

19 So I'll just take the three areas that I
20 mentioned as examples, the first being rare diseases.
21 And really this is more or less a recap of things that
22 happened at the public meeting or discussed at the

1 public meeting yesterday.

2 But in rare diseases, when I was at the
3 agency, even before I came to the agency, I worked in
4 rare diseases. There's an interest in several things
5 to accelerate drug development there.

6 One is the use of patient registries or
7 natural history studies, which may exist in rare
8 diseases simply because the disease is rare. It's
9 often easier to build a more comprehensive patient
10 registry. And those are rich data sources that can
11 inform a trial design and possibly even contribute data
12 to the trial when you can't recruit enough patients to
13 have a fully powered, randomized trial that you'd like
14 to have.

15 Also there might be interest in borrowing
16 information from earlier trials of the same drug or
17 trials of similar drugs in the same class or with
18 similar mechanisms of action. This could be, for
19 example, borrowing control data from an earlier phase
20 trial in the same drug to supplement the recruitment
21 that you're able to get in your later trial.

22 There may be information on disease prevention

1 from a natural history study that you could use to
2 improve your analytical model. I'll allude to an
3 example of that in a few slides.

4 There might -- as I've already mentioned,
5 might be prior information from earlier trials, maybe
6 not just the control arm, but maybe the treatment
7 effect itself. Is there information you could borrow
8 in a formal Bayesian way, for example, to help with the
9 power in a trial if you're not able to recruit enough
10 patients to give you adequate power.

11 And then finally are there ways to work with
12 the heterogeneity that's so inherent in many rare
13 diseases and look at endpoints that somehow maximize
14 the power in the presence of this disease
15 heterogeneity.

16 So, and I'll give an example where this was a
17 recent approval of Brineura in a very rare form of
18 Batten disease. This is the announcement of the
19 approval. It was a very rare disease. The sponsor was
20 able to run a single run trial. Much collaboration and
21 back-and-forth with the FDA statistical review team and
22 clinical reviewers about how to get the information

1 needed to go in the label.

2 And the label of the drug pictured here
3 actually has comparison of the primary endpoint, and
4 this is a time-to-event endpoint for probability of no
5 decline in motor function. And it's compared to an
6 external data source, a patient registry, which is
7 fairly unusual for the agency to take this as evidence
8 for approval, and then also describe the effectiveness
9 weight in the label.

10 So this is an example to show that we do have
11 -- okay, first of all, it's not we. I'm not here
12 anymore. This is just an example to show that FDA does
13 -- is accepting of innovation. This was an extremely
14 rare disease that came through Julie Beitz's Office of
15 Drug Evaluation.

16 All right. The second bucket, Bayesian
17 applications. Why would the agency ever want to go
18 Bayesian? Well, there have been a number of proposals
19 made to the agency or discussions within the agency,
20 things we're on record as accepting or at least
21 considering. A lot of applications in the area of
22 safety data, and this might seem natural because safety

1 data accumulate over the lifespan of the drug, and
2 updating the information about risk is something that
3 can be done fairly nicely with Bayesian methods.

4 One example I cite here is the interest in
5 using existing control patients for large
6 cardiovascular risk studies to just make more efficient
7 use of the high risk patients that are required in
8 those studies.

9 And another example of course in oncology,
10 early phase dose finding might use Bayesian methods,
11 Some continuous reassessment methods employ Bayesian
12 methods, as well as Bayesian adaptive trials that might
13 base an interim decision on an accelerated endpoint
14 such as tumor shrinkage or progression-free survival,
15 for example, or response, to basically see if that
16 treatment effect can predict the treatment effect on
17 the clinical endpoint, which is usually mortality. So
18 an adaptation might take place based on a Bayesian
19 calculation of the predicted probability of success on
20 the other endpoint.

21 And then I've already mentioned rare diseases.
22 There's many innovations in rare diseases that are

1 frequentist. There's also innovations that are
2 Bayesian. The example I just gave you was a
3 frequentist model-based analysis with external
4 controls. There've been other proposals to incorporate
5 prior information from early trials for rare diseases.
6 There might be a use for the information about disease
7 progression in the analytical model. I've already
8 mentioned both of those.

9 A third possibility is using shrinkage
10 estimators, some kind of empirical base estimator in a
11 rare subset, maybe a rare genotype of a disease, where
12 you would never be able to get enough patients in your
13 trial to estimate an effect in that subtype with just
14 those patients alone. So some type of borrowing is
15 usually needed.

16 And then, a very good example that was talked
17 about in the rare disease meeting yesterday, borrowing
18 data from adult trials to help you reduce the number of
19 children you need to study in your pediatric trials,
20 something the FDA has talked about publicly and has a
21 case study for that was presented last year in a
22 pediatric meeting.

1 And then, I have an example of a Bayesian
2 adaptive trial. This was a trial in septic shock. It
3 was a Phase II/III trial that had planned enrollment to
4 look at any of four doses, try to find the -- try to
5 optimize the dose to take into the Phase III trial,
6 then run the Phase III trial and the final analysis
7 incorporated data, all of the data, on the drug that
8 was under study.

9 And this was a fairly innovative design. It
10 included adaptive randomization. It included adaptive
11 interim decisions based on predicted probabilities of
12 success, and it also had the option to end the study
13 for futility as well.

14 And then the third bucket is the
15 collaboration. So collaborative efforts that would be
16 considered innovative, I group these under the rubric
17 of master protocol, but there are many types. The
18 general idea is that you study multiple diseases,
19 multiple patient subgroups that are biomarker-defined
20 and/or multiple therapies under one overarching
21 protocol.

22 We've actually heard from the audience about

1 I-SPY 2, which was really a screening trial to come up
2 with the best treatment in different genotypes of
3 adjuvant breast cancer. The Lung-MAP trial, another
4 example on the other end of the spectrum, this was
5 setup to give confirmatory evidence of drugs running in
6 parallel under the same protocol but firewalled against
7 each other and not compared to each other.

8 The DIAN-TU trial in a rare genetic subtype of
9 Alzheimer's disease, a very innovative, collaborative
10 trial with multiple sponsors contributing their drugs,
11 looking at this rare disease and use of shared control
12 patients among the sort of sub-trials in that, as well
13 as use of a natural history study to inform the
14 analytic model.

15 And then, finally, the ADAPT master protocol
16 for drug-resistant pathogens and the development of
17 antibacterials, which is hoping to get sponsors to
18 contribute drugs so that some efficient use of patients
19 can be made.

20 Basically or briefly in master protocols,
21 there's opportunities to innovate when you setup the
22 trial infrastructure. There's also opportunities to

1 innovate in developing a common protocol and there's
2 many advantages, including common screening platforms,
3 that identify biomarker profiles and then move patients
4 to the appropriate randomization arms.

5 The kinds of complex innovative designs that
6 we can see in these protocols might involve adaptive
7 randomization or adaptive enrichment. They may involve
8 use of external and historical control data, possibly
9 in conjunction with concurrent controls, so that both
10 control data sources are combined for the primary
11 comparisons, possibly sharing control group across
12 protocols or across sub-trials within a master protocol
13 if it makes sense for the biomarker categories being
14 studied and then possibly model-based analysis methods,
15 hierarchical-based models looking at subgroups, tumor
16 types and so forth.

17 And this is an article that Dr. Woodcock, the
18 CDER Center director and I, wrote on master protocols.
19 Raji Sridhara, on our panel, has worked with many
20 master protocols in oncology, and she and I both worked
21 on the Lung-MAP master protocol.

22 FDA has come out fairly openly endorsing the

1 use of these collaborative effort, seeing them as an
2 efficient way to use patient resources and also really
3 possibly the only way to go as precision medicine gets
4 more and more precise. It's just going to become
5 harder and harder, we believe, to run standalone
6 programs in some of these disease areas.

7 And then I haven't -- in addition to all the
8 examples I just mentioned, FDA worked very closely with
9 our colleagues in NIAID on an Ebola platform trial. It
10 went off with only one drug, but it was setup to have
11 multiple drugs if they were available.

12 There was a reason to go to master protocols,
13 a concern in dealing with this epidemic that the drugs
14 that were available would be in a very limited supply.
15 We needed to look frequently at the results, basically
16 looking after every pair of patients to see if we could
17 stop.

18 And the epidemic nicely went away before the
19 trial made it. Dionne Price, who's moderating today,
20 was one of the key authors and worked with Michael
21 Proschan and Lori Dodd at NIAID on the design. It is a
22 Bayesian adaptive trial, as I mentioned, with frequent

1 looks at the data. It used a non-informative prior, so
2 it's been called barely Bayesian.

3 And I will say interestingly, if you Google
4 this trial, it's called Prevail II. The trial ended
5 with a posterior -- it stopped early, I think 72
6 patients. There was a posterior probability that the
7 drug ZMapp was superior to the control. So it was the
8 ZMapp plus standard of care contribute -- being
9 superior to the standard of care.

10 The posterior probability I think was about
11 91.2. But if you look at the way the trial was
12 announced, in almost every public announcement the
13 result was given as not statistically significant, did
14 not reach statistical significance.

15 So this was a case where you pre-specified the
16 analysis in terms of a posterior probability. But
17 somehow the announcements always turned it back to
18 relative statistical significance, which I thought was
19 interesting. But anyway, it's an example of a complex
20 trial.

21 So those are examples. There's many other
22 ways to be complex. The topic for today is whether --

1 not whether, but given that FDA under PDUFA VI and the
2 21st Century Cures Act is accepting of innovating trial
3 designs, what types of these trial designs does the
4 panel think would facilitate the advancement of drug
5 development, particularly in areas of unmet need. I
6 cite two here, rare diseases, antimicrobial agents
7 where we're desperately trying to encourage more drugs
8 that are good to be developed.

9 And then second, what factors impact the
10 perceived acceptability of innovative designs. There's
11 a lot of "anecdotal evidence", quote, unquote, out
12 there about what FDA will or won't accept. And it's of
13 interest to us to hear how we can get a more consistent
14 message out -- not we again, FDA.

15 And third, are there other outreach or
16 research activities, areas for collaboration that might
17 further advance the use and acceptance of these
18 examples that I gave, but also other innovative
19 designs, with the common goal in mind that the idea is
20 to make drug development better.

21 So with that, we have two distinguished
22 panelists who will react. The first is Roger Lewis,

1 who's already introduced himself, and following Roger
2 is Frank Harrell.

3 DISCUSSION

4 DR. LEWIS: Thank you very much. I've decided
5 to organize my initial comments according to each of
6 the three questions, so the first question about what
7 type of innovative trial designs which facilitate
8 advancement.

9 In my mind, the key is the matching of the
10 design to this scenario, again addressing what the true
11 threats to success are in the development scenario or
12 domain. I think we need to address these threats and
13 focus again on getting the right answer to the
14 question, either to inform regulatory decision-making
15 or clinical adoption of the therapy being investigated.

16 So to drive this, I believe that we need two
17 thing. We need a catalog of options that are
18 relatively small Swiss Army knives that can be used in
19 scenarios that commonly come up, threats, unknown rates
20 of enrollment, endpoints, those sorts of things.

21 But we also need to have an explicit room for
22 creativity when the relatively better understood of the

1 complex designs actually don't address the real threats
2 to success or the program. And there need to be some
3 guardrails around that creativity, many of which were
4 already discussed. But I think they include the need
5 for rigorous pre-specification of the design, if we're
6 talking about a confirmatory space.

7 And the simulations that are used to evaluate
8 the performance of that pre-specified design need to be
9 realistic. They need to consider things like missing
10 data, time to information, potential bias, secular
11 trends, differences by sites and then also sensitivity
12 of the design to violations of various assumptions,
13 very similar to what Dr. Goodman pointed out.

14 I think we need to be explicit in the fact
15 that there are always tradeoffs that must be made in
16 design decisions and allow for weaker performance in
17 areas that are less important to drive the ultimate use
18 of the data and therefore not allow, for example,
19 concern over in some settings, inflammation of type one
20 error rate or concerns over bias and estimation trump
21 really important advantages that can be obtained
22 through adaptation that are more important in this

1 specific setting.

2 So we need to be transparent about where we're
3 making compromises in our designs, and what it is that
4 is driving those compromises in terms of improved
5 performance in other areas that are more important.

6 Secondly, believe it or not, this is the
7 second point, I think we need to allow the explicit
8 sharing of information among subgroups. The point was
9 made about a rare disease subtype where you may never
10 have enough information in that cell and you may want
11 to borrow information, for example, using a Bayesian
12 hierarchical model.

13 I think there are many more situations in
14 which we often think we have enough information,
15 whereas if you use a shrinkage-based estimate, which I
16 think is actually a better estimate, you find out that
17 that can qualitatively affect the decision you might be
18 able to draw.

19 And I think we need to further develop
20 experience, both from a design point of view and a
21 regulatory point of view with the interpretation of
22 estimates that are from hierarchical models.

1 And lastly for this question, I think the
2 point that Dr. Harrell made about endpoints is really
3 critically important. We need to show greater
4 flexibility in identifying endpoints that are both
5 informative and capture what's important to patients
6 and their families.

7 I think there is a tremendous inertia based on
8 approved regulatory endpoints that is really stifling
9 and that we need to consider both endpoints that can be
10 more rapidly informative and therefore help drive
11 efficient adaptive design, but also frankly drive final
12 decision-making. That was my noncontroversial comment.

13 For question two, and I may have been a little
14 sleep-deprived when I wrote down my thoughts here, what
15 factors impact the perceived acceptance of innovative
16 designs?

17 Well, my first two were precedent and rumor.
18 There, precedent I think is self-explanatory. The
19 number of comments I hear about what the FDA definitely
20 will not accept that has never been stated by anybody
21 who actually hasn't been employed or formerly employed
22 by the FDA, is just phenomenal. And I think it's

1 interesting for us to consider what are the actual
2 human factors or organizational pathology that drives
3 the incessant repeating of these rumors.

4 First, my next line I wrote the reliance on
5 data-free opinions of regulatory affairs specialists.
6 It is amazing to me how a team that is working
7 extremely hard to come up with a good design can be
8 shut down by a regulatory affairs consultant who simply
9 says, based on no information whatsoever, the FDA will
10 never accept that, and then the team says, okay, we're
11 done.

12 And if we could do something to corral those
13 people or hold them to some evidentiary standard, I
14 think that would be very useful. I will never be
15 employed by anybody who works in that area.

16 I think a real issue is the variability of
17 review groups within the agency and disincentives to be
18 flexible within the agency. It is my opinion that --
19 or my impression, I should say, that the statisticians
20 working at the front line within the agency are very
21 limited in the time that they have available to
22 understand complex designs.

1 And that leads to a risk, or a perceived risk,
2 in the sense that it's easier to resist a complex
3 design when you really haven't had the time to truly
4 understand it. And I think we need to find some way to
5 support regulatory professionals so they have a time to
6 do their job well when their job is necessarily more
7 complex than it might otherwise be.

8 I think another disincentive is a lack of
9 skill and experience of statistical personnel in
10 academia and industry and within the agency. I think
11 there is a need for a general effort to increase the
12 availability of software that allows one to simulate
13 slightly more complex designs so people start to
14 understand what affects the performance.

15 And I do think that within industry there is a
16 disincentive to be innovative. And this was explained
17 to me by a statistician who I will not name, who
18 basically said I don't really think this drug is likely
19 to be very good. So if I design an innovative design
20 that might actually give it a better chance of success
21 and it fails because the drug's a dud, my design will
22 be blamed and my job is at risk. But if I do exactly

1 the last three failed trials that we've done and the
2 drug fails, my job is secure. And so, I think we need
3 to understand some of the organizational incentives
4 that exist within industry.

5 For question three, are there additional
6 outreach or research activities that might further
7 advance the use of these designs, I just want to
8 endorse the point that these collaborative efforts,
9 often driven by patient advocacy groups to design
10 platform trials to focus on finding the most effective
11 treatment for a disease as opposed to exquisitely
12 pinning down the treatment effect of each individual
13 therapy, I think that's a key thing that we need to
14 emphasize and support.

15 And then finally, as I mentioned earlier, I
16 think that if we subjected our traditional designs to
17 the same level of scrutiny and simulation that we do
18 for complex designs, we would learn some things about
19 the limitations or lack of pre-specification of
20 traditional designs.

21 The one that jumps out at me is how often I
22 see a trial that uses an O'Brien-Fleming stopping rule

1 and there's nothing in the SAP that talks about overrun
2 or missing data or whether or not they've worried at
3 all about what the DSMB is going to do if they're just
4 close to the stopping boundary on either side, by the
5 way, or not. And if we require the same level of pre-
6 specification there, we would be setting a more equal
7 playing field for traditional and complex innovative
8 designs. Thank you.

9 DR. HARRELL: Well, those were phenomenal
10 comments. My comments are not nearly as interesting
11 and they're more focused on purely statistical things.

12 But I want to start with a hypothesis. The
13 hypothesis is that Bayesian decision-making using
14 skeptical priors will ultimately be shown to work
15 better than using historical data. And the Ebola trial
16 might be a case study in that, and I would like to see
17 somebody test that hypothesis.

18 So if you're going to be borrowing
19 information, there are a number of concerns. And I
20 tend to be more skeptical about historical data than
21 the average person is. And I'm especially skeptical
22 when control data only are borrowed and just want to

1 make a note in passing that anytime you're borrowing
2 historical data for a control, it has to be covariate-
3 adjusted. To get the average for the control from the
4 historical data is irrelevant. It has to be completely
5 covariate-adjusted.

6 So if you're going to borrow information,
7 there's various approaches to doing it, and I favor the
8 mixture of priors approach, which is called dynamic
9 borrowing. But I think that's a really bad name
10 because you're setting the amount of borrowing upfront
11 by the mixing proportion.

12 And this approach has a lot of advantages.
13 It's only dynamic in the sense that when you're done
14 with the study, you can get the posterior probability
15 that the underlying treatment efficacy is coming from
16 which source of the prior. So you can solve for that
17 after the fact. But otherwise, you're just setting how
18 much borrowing to do.

19 And there's advantages in the interpretation
20 because the amount of borrowing, or the mixing
21 proportion -- you're mixing say a skeptical prior that
22 you would make a study stand on its own with versus

1 historical data where it might be an optimistic result
2 from adults that you want to use partially for kids.

3 The mixing proportion is the probability of
4 applicability of the adult data. So you have a very
5 natural way to state that and interpret it. And you
6 can actually elicit that, not only as just a single
7 number, but you could get a whole distribution of
8 applicability from a variety of experts and factor that
9 in when you're calculating the posterior. So there are
10 a lot of issues in terms of borrowing.

11 I also want to mention that if you're
12 borrowing, there's no alternative to Bayes. We just
13 don't have the machinery in the frequentist world to
14 handle borrowing, and so Bayes really becomes
15 necessary.

16 I want to turn to another sort of complexity,
17 which is actually simple, but most people think it's
18 complex, which is fully sequential designs. That's
19 something that hasn't been mentioned yet. And we don't
20 ever see them done except in sequential response-
21 adaptive randomization, like the classic ECMO trial.
22 But I'm speaking of sequential non-adaptive trials.

1 So if you think about the last time you've
2 worked on a sample sized calculation, if you've ever
3 done a sample size calculation, you know it's not
4 science. You know it's voodoo much more than science,
5 and you know it's based on making up things.

6 And David Spiegelhalter has written about this
7 very eloquently, that when you're doing a power
8 calculation, if it uses unobservables, you're making a
9 lot of problems for yourself and you're usually coming
10 up with a very unrealistic power calculation.

11 So he and others show how to do Bayesian power
12 calculations that don't use any unobservables, and you
13 don't assume a point for the effect, but you assume a
14 whole prior distribution for the efficacy that you
15 don't know.

16 But once you get into the fully sequential
17 game, you can get past all of the voodoo and you can be
18 like a physicist. So physicists say we're going to
19 stop experimenting when we have the answer. And so,
20 with the Bayesian world, the final answer that you get
21 allows you to ignore all previous answers that you had
22 along the way.

1 So all the previous posterior probabilities
2 that calculated one person ago, three persons ago, four
3 months ago, they're all forgettable, and then you get
4 your final posterior distribution. So there's no way
5 nor means to factor in the stopping rule or the
6 schedule of looks in the data.

7 So this allows you to look after every patient
8 or look every week or every day, doesn't matter.
9 There's no type one error to inflate. There's nothing
10 that gets messed up with the posterior probability.

11 So if -- to me, if sponsors could get into
12 incremental budgeting, you could be doing incremental
13 trials all the time and not assuming that you have some
14 real notion of what the efficacy is that you don't want
15 to miss. So I see tremendous bang for the buck in
16 fully sequential studies.

17 The last comment I wanted to make is about the
18 simulation. I don't think the simulations, if you're
19 simulating type one error, can ever know all of the
20 things that you need to know to accurately estimate the
21 type one error. I think it's futile.

22 A recent blog by William Briggs discusses the

1 lady tasting tea experiment, the famous one by Fisher.
2 And he questions that you can actually calculate a P
3 value from the data only given what Fisher gives us
4 about the way the data were presented to the lady and
5 not knowing what the stopping rule was. You might not
6 even be able to calculate a P value at all.

7 And so the idea that you can know the
8 intentions of the investigators when you're writing the
9 code, as Roger talks about, the code needs to have
10 everything you know about. But you have to know the
11 intentions of the investigator. And the chance of your
12 knowing enough of that to write accurate code is very,
13 very low. And so, to me that's a futile exercise,
14 although you can get in the right ballpark. I will
15 grant you that.

16 If on the other hand, you're simulation's
17 giving you Bayesian power, such as the probability that
18 the credible interval will be somewhere or the
19 probability that the posterior probability will ever
20 exceed 0.95 for efficacy or 0.8 for harm or 0.9 for
21 similarity, those are the sort of things you can
22 simulate really easily without hidden assumptions.

1 And that really changes the way we think about
2 the problem because the probabilities that you're
3 simulating are prediction mode probabilities. Based on
4 what you know, we're trying to predict what we don't
5 know, whereas in the frequentist world, you're assuming
6 what you not only don't currently know, but you can
7 never know, which is that the null hypothesis is true
8 or the alternatives is true with a 20 percent effect
9 size. The Bayesians really wouldn't have much to do
10 with that way of thinking.

11 PANEL DISCUSSION

12 DR. PRICE: Thank you. So we will move to
13 question one. But we'll be somewhat adaptive again.
14 So if you would like to respond to question one or
15 respond to Doctors Lewis or Harrell, please let us
16 know.

17 And we have a suggestion to try a different
18 method. So we will try this for this session and see
19 how it goes. Instead of notifying Robyn and I, if you
20 could just place your tent up, we will call on you,
21 your tent card. So I see Dr. Emerson's tent card.

22 DR. EMERSON: So I appreciated the comments

1 from both the speakers. And the things that I would
2 just like to really applaud is Frank talking about the
3 true Bayesian measures rather than something that I
4 don't think has very good foundations, which is
5 predicting -- using Bayesian statistics to predict the
6 frequentist result.

7 You know, what I want to do is I want to get
8 the Bayesian inference from that. And then, to me, the
9 the strength of the Bayesian approach is -- and this
10 I'm going to go out on a limb and state, is that
11 whenever you're borrowing information from another data
12 set, it better be Bayesian.

13 I mean it's very important to incorporate your
14 uncertainty in all of this, and that does far better
15 than some of the measures that will just use a point
16 estimate and try to advertise -- average that in.

17 I will say that in the rare disease thing that
18 I am very nervous about, which is people hiding behind,
19 oh, this is a rare disease and we can't get enough
20 patients.

21 And I'll just note examples in the not too
22 distant past where one company presented a large

1 clinical trial in the exact same disease and couldn't
2 get approval. And another company followed with a much
3 small clinical trial later and was able to invoke it
4 was a rare disease, you know, 12 versus hundreds of
5 patients.

6 And so, there will always be the motivation to
7 say we have to go to this data. But I think the
8 comments that were made about needing to really pull in
9 all of the data, not selective data, is very important
10 to do that.

11 That the simulations that are done, which
12 those simulations again are not really in the Bayesian
13 probability space. They're really in a frequentist
14 probability space. But they're useful. You need to
15 know that as a very important aspect to do. And then,
16 I think the simulations that you do are fairly
17 comprehensive and are far more comprehensive than a lot
18 of the frequentist approach.

19 Roger's comment about if you look at a fixed
20 sample design that's often done by assuming
21 proportional hazards, no time varying treatment effect
22 and things like that, it's not very robust. You've got

1 to model something that's outside that range. And I --
2 from what I've seen of the simulations you do, you're
3 far better at incorporating lots of different
4 probability models than we tend to do with a standard
5 frequentist design.

6 DR. PRICE: Dr. Goodman?

7 DR. GOODMAN: A few things. First, you know,
8 I think it's definitely an advance that, you know, we
9 get the acceptance of -- particularly in real rare
10 diseases, of information from other sources that we
11 might not otherwise have used in the past.

12 On the other hand, we have to keep our eye on
13 the ball, which is we want to get to the truth. And
14 the people at the FDA know better than anybody how
15 enrollment in a clinical trial should be actually an
16 approved therapy because it cures so many people.

17 And it's very, very possible in that one, in
18 Batten disease, that if you actually could get kids --
19 if that was kids or adults, I actually don't know
20 Batten disease -- enrolled in the trial, you would not
21 see the same fate as you saw in the historical control
22 group, and you know that. But if you can't get them,

1 you can't get them, and you don't want to never approve
2 drugs.

3 But I think the kinds of activities that could
4 done to buttress these sorts of approved designs is one
5 of two things. First of all, to do maybe as exhaustive
6 meta-research as you can, looking at the fate of
7 control groups or registry prognosis versus the
8 prognosis in control groups of clinical trials. So
9 just see a priori how different that often is and how
10 reliable this can be.

11 Of course, you always end up arguing it in
12 each particular case. But it's very useful to have
13 that on a systematic basis. But perhaps as valuable,
14 and certainly this is gotten a lot of attention in the
15 safety realm where there's been a lot of, you know, ink
16 spilled on lifecycle approaches where you're looking at
17 safety as it comes in over the lifecycle of the drug,
18 even after approval.

19 In this case, you're actually not sure about
20 efficacy, not just safety. That's what's more unusual.
21 And if there's any way to continually monitor the
22 landscape and look at the natural history -- the,

1 quote, unquote, "natural history" of the disease on or
2 off the drug and see how that has evolved, it would
3 inform you both about that drug, but also inform you
4 about the future, about using these sorts of control
5 groups because while it's great that the FDA's
6 approving these sorts of designs in areas of special
7 need, it doesn't necessarily -- you don't know
8 actually.

9 They don't escape the laws that we've learned
10 for other diseases. That is, these decisions could be
11 wrong, which is not to say they didn't use the right
12 approach. But they could be wrong, and they could be
13 wrong at an unacceptable frequency.

14 So the more we can learn prospectively about -
15 - with the experience about the accuracy of these
16 judgments, the better. I had something else, but I
17 actually forgot it right now. I'll come back to you if
18 I remember it.

19 DR. PRICE: Dr. Chan?

20 DR. CHAN: I just have a couple comments to
21 add too. There's lots of discussion already in terms
22 of the types of innovative trial design that we really

1 need.

2 One is obviously we talked a lot about the
3 rare disease area in terms of borrowing data from
4 whether it's registry of other types of study. But I
5 think the same mechanism would also apply when we are
6 studying a new -- maybe studying a new patient
7 population or a new compound where we might have Phase
8 I data. And when we are going into Phase II, looking
9 at the proof of concept, how can we incorporate the
10 prior trial's data into the decision-making at all.

11 I know in a lot of companies are already
12 trying to do those kind of incorporating the data into
13 the decision-making. So the framework with the
14 historical borrowing definitely is something that is
15 really worth a try.

16 Actually, I'd like to see more maybe in the
17 confirmatory arena, how the historical data borrowing
18 can be done because that involves a lot about how do
19 you weight the control data versus the concurrent data.
20 And we talked a little bit about the master protocol
21 example when you have several new treatments being
22 introduced into the trial, but maybe over time, over a

1 length of a year or two, and how do you consider those
2 kind of control data when you -- in the first period of
3 the trial versus the last period of the trial. And
4 some of those are a more complicated issue. I think
5 those are the things we need to spend a bit more time.

6 The other part is the biomarker. I know here
7 in the drug maybe really more specific. We talk about
8 precision medicines, but using the biomarker guide in
9 treatment trial designs, I think those would also
10 involved a lot of adaptation potentially and could
11 potentially change the estimate during the course of
12 the trial. So that would require more the complex
13 simulation to help us to understand what's the
14 implication, difference scenario primarily.

15 So those are the two types I can think of that
16 would be really critical to study a little bit more of
17 the potential. Thank you.

18 DR. PRICE: We'll go back to Dr. Goodman, who
19 remembered his third point.

20 DR. GOODMAN: Yeah.

21 DR. PRICE: And I'll just remind everyone when
22 speaking, please lean into the mic so our audience can

1 hear us all. Thank you.

2 DR. GOODMAN: Yeah. So we all lean in.

3 Everybody leans in. Okay.

4 So this is actually just to amplify a point
5 made by Roger, which is the importance of communicating
6 priorities that are appreciated by the leaders to all
7 the different review groups.

8 I'll just give a little anecdote of my own
9 experience. Now, this is a long time ago, and I
10 recognize it's a complex organization. But there was a
11 company that was developing a diagnostic device. They
12 proposed that -- they were in oncology products and
13 they were told their trial was unacceptable. And they
14 were literally told to consult with me. I don't know
15 why. So they did.

16 We redesigned it, and all the comments were
17 right. They were very insightful. They were right.
18 We redesigned the trial. It was shifted over to
19 another group not within oncology, and not only -- and
20 in the second group, we were told that the new design,
21 which was exactly with the prior group had been -- told
22 us to use, was unacceptable.

1 They used new ideas that they weren't ready
2 for, like predictive value. The review groups had
3 never used predictive value before, and they wanted to
4 see it in terms of sensitivity and specificity. I'll
5 just leave it there. And ultimately, the trial that
6 FDA itself had internally recommended was turned down.

7 So these can occur among the leadership. But
8 I think the organizational challenge is how you get --
9 and I think Roger said this, how you get this
10 understood by review groups who are the affected
11 decision-makers.

12 And we're talking about levels of
13 sophistication here, one, two, maybe three levels above
14 where they might have been operating, you know, above
15 their comfort level. And I think this is no small task
16 for a organization as complex as this. So that's a
17 task for the agency.

18 You know, whatever's decided here, you know,
19 that has to penetrate down, or if it's outside of their
20 comfort level, there has to be procedures internally,
21 and maybe you've developed these. I don't know, where
22 it's kicked up to a level where it is within the

1 comfort zone. So they don't feel that, you know,
2 certain kinds of designs are necessarily within their
3 purview.

4 That's an organizational challenge for you.
5 But I worry that at the top levels, there's tremendous
6 amount of -- you know, can be a lot of sense,
7 flexibility and wisdom. But this may or may not
8 penetrate to the levels where the decisions are being
9 made.

10 DR. PRICE: Dr. Lee?

11 DR. LEE: Yes, thank you. I have three points
12 to make. First, regarding what type of innovative
13 trial design will facilitate the advancement of drug
14 development, Dr. LeVange already mentioned like
15 platform design and the master protocol, et cetera. I
16 think really we need to do more of this type of a
17 design in the sense that there are basically two
18 components in terms of what we can make of that
19 advancement, okay?

20 And the adaptive design is all about learning
21 and confirmation. So there's two steps. You know, we
22 kind of iterate between the two, and for example like

1 platform design or the master protocol, this type of
2 design can be very efficient in providing initial
3 screening of the -- you know, the efficacy and toxicity
4 of the agent, right, or the drug.

5 So if we do more of this kind of platform
6 design and it can be a continual process rather than a
7 one trial, one drug and one population at a time, and
8 it can usually increase the efficiency.

9 But this, the learning platform, and with that
10 information, then we can move into a confirmatory
11 platform by designing more specific kind of a smaller
12 trial to further test the finding.

13 So what I view is that we need to do better in
14 terms of learning and confirmation, and learning and
15 confirmation, and, you know, that if we can provide the
16 framework of that, you know, from the FDA's
17 perspective, it would really help to move the field
18 forward.

19 The second comment is regarding again the
20 inferential framework. And I would want to emphasize
21 again that the traditional framework of the null
22 hypothesis significant testing and the P value-based

1 approach is very limited.

2 You know, we assume the fixed effect of a
3 certain treatment effect either under the null
4 hypothesis or under the tested hypothesis, and try to
5 control type one/type two error rate, et cetera.

6 You know, we need to move beyond that, and
7 really thinking about the distribution of treatment
8 effect and not just the efficacy, but toxicity, et
9 cetera, okay?

10 So I think that again much has been said
11 about, you know, the different approaches, like -- but
12 I think the right inferential framework is still very
13 important. And we need to really go beyond our comfort
14 zone in terms of more fixed kind of a traditional
15 approach.

16 So that leads to my third point is that also
17 has been mentioned, like Roger mentioned about we need
18 to have increase in availability of the software tools.
19 So at MD Anderson, that's one of our goal, is not just
20 to really derive new methods, but also provide tools,
21 you know, to learn and to implement those.

22 So we have two kinds of tools under

1 development. One is the downloadable software. You
2 know, you can download to your own PC, and then run the
3 simulation.

4 But recently, that we developed application
5 using the shining tool, which is all you require is the
6 browser, okay? So we have two kinds of tool. You can
7 just Google MD Anderson software, download our software
8 online, and then, you know, you can kind of -- these
9 are all freely available.

10 And I know that we have our colleagues in --
11 you know, in different areas they develop tool, you
12 know, like in academia or in industry setting. And I
13 think these are all good. You know, once we -- once we
14 put the tool in place and then people can just use it,
15 and learn from it.

16 I have met some, quote, unquote, "thought
17 leaders", and all these are the expert in the field.
18 They have very strong opinion but based on very little
19 data or based on very little kind of knowledge.

20 You know, I really -- it's a humbling
21 experience to me, okay? So then when we start to
22 learning about this new method, that they design the

1 novel design, okay?

2 I would like to consider myself as a student
3 of this rather than expert of this, okay? Again, you
4 know, I think you all need to admit that whatever we
5 do, whatever we know, you know, that there are probably
6 more than what we know, what we understand.

7 And again, you know, if you had the tool
8 available to people and then we can learn from it. And
9 we can kind of debate about what assumption to use and
10 what kind of result we'll get. I think we'll do
11 better.

12 DR. PRICE: Thank you. Dr. Berry?

13 DR. BERRY: So I really like the comment of
14 Peter that he's a student of this.

15 I think to answer this question, all of them,
16 and innovations that aren't here, the really wonderful
17 place about where we are is I think after perhaps 70
18 years of using agricultural experiments in medical
19 trials, and we haven't innovated the clinical trial,
20 but yet we have phenomenal drugs. We have phenomenal
21 understanding of disease. We have personalized
22 medicine, that we are now getting into wearables. The

1 complexity of what's coming in the next 25 years are
2 going to meet designs we don't know about yet.

3 We may see master protocols the major way in
4 which this is done. It may be incredibly complex to
5 better answer the questions. And I think we are all
6 students in this emerging clinical trial science.

7 So to limit these innovative trial designs, I
8 don't think anybody here wants to do that. And every
9 one of them that LISA put out I thought was an
10 incredibly nice solution for the difficult thing that
11 they were in.

12 And the hard part is I think exactly Dr.
13 Goodman's point, is you are the arbiters of that in
14 some level, and to be able to spread that within the
15 FDA to arbitrate what is appropriate and is it
16 appropriate to answer those questions is a really tough
17 place. And the FDA is moving incredibly in that, and
18 that will be one of the challenges to meet that.

19 So this innovative trial design, to put
20 shackles on it in any way, or to, as Roger likes to
21 say, to fight the battles of previous that we've seen
22 failures, when the world is changing so much in terms

1 of the innovation, the science, the medical that we've
2 got to innovate the clinical trial moving it forward.

3 DR. PRICE: Dr. Sridhara?

4 DR. SRIDHARA: So I think, you know, Scott
5 brought this up very nicely, that we have to keep in
6 mind that no one clinical trial design fits every type
7 of hypothesis that we are going to test.

8 So I don't think we want to corner into any
9 one particular design. But there are some aspects that
10 I think we can keep, you know, think about when we're
11 doing any of these.

12 One is to have a good knowledge of natural
13 history of the disease. If we can work towards knowing
14 that better, understanding the disease itself is good.
15 The second thing is we have to have measurable outcomes
16 in reasonable time. And what are these measures and
17 what would make a useful inference and that would
18 actually benefit the patients.

19 If we can keep that in mind, a measurable
20 outcome that will directly influence how the patient
21 can feel or function is very important.

22 Then, you know, if we are talking about

1 precision medicine, then another thing -- another key
2 thing to keep in mind is diagnostic assays that are
3 being used and are they standardized. Often we see one
4 that's used in the lab of the investigator and then
5 another one coming from a manufacturer who may be
6 manufacturing this, et cetera.

7 So I think standardizing some of these or some
8 of the antibodies that are used, et cetera, is very key
9 thing in some of these as well. So there are other
10 external things that we need to think about before we
11 get into this.

12 I also appreciate that, you know, this complex
13 versus adaptive designs because you can think of very
14 complex designs in, for example, hematological
15 malignancies where you have induction followed by
16 consolidation and then maintenance. And you could be
17 introducing new treatment in any of these three, and
18 how do you put this all together.

19 So this kind of a dynamic treatment strategy,
20 and how can we test these? And those are very
21 important questions too. And I think we have not
22 addressed any of that type of complex or adaptive

1 designs.

2 They are adaptive in the sense that those who
3 get induction, not necessarily all of them go into
4 consolidation. It depends on that they do to respond
5 to the therapy or go to maintenance.

6 So it is by practice of medicine and taking
7 care of the patients, you've got to do this. And I
8 don't think we have touched on some of these complex
9 type of clinical trial designs.

10 DR. PRICE: Dr. Bretz?

11 DR. BRETZ: Yes. When I see the term
12 innovative trial designs, I wonder whether this is
13 confined to the discussions we had so far or whether we
14 can even broaden it.

15 And maybe it's not the time today to talk
16 about digital data and real-world data. But I think
17 there's a huge field that we as a community, as a
18 society are moving towards into digital drug
19 development age, and especially the use of data
20 science, technologies, methodologies, whatever they
21 are. But they go well beyond statistics.

22 And I think that will also raise some

1 important questions about trial designs and many
2 innovative concepts. I'm not sure again whether we're
3 going to discuss these today. But obviously these
4 amount of technologies may bring, or so that's what
5 they're claiming, bring the trial to the patients,
6 which obviously have many consequences.

7 We have novel endpoints which can be assessed
8 based on available designs or sensors, huge volumes of
9 data. And the endpoints could be very different, maybe
10 imaging being analyzed by algorithms rather than by
11 human readers.

12 I think that all also has implications on
13 trial design aspects, which go well beyond the
14 discussions that we're having here. So at least I
15 thought I'd mention this, that we don't forget about
16 this type of innovative trial designs.

17 DR. PRICE: So just looking at the time, this
18 is a very good discussion, so we're going to continue.
19 But at any point, if you want to answer any of the
20 other questions, feel free. So we are going to move to
21 Dr. Zhong.

22 DR. ZHONG: I completely agree with Dr.

1 Sridhara's comment there. I think that's the kind of
2 trial that we should target immediately and especially
3 like Roger pointed out early on.

4 I mean, in the area of like not so well-
5 understood trials, just, I mean, this something we have
6 to target now immediately. It's kind of bring up the
7 public learning and awareness of the FDA's openness to
8 innovation and kind of correct the incorrect perception
9 in the industry or the consultants there.

10 At the same time, I think that I agree with
11 the last two comments, where we should -- from Scott
12 and Frank.

13 We should keep our options open, right? I
14 mean, the technology changes so quickly in this space.
15 Maybe in like a wearable device, a digital or even big
16 data. And even the statistical methodology also
17 evolves. And we all are students to the new
18 development of the technology and statistics.

19 So I completely agree with -- even though we
20 have some structural needs that we need to start the
21 problem with, but we also have to keep our mind open on
22 different type of innovative scientific evolve.

1 All right. So now, I would like to talk about
2 like the brief point that I made about rare disease. O
3 mean, I'm on the bio and also pharma working groups,
4 and sometimes, I mean, people kind of think that we all
5 stick to like a rare disease.

6 But think about in sometimes, I mean, there's
7 some disease that not rare, right? For example,
8 Alzheimer's disease and cardiovascular disease. But
9 there's some phenotype or subtype of the disease within
10 those kind of common disease that I think -- I mean, as
11 a concept, I think we have to think about this is a
12 small population, as LISA correctly pointed out early
13 on. It's a small population. So I think we should be
14 aware of that.

15 And then, in terms of platform trial design,
16 there's also like at the development in the industry
17 and also in the technology as well. In this space, I
18 mean, there a lot of collaboration across the industry
19 within different companies. And one company could own
20 multiple entities.

21 For example, for the treatment of Alzheimer's
22 disease, and I mean one company could own different

1 entities or markers.

2 And then, we talk about the platform trial
3 designs or master protocols. On the surface, it looks
4 like maybe from one company, but in fact, I mean, that
5 one company may be working on multiple different
6 companies, on multiple different entities or markers
7 there.

8 So please, one thing to think about is, again,
9 the world kind of changes, not for sometimes things
10 like one company but it could be multiple company
11 collaboration within one company or multiple companies.

12 DR. PRICE: Dr. LeVange?

13 DR. LEVANGE: Yeah. I just wanted to respond.
14 These are really fabulous comments. And just to make
15 sure, in case -- I thought I made it clear, but if I
16 didn't, so that the examples I gave were things FDA has
17 already reacted to.

18 And they were not meant to be only the things
19 that we're discussing here. They were just examples.
20 The intent of the complex innovative design project
21 under PDUFA VI and the 21st Century Cures is to look at
22 other complex designs. What is the future?

1 So that might include, as Frank said, real-
2 world evidence, not something we were particularly
3 focusing on today. There's another PDUFA VI
4 commitment. Aloka's involved in with that on real-
5 world evidence. But it certainly comes in, the types
6 of data sources you can come in, the wearable devices,
7 the types of designs that Raji's talking about.

8 All of these are -- you know, this is really
9 wide open. And you'll hear about this similar this
10 afternoon. The purpose of the pilot is to get sponsors
11 to innovate basically.

12 The FDA is tied with what they can talk about.
13 We can't talk about designs, we -- the FDA cannot talk
14 about designs they are reviewing. They're
15 confidential.

16 So until the drug is approved, which can be
17 years later, you're not going to know that FDA accepted
18 that design, or FDA can talk about designs that are
19 presented at an advisory committee, but that's pretty
20 much it.

21 So the whole purpose of this pilot is to open
22 the door for sponsors to bring in more innovative

1 designs well beyond, you know, the examples I used,
2 which are now, you know, a few years old and are
3 getting stale.

4 And then the last thing, just in case anybody
5 is holding back and wants to talk about this, the
6 simulation part isn't meant to be limited to Bayesians.
7 There have been a couple comments. Yes, Bayes designs
8 require simulations if you want to -- well, they always
9 require simulations. And then, they may require
10 simulations for frequentist characteristics if that's
11 what people think is important. But some people don't.
12 Looking at Frank, there.

13 But there are other complex adaptive designs
14 that have nothing to do with Bayes that still require
15 simulations. And there had been up until the time we
16 were doing the PDUFA VI negotiation some concern that
17 FDA was not accepting, at least in some therapeutic
18 areas, an adaptive design that required a simulation
19 because it's very easy to make a simulation space where
20 there's a point that you exceed alpha 0.05. And so,
21 it's very easy to ding simulation or that particular
22 design.

1 So the simulation aspect, which we'll talk
2 about after lunch, isn't tied to Bayesian. That's a
3 complex adaptation maybe on two or three factors, and
4 how does FDA view those, and how do sponsors get those
5 in the door.

6 That's a possibility for a pilot that you'll
7 talk about also this afternoon. Bayesian trials are a
8 possibility. Other real-world evidence, all of these
9 things are open. I just didn't want you to think that
10 you only could react to the three little examples I
11 gave, so --

12 DR. PRICE: Dr. Marchenko?

13 DR. MARCHENKO: Thank you. I don't want to
14 repeat what everybody said already. I think a lot of
15 good designs were mentioned.

16 But going kind of back to what Frank said,
17 it's not just about real-world data, where we see big
18 data. As sponsors, we collect a wealth of data, and
19 not to use these data, I think it's not right.

20 So where I see probably advancement of drug
21 development with regard to designs would be, yeah,
22 Bayesian designs or hybrid designs which can

1 incorporate the totality of the data and give us a
2 better decision based on the whole data because where I
3 see right now, we look at the whole problem data only
4 when we do the submission and the issue change.

5 Then I just wanted to note with regard to
6 master protocols, I don't think the hesitation of
7 sponsors are necessary in complexity of designs. I
8 think the hesitation of sponsors in the lack of full
9 understanding of the design and what is happening
10 behind the scenes, specifically maybe how fast the data
11 can be available.

12 What are the decision criteria which affect
13 their specific drug, because we do need to remember
14 that their drug, which they give to these master
15 protocol, is a part of some kind of development
16 program. So we do need to make sure the benefit, even
17 for sponsors, is greater than the loss when they
18 contribute to those master protocols.

19 But there are no questions. Master protocol
20 is a great idea and platform for us to try to cure
21 diseases.

22 And with regard to the next question, maybe

1 I'm just too blind, but I think that the lack of final
2 or revised draft guidance on adaptive designs bring a
3 lot of speculations about what FDA actually accept or
4 doesn't accept and how less well-understood designs are
5 understood by the public.

6 And with regard to the third one very quickly,
7 I think we discussed again specific master protocols,
8 designs which definitely helpful. But then, there are
9 others opportunities for us to collaborate through
10 different scientific working groups which are available
11 under different societies, so we can put together.

12 DR. PRICE: So, thank you. I'm looking at the
13 time and want to allow a couple minutes for the
14 audience. So we'll take Dr. Lieberman and Dr. Beitz,
15 and then, I'll do a time check to see if we need to
16 move to the audience.

17 DR. LIEBERMAN: Okay. Thank you. So just --
18 I don't want to repeat, but just again sort of data
19 source -- different data sources incorporating in
20 clinical trials. So the real-world data, I think it's
21 almost like -- it leads to the topic of can we start
22 looking at endpoints and how endpoints in clinical

1 trials could actually -- or the real-world endpoints be
2 reflected in what we collect in clinical trials?

3 The other one is actually the sharing of the
4 clinical data for the control arms. And I know there's
5 a lot of initiatives of that. So master protocols are
6 not always available. So if there's a way of really
7 thinking what are the right methodologies to really
8 incorporate the control arms from the other studies
9 that were just completed or very recently, so really
10 there's focus on data sharing.

11 And as I just talk about the next points, I
12 think, you know, some of the perceived just operational
13 complexities of these trials might be a roadblock on
14 both sides. And then with master protocols, or even
15 the more complex decisions that have to happen, and you
16 have a DNC and data coordinating center, it's like the
17 industry. I'm not in charge of a lot of these complex
18 decisions, so that could be another perceived.

19 DR. BEITZ: So I was intrigued by the comment
20 that Dr. Lewis made calling for a catalog of options
21 that can be used in scenarios that commonly come up
22 while leaving room for creativity and flexibility.

1 And I was wondering if any of the panel
2 members had some ideas about how we all could move from
3 individual case examples to something more along the
4 lines of a catalog of options.

5 DR. PRICE: Before we moved to the audience,
6 does anyone have a response to Dr. Beitz? Dr. Lewis
7 and Dr. Goodman, and then we'll go to the audience.

8 DR. LEWIS: So this is a very partial answer
9 to the question. I think it's tied to the development
10 of software. So software packages have some defined
11 options, and so the space of options within software
12 packages essentially creates a de facto catalog.

13 And if the software has the capability to
14 simulate the performance of its options under a variety
15 of assumptions and violations of assumptions, it
16 creates a natural synergy where you both have defined
17 reproducible options, and a mechanism for evaluating
18 the performance of those options, so I think that's a
19 partial answer.

20 DR. GOODMAN: Well, maybe I'll give another
21 partial answer. I think so much of this depends -- and
22 this is going to be repackaging the prior comment -- on

1 knowledge, or what you think you know about the
2 reliability of your data sources and what you think you
3 know about the natural history of disease.

4 And the natural history of disease is often
5 quite different than the natural history of disease
6 detected through all these different means, whether
7 it's through sensors, whether it's through medical
8 records, the prognosis, the course of that disease is
9 often quite different than what we measure, either in
10 clinical trials or in other settings, and it's
11 constantly changing.

12 I remember the ECMO examples. It's a famous
13 one I remember in the way back when, going to back-to-
14 back conferences, one where it was discussed by
15 statisticians, and literally the next week I went to a
16 pediatric conference.

17 The statisticians were all discussing the
18 nuances of the trial design, given a background
19 mortality of 80 percent. The pediatricians weren't
20 talking about that at all. They were talking about
21 whether it was optimal therapy, and the fact that 80
22 percent wasn't close to what they were observing. They

1 were somewhere like 30 percent mortality rate. And
2 that would change all the calculations.

3 So I think that the challenge of new data and
4 new data sources is that we don't a hundred percent
5 know what it is the disease that we are detecting
6 anymore. Measuring blood pressure once a month, which
7 might be a given risk factor with well-defined
8 characteristics, is very different than measuring it,
9 you know, 50 times a day. That's not the same risk
10 factor.

11 So the kind of research that would make a lot
12 of this, these innovative designs more possible is
13 continuously either meta-research or the research into
14 the validity of these measures and also the natural
15 history of the diseases or risk factors as measured in
16 these different ways because it's not the same.

17 The more secure we become in that knowledge,
18 the more secure we can build the foundation of these
19 designs, which often assume a lot more knowledge than
20 we sometimes have with them -- than we need to have
21 when we design the clinical trials with the concurrent
22 control group.

1 And one thing on the sharing of data, which is
2 somewhat related, is it's very different if you're
3 sharing data were you already know what the result is
4 in the control group versus prospective sharing.

5 So if we're using control groups from --
6 historical control groups or control groups from other
7 trials where we already know what the answer is, then
8 the decision to share by itself is going to be
9 contingent often on whether the fate of that group was
10 good or bad. And we can't assume that that's a stable
11 property.

12 So sharing prospectively is profoundly
13 different than sharing in groups that have already been
14 observed. And you can be sure that that sharing
15 decision will be partly based on what will make the
16 therapy look good.

17 AUDIENCE Q&A

18 DR. PRICE: Let's move to the audience. We
19 have time for maybe three or four comments or questions
20 per person -- one per person, please. And if you want
21 to begin in the back?

22 QUESTION: Thank you. My name is Cathy

1 Collet. I'm an ALS advocate. I can't tell you how
2 happy I was to see these presentations, especially in
3 this last session. I think they can be extremely
4 helpful for an extremely challenging disease.

5 My question, it's a very practical one though.
6 I see this wonderful embracing of innovation. About a
7 month ago, we got ALS draft guidance from the FDA that
8 really did not embrace innovation.

9 What are drug developers going to do? What
10 are sponsors going to do when they have actually
11 conflicting guidance? And my fear is that the guidance
12 that embraces the innovation that could really help
13 won't be taken up because there might be some that is
14 actually dampening that.

15 DR. LAVANGE: So, right. So we are hoping
16 that the pilot program will be embraced. This is
17 really a case where I think the pilot program could be
18 embraced. And we'll talk about that this afternoon.

19 But the idea with a complex innovative design
20 pilot is that sponsors that have an innovative design
21 will be able to get additional interaction with the
22 FDA. And in exchange we, hope to be able to talk a

1 little bit more publicly about the design.

2 I'm looking at the lawyer who's going to be on
3 the panel this afternoon to walk us through this. But
4 that was in fact the intent of the pilot, is to be able
5 to approach the FDA with a design that's not standard,
6 that may be something they haven't seen yet and get
7 reaction.

8 But the other -- you're coming from a patient
9 advocacy group, I believe. And so, the other avenue is
10 that patient advocacy groups have worked through the
11 CPIM, the Critical Path Institute. Dr. Chakravarty
12 could talk a little bit more about that, and I'm sure
13 you're aware of it.

14 But some of these patient advocacy meetings
15 are exactly what spawns the idea of the collaborative
16 efforts and master protocol efforts. And one of the
17 advantages of those efforts is that the group
18 organizing the master protocol can oftentimes get
19 regulatory interaction and discussion at a very broad
20 level, even before you know exactly which molecules may
21 be coming in the door.

22 You can get feedback about the collaboration

1 itself, the design, whatever innovations might be
2 there. That's in fact one of the advantages of those
3 coordinated efforts. So maybe either one of those
4 might help, and I'm sure Dionne, Aloka and others could
5 talk to you more at the break.

6 DR. PRICE: And I think Dr. Emerson wanted to
7 respond as well.

8 DR. EMERSON: Yeah. Just a real quick
9 comment. We talk a lot about innovation, and really
10 what we want is we want proven -- innovations that are
11 proven effective. And you know, we are experimenting a
12 lot in clinical trials. And it's not true that we're
13 any better at thinking up something than the medical
14 community is.

15 A lot -- most treatments don't work, and so a
16 lot of those things that we might think work may not.
17 And so, I think we do need to pay attention to that.
18 And we do need to start making certain before we go too
19 far on some of these things that then won't pan out.
20 We don't want to degrade the performance of our
21 approved drugs.

22 DR. LAVANGE: Well, and that's a great -- I

1 meant to say this earlier. Thank you, Scott. That's a
2 great lead-in.

3 So what's innovative today is not innovative
4 tomorrow. What's innovative at the FDA may not be
5 innovative in academia or industry. It's beauty's in
6 the eye of the beholder.

7 Sometimes what all we need -- sometimes all is
8 meant by innovation, when I think about it, are just
9 things that you don't have a precedent for the FDA
10 having accepted it, that that could be the definition
11 of innovation in some eyes, to the regulatory affairs
12 people that Roger referred to.

13 If the FDA hasn't been on record as accepting
14 of this design, which in fact they may have, you just
15 don't know it because the protocol's still running,
16 then it's innovative because there -- and there's no
17 guidance on it.

18 I mean, that's the problem, is what does
19 innovative mean here, and we're not necessarily talking
20 about the latest cutting-edge design. We could be
21 talking about something that's not innovative at all in
22 the eyes of academia, but may be considered

1 regulatorily innovative because there's no track record
2 inside the agency.

3 And just to reassure Scott, nobody's talking
4 about lowering standards here. We only want good
5 drugs.

6 DR. EMERSON: But in medicine --

7 DR. LAVANGE: We only want good drugs.

8 DR. EMERSON: -- certainly there's been plenty
9 of innovations that everybody believed that were proven
10 wrong, and I don't think we're any better in
11 statistics.

12 DR. SRIDHARA: So I just want to say that, you
13 know, for the person who brought up this issue, we hear
14 you. And we heard from the rest of the panel here as
15 well that there are differences in the way we give
16 advice between divisions, et cetera, and we will strive
17 hard to make it as uniform as possible. So we hear
18 you, and we will work on it. Thank you.

19 DR. PRICE: And there are mechanisms, as Dr.
20 LeVange mentioned, to still bring in innovative design.
21 So for time's sake, we'll go to the second mic now.

22 QUESTION: Good morning. My name's Mat Davis

1 from Teva Pharmaceuticals. I want to respond to the
2 very first comment that talked about the barrier that
3 we have to overcome as sponsors to get over the barrier
4 of precedence and rumor that we discussed. And I think
5 that legislation such as PDUFA VI and the 21st Century
6 Cares Act, as well as situations like this help us to
7 overcome that quite a bit on the sponsor side.

8 I think the second thing that we need to
9 overcome is the barrier of the amount of time that
10 these type of innovative statistical designs take. And
11 I think we're overcoming that with the advent of new
12 statistical methodology, new software available to us.
13 So I think we're making a lot of progress.

14 The third barrier I'd like to bring up that I
15 don't know has been discussed today is the barrier that
16 we face sometimes in trying to make sure that once we
17 do get one of these innovative clinical trial designs
18 agreed to with the FDA, that that agreement will hold
19 throughout the lifecycle of that specific design.

20 Some of these designs can take years to
21 accomplish, and you can see that sometimes we'll have
22 statistical reviewers change. We'll have clinical

1 reviewers change, and then some of the opinions on the
2 appropriate -- and of that type of trial design may
3 change by the time we embark on the trial to the time
4 that the design end.

5 So I would be interested, if not comment now,
6 but to think about later, what types of potentially new
7 avenues we could have to ensure that once we agree on a
8 trial design at the outset, by the time the trial
9 finishes it will still be as appropriate as it was when
10 we designed it in the first place. Thank you.

11 DR. PRICE: That is great feedback which we
12 will take into our thought process. And we do strive
13 for consistency. And science does evolve, but you're
14 right. We do need to think about if you come in with a
15 design over -- it does take time, and over time, the
16 considerations that that design started prior to maybe
17 changes in the science.

18 And hopefully with the pilot program again, I
19 hate to sound like a broken record, but we will have
20 discussions throughout the process. And I'll move to
21 the third mic and then the second, and we will then
22 break for lunch.

1 QUESTION: Hello. My name is Mei Chin (ph)
2 and I'm officially from CDRH, but now I'm the detail in
3 CBER. So I just wanted to echo what Raji said about
4 the device. When we designed the clinical trial, we
5 needed to consider the diagnostic device which
6 classified patient marker status.

7 Because the device measuring biomarker are not
8 all subject to measurement error because they are not
9 particularly for size, or they may not be particularly
10 accurate.

11 So I think the -- so considering the device
12 early at the design stage is very important because
13 different device may identify different set of what
14 patient publishes, such as biomarker past-through.

15 So a device which have poor measurement
16 performance could potentially lead to the loss of
17 statistical power and also dilute the treatment effect
18 factor.

19 And a major challenge that we haven't been
20 facing is that sometimes in the clinical trial at the
21 baseline, a lab developed a test which often is not
22 perfectly precise or accurate is used to classify the

1 patient marker status. So I think we have been seeing
2 this over and over again in a lot of statistic issues.
3 So that's just my comment. Thank you.

4 DR. PRICE: Thank you. And our final question
5 from the audience?

6 QUESTION: Actually, that was really spot on,
7 because, I mean, breast cancer is where we work I-SPY.
8 And as someone had mentioned subtypes in rare diseases,
9 it's sort of becoming difficult to look at our trial as
10 the one fit model.

11 Patients respond differently to drugs and
12 we're noticing the biomarkers are going to be something
13 that we really need to find a path through the FDA for
14 regulatory approval of how do we utilize our data in a
15 trial moving forward to get regulatory approval of
16 those biomarkers in conjunction with those drugs.

17 And it doesn't seem like there's a very easy
18 path to see, as far as like how do we do this. Two, we
19 don't just work with U.S. drug makers. We work with
20 international folks, and how to get these innovative
21 designs and the data from this accepted pretty much
22 across the world.

1 How do we, you know, get a little more, you
2 know, standardization, talking about the patient-
3 reported outcomes? How do you get these pieces to work
4 in parallel? How do we utilize this data, and frankly
5 make it work both in the biomarkers, both in
6 international? That's the questions we're dealing
7 with.

8 DR. SRIDHARA: So we do have collaborations
9 with foreign regulatory agencies. There are MOUs, and
10 we do discuss with them on topics which are in some
11 areas where it is not related to any product, but just
12 the methodology itself as we do with the statisticians.

13 But within, for example, in oncology, we have
14 regularly monthly meetings with six of the regulatory
15 agencies where we do discuss with them specific
16 products and what we are seeing and we do exchange our
17 views.

18 It's not to say that we influence them in
19 their decisions. We all have our own regulations and
20 we have to follow them. But we certainly exchange our
21 views and the way we are thinking about a particular
22 method or some of the data that we are reviewing. So

1 it is happening, and we do discuss with regulatory
2 agencies.

3 QUESTION: Thank you.

4 DR. PRICE: Thank you. This has been a great
5 morning. We look forward to the afternoon. We will
6 break now for lunch, and reconvene at 1:00.

7 (Whereupon, the foregoing went off the record
8 at 12:08 p.m., and went back on the record at
9 1:09 p.m.)

10 DR. PRICE: Good afternoon. We will move
11 forward into our first session of the afternoon. We
12 have two new FDA colleagues joining us on the panel,
13 and I will begin by asking them to introduce
14 themselves.

15 DR. IRONY: Good afternoon. I'm Telba Irony.
16 I'm deputy director in the Office of Biostatistics and
17 Epidemiology at CBER, at the FDA.

18 DR. PERMUTT: Tom Permutt, Stanford drug
19 evaluation and research. I'm associate director for
20 statistical science and policy in the Office of
21 Biostatistics.

22 DR. PRICE: And our first presentation of the

1 afternoon be given by Dr. John Scott, who is the acting
2 director of the Division of Biostatistics, in CBER.

3 SESSION III: CLINICAL TRIAL SIMULATIONS FOR
4 CONFIRMATORY TRIAL DESIGN AND PLANNING
5 PRESENTATION

6 DR. SCOTT: Thanks, Dionne. It's really a
7 pleasure to be here today for this workshop that I
8 think is really important and productive.

9 During the morning, there was a fair amount of
10 incidental discussion about clinical trial simulations.
11 In this session, we're really going to focus on that as
12 a topic in and of itself, and try to hear some opinions
13 from our panelists and from you the public about this
14 topic.

15 So my goal is to give an overview of what
16 we're talking about when we talk about clinical trial
17 simulations in this setting and to raise some questions
18 maybe for discussion.

19 So clinical trials have a variety of important
20 operating characteristics and roughly what we mean by
21 operating characteristics is expected behavior under
22 certain clinical, operational or statistical

1 assumptions. Those operating characteristics guide
2 trial design and interpretability. And one way of
3 estimating trial operating characteristics is to
4 simulate large numbers of clinical trials and to
5 observe their outcomes.

6 So in terms of when you reduce simulation for
7 this purpose or why, it is true that for many clinical
8 trial designs, including some complex designs,
9 statistical theory is available that provides estimates
10 of important operating characteristics or at least
11 bounds on those characteristics.

12 But you might prefer to do simulations or you
13 might need to do simulations in at least a few
14 different kinds of cases. One, if you're talking about
15 complex designs that have multiple adaptations,
16 statistical theory might not invite you with estimates
17 that you can really use.

18 Bayesian trial designs, as we discussed in the
19 morning, often, maybe always, require simulation. And
20 we also might want to use simulations in small sample
21 designs such as you would use for studying rare
22 diseases, because the asymptotic theory that tells you

1 what happens as sample sizes get large can be
2 unreliable with small sample sizes.

3 So this is a summary of some of the kinds of
4 things we're thinking about or talking about when we
5 talk about operating characteristics. So there's
6 traditionally a lot of focus on the type one error
7 probability of a hypothesis test. That's the
8 probability of rejecting and null hypothesis that's
9 actually true.

10 In addition to the type one error probability
11 in the sense of mostly concluding the drug is effective
12 when there's literally zero effect, you might also be
13 interested in falsely concluding it's effective when
14 there's an effect that's smaller than some minimally,
15 clinically interesting effect.

16 Power is very important, expected sample size
17 for studies that have variable sample size, group
18 sequential, or other adaptive designs.

19 Estimation properties, we don't always put in
20 the category of operating characteristics. But because
21 simulations can help in this area too, we sort of
22 grouped it together. So this would be things like the

1 mean squared error of estimates, maybe the bias, if Tom
2 will forgive me for saying bias.

3 And then, most of the things I mentioned above
4 are primarily for frequentist statistical designs. If
5 you're talking about a true Bayesian clinical trial,
6 you might look at some alternative operating
7 characteristics such as the Bayes average error or the
8 maximum posterior probability of the null hypothesis in
9 a rejection region.

10 So this is -- I focused on this slide on type
11 one error probability. This is the logic of how these
12 simulations work. The logic is pretty much the same no
13 matter what you're trying to estimate by simulation.

14 So, but for type one error probability, you
15 would start by assuming the null hypothesis is true.
16 There might be many different ways of making that
17 assumption. You would generate trial data under that
18 hypothesis according to the design of the trial.

19 You would apply the trial analyses and the
20 decision rules to that data, repeat that process a
21 large number of times and then the proportion of times
22 that that process led to a conclusion of effectiveness

1 would be an estimate of the type one error probability
2 of the trial.

3 So these are several complications or areas
4 where questions arise when you're talking about using
5 simulations in this way, and I have a slide focusing on
6 each of these separately afterward.

7 One is defining the null space, or more
8 generally defining the simulation space. Two, is the
9 scope of the simulations, how detailed, how many, how
10 much. The third is -- I'm calling it multiple testing
11 or multiple hypotheses. Really it could just be called
12 complexity of decisions is a complication with
13 simulation.

14 The fourth is applying these ideas in Bayesian
15 settings with informative priors, and then finally,
16 sort of resource issues and review issues.

17 So in terms of defining the null space, there
18 are typically many different ways for a drug to be
19 ineffective. We don't test what, you know,
20 statisticians call simple-versus-simple hypotheses.
21 There's a lot of different ways for a drug to not work.

22 So as one contrived example, suppose you're

1 studying a drug for a very aggressive cancer and
2 historically you know that the median survival in this
3 condition is about a year.

4 So when you're doing your simulation, the drug
5 could be the same as the control. That would be the
6 null hypothesis is true. There's no effectiveness.

7 But the control could have one-year median
8 survival, as you would expect, or the control could
9 have five-year median survival, which would be
10 surprising in the disease, or mathematically it could
11 have a thousand-year median survival, which cannot
12 happen in human beings. But it's still in the sort of
13 mathematical null space of the hypothesis.

14 So when we do these simulations, should we be
15 simulating all possible null configurations or a sample
16 of all possible null configurations or just the
17 clinically plausible or important configurations? And
18 how do we draw the line there?

19 In terms of the scope of simulations, in
20 addition to an assumption about the treatment effect,
21 you typically need to make assumptions about many other
22 parameters when doing these trial simulations.

1 You make assumptions about clinical
2 parameters. What is the true control rate in a trial?
3 You will make assumptions about statistical nuisance
4 parameters, such as the variance of an estimate. And
5 you might make assumptions about operational
6 parameters, such as the accrual rate to the trial or
7 even the accrual per site in a multisite trial.

8 And so when you're talking about the scope,
9 the total number of combinations of parameters is
10 obviously infinite. So what kind of exploration of
11 that space do you need to do to be reasonably assured
12 that you have a good estimate from a simulation?

13 And then if you just look at one dimension, if
14 you just look at, for instance, the control rate, you
15 might want to explore control rates between 20 percent
16 and 50 percent because that represents your uncertainty
17 in a given trial. But should you do simulations at 20
18 percent, 30, 40, and 50? Should it be every five
19 percentage points? All of these are sort of technical
20 implementation questions that need a lot of work.

21 In terms of multiple testing or the complexity
22 of decision, when we talk about simulations, typically

1 the focus is on the primary analysis of a primary
2 efficacy endpoint.

3 But as we all know, actual decisions, actual
4 interpretations of clinical trials are complicated.
5 They depend on primary and secondary endpoints,
6 possibly multiple primary endpoints, and they also
7 depend on safety or risk.

8 And so, as we're talking about doing a
9 simulation to get at what we think is our chance of
10 making an erroneous conclusion, can we make simulations
11 that encompass all of those multidimensional
12 considerations.

13 I want to talk specifically about Bayesian
14 settings. I also want to emphasize, as Lisa said in
15 the previous session, when we talk about simulations,
16 we're not only talking about simulations for Bayesian
17 designs. There are other applications, other very
18 important applications.

19 But the simulations become particularly
20 important in Bayesian settings. And what we even mean
21 by Bayesian setting is not always immediately clear.
22 There are a lot of trial design proposals that use

1 Bayesian calculations, but rely on decision rules that
2 are chosen to satisfy frequentist operating
3 characteristics, to have a fixed type one error
4 probability, and, you know at least a rough estimate of
5 a type two error probability.

6 So when we're doing a trial of that kind, if
7 it doesn't borrow prior information, the considerations
8 are generally the same as in a non-Bayesian setting.

9 But when it does borrow prior information, the
10 definition of the null space becomes really hard to get
11 your hands on because your conditioning on data that
12 have already been observed.

13 And if you're talking about the null
14 hypothesis being true, you have to ask yourself were
15 those data that were observed generated misleadingly
16 under a null hypothesis or were they generated -- are
17 they from an entirely different distribution from the
18 new trial. And the way you set up those simulations is
19 pretty unclear.

20 On the other hand, if you're doing a true
21 Bayesian design where you're not looking directly at
22 type one error probability, this would be a design that

1 follows the likelihood principal where inference is
2 based on the interpretation of posterior probability
3 distributions. These raise entirely different issues.
4 It's still important to do simulation, but the
5 interpretation is not the same.

6 So in terms of resource issues, doing
7 simulations can be computationally intensive. They can
8 be computationally intensive for manufacturers or
9 applicants who want to include simulations in their
10 poses and also for FDA doing review of those proposals.

11 On the computational front, there has been
12 over the past 20 years dramatic and constant progress
13 toward getting more sophisticated computational
14 techniques and hardware. But there are still some
15 problems that at least now, who knows in a decade, but
16 at least now are essentially impossible to simulate.

17 So if you're doing a complicated Bayesian
18 analysis with a lot of MCMC inference and you have to
19 repeat that many thousands of times in a simulation,
20 that can become intractable, depending on the
21 specifics.

22 And as I mentioned, reviewing simulations can

1 be resource-intensive for FDA, and there are
2 implications for FDA review timelines, workload,
3 training reviewers who may not be accustomed to
4 reviewing these types of proposals and also the
5 software for doing the simulations.

6 One thing to consider, talking about
7 simulations, is how do you report a simulation. How do
8 you convey the findings of a simulation? And this is
9 not an area where there's a template. It's an area
10 where there's best practice sort of actively
11 developing.

12 But some things that would be included in a
13 simulation report would be a description of the trial
14 design, some examples of hypothetical trial outcomes,
15 if you ran through the trial a few times, the scenarios
16 that are going to be simulated, the estimates of
17 operating characteristics from each of those scenarios
18 and then an overall summary of what this tells us about
19 the design of the trial.

20 And in some cases, it may include simulation
21 code, technical details for the simulation and
22 statistical derivations.

1 So in terms of FDA's review of simulations,
2 this is another area where we don't have policy. We
3 have developing practices which are not necessarily
4 exactly the same in every review division or for every
5 reviewer.

6 But some things that a review may include
7 would be verification with the applicant's own
8 simulation code or the off-the-shelf software that the
9 applicant used for their simulations or it could
10 include verification with code written by the
11 statistical reviewer or with other off-the-shelf
12 software to try to get a kind of second opinion. And
13 it also may include exploration of additional scenarios
14 that the applicant didn't consider.

15 As of now, there's not a standard acceptance
16 criterion for when operating characteristics are good
17 enough or when our estimates are precise enough. This
18 probably needs to be situation-dependent and certainly
19 is now.

20 All right. So I'm going to run through the
21 questions that we've setup for the panel to discuss,
22 and then I'll turn it over to our lead discussants who

1 I think in order on the program were Scott Berry, Cyrus
2 Mehta and Karen Price.

3 So question one, regarding the scope of type
4 one error probability simulations, should all
5 mathematically possible parameter values for which the
6 drug is ineffective be included or only values that are
7 in some sense clinically plausible? And if the latter,
8 how do we define what's clinically plausible?

9 Question two, how should error rate
10 simulations be conducted when formally borrowing prior
11 information in a Bayesian framework? And what does
12 type one error mean in that setting, and should we be
13 considering other kinds of error rates more closely
14 tied to a Bayesian approach?

15 And question three, what are some practical
16 suggestions for implementing trial simulations, for
17 example the number of simulation iterations,
18 computational details or details about how this should
19 be documented.

20 I also have -- there's a question four, which
21 is -- I think it would be ambitious to think we'll get
22 to it, and it's more technical, so we'll stick with

1 these three for now. So I'll turn it over to Scott.

2 DISCUSSION

3 DR. BERRY: Okay. Thank you very much, John.
4 First I want to pause and reflect that how really
5 exciting this is and what the question's FDA's asking,
6 and the innovation that they're really pushing the
7 industry for here of the clinical trial simulations,
8 the adaptations, so just the questions being asked I
9 think are -- is really very, very exciting.

10 Let me say something about simulations. The
11 word simulations, I find that that term in itself is
12 almost a dirty word, that we're used to this being
13 predicting who's going to win the NCAA tournament,
14 where is a hurricane going to go, these types of
15 things, that it's forecasting and predicting
16 hypothetical scenarios.

17 When we use simulation in this space, it's
18 numerical integration. It's very simply numerical
19 integration. We're not forecasting anything. We're
20 calculating an integral and calculating various
21 quantities from that integral.

22 The idea of being able to do those numeric

1 integrals using simulation as the general term for
2 doing that, what it allows us to do is move designs
3 away from boxes. We can do pencil and paper
4 calculations of type one error and power in very
5 restricted scenarios where the design is a box.

6 As soon as the design becomes any shape other
7 than that, it's rare that we can calculate on pencil
8 and paper those quantities. And hence, we do numeric
9 integration. We calculate through simulation what are
10 the characteristics of the funny oval-shaped design
11 being proposed.

12 There's a beautiful aspect of this numerical
13 integration/simulation that you can calculate amazing
14 quantities that you can't do on pencil and paper in
15 other situations. And I think it's had actually a
16 strange negative consequence in drug development.

17 So for example, you can calculate in my Phase
18 II trial, what's the probability this dose is selected
19 as my minimally effective dose. You can't do that on
20 pencil and paper. We don't know that running a Phase
21 II trial; hence, we run an amazing number of Phase II
22 trials with three doses and 80 patients because we know

1 the power of a P value test of parallelized
2 comparisons, despite the fact that nobody actually
3 likes to do that in a Phase II trial. It's what we can
4 calculate on pencil and paper.

5 Now we can simulate innovative dose response
6 modeling. We can simulate the probability that a dose
7 is selected and is moved to Phase III. What's the
8 probability we make a go decision in a Phase II/III
9 seamless trial? We can't do that on pencil and paper.
10 We can calculate it exactly in numerical integration.
11 We can calculate how much drug is going to be used in
12 this trial, what's the distribution of that for drug
13 supply.

14 So there's an amazing amount of things that we
15 can then calculate. And then, we end up iterating the
16 design invariably by simulating and investigating. And
17 I was really glad John brought up the idea of looking
18 at individual single simulated trials and showing that
19 to the team and them seeing a trial run to the end and
20 saying, oh, hey I didn't like that result. Oh, wow if
21 that happened, that's a bad result.

22 It's amazing how often that happened, and then

1 that turns into an adaptive design. Let's mitigate
2 that type of failure that we can see coming within the
3 situation. And I'll give you a lighthearted scenario
4 that happened to me more than once.

5 I take their -- the fixed trial given to me
6 that has 80 percent power for a hypothesized delta. I
7 simulate the trial and show them example trials, and
8 that delta's a nice effect. And they look at me and
9 say if I run that trial, 20 percent of the time I fail
10 with my delta. Well, wait a minute. This is not a
11 good trial design.

12 They didn't understand what power was. Power
13 to them is a threshold that means that the FDA's going
14 to approve my trial. And a good statistician will get
15 me a smaller n with the same power. It's a weird game,
16 but simulation brings that out and shows it in complete
17 detail of that.

18 So the idea of being able to use simulation,
19 computer-aided design, is really a nice step forward
20 and the review of course brings about various problems
21 as John brought up, the various questions.

22 Many of these questions revolve around the

1 idea of type one error and the idea that has been
2 engrained in our heads of strong control of type one
3 error.

4 If there's an infinite number of null
5 scenarios, our design can't be approved by a control of
6 simulation -- by simulation because we can't simulate
7 an infinite number of scenarios. And that sort of
8 cycle is what many of this goes to.

9 So the idea of being able to simulate from the
10 null, we do simulate from the null a great number of
11 scenarios. There are strange scenarios where it's not
12 clear if it's a null or not.

13 When you do enrichment designs, personalized
14 medicine-type designs, and you could make a conclusion
15 within different subsets, you might miss and hit at the
16 same time. Is it a type one error and a type two
17 error? Is it not an error? These are hard scenarios.
18 They're really therapeutic to go through and recognize
19 that these can happen, and what do we want the trial to
20 do in these different scenarios?

21 So the idea of being able to simulate type one
22 error and demonstrate that I think is wonderful. We've

1 presented many grid search scenarios. We take expected
2 scenarios, and then we double them and half them. And
3 we do four or five within there. And then we take
4 dropout rates and we vary that over a scheme and show
5 the characteristics of the trial with different dropout
6 rates.

7 Sometimes enrollment rate changes the
8 characteristics of the design, especially in an
9 adaptive design. So we change enrollment rates within
10 the trial and we demonstrate that.

11 An interesting thing happens with simulating a
12 null scenario, is that we simulate -- and suppose you
13 got it exactly right, and your trial is calibrated to a
14 5 percent error rate. And I simulate a hundred nulls.
15 Half of them have elevated simulated type one error.
16 They'll be above 5 percent. You'll be at 5.03 percent,
17 5.8 percent.

18 We know through the natural error of that
19 simulation that we get above, so it's understanding
20 that. So we might even have a particular delta that
21 above this value is above simulation if we simulate
22 above 100,000 scenarios from every null.

1 And we may do 300 null hypotheses with 100,000
2 simulations of each trial to characterize the
3 probability of an incorrect conclusion in order to
4 justify that the design is a confirmatory, adequate and
5 well-controlled trial.

6 And I think as our simulations get more
7 advanced, they get faster, our ability to do this is
8 better, we can do much more of this within the adaptive
9 design report and submitting these to regulatory
10 agencies.

11 So in terms of the type one error probability
12 scenarios, we can't simulate every possible value. I
13 appreciate the question and it brings up this idea of
14 theoretically understanding on every scenario. But we
15 can do a very nice grid search for what that type one
16 error is.

17 Sometimes we even do modeling of the results
18 of the simulations to look at the effect of a factor,
19 and it looks like that factor doesn't affect type one
20 error. And a model can demonstrate that on the results
21 of the simulation in order to give further
22 understanding of the behavior of the design.

1 I believe that there is no such thing as a
2 design that's not well-understood if it's been
3 simulated. You understand everything about the design
4 as long as it's been simulated under that scenario. So
5 we can lose that nomenclature eventually as we simulate
6 trials.

7 One other thing I'll bring out about
8 simulation is that we've proposed post-trial
9 simulation. So we do a grid search which includes
10 nuisance parameters, event rates, median survival. And
11 we've done median survivals of six months, nine months,
12 a year, 18 months and two years.

13 And then we can go back when the trial's over
14 and bootstrap the trial over again, taking every
15 patient from every arm equally likely, and it's a
16 guaranteed null hypothesis. And what's the behavior of
17 that, just for further understanding after the fact
18 when the trial's over.

19 It's not something that, you know, you might
20 even get a 2.6 percent type one error, and we can
21 understand what that is. But it's further
22 understanding after the fact of the trial, based on the

1 prospectively defined trial that was run during the
2 course of it. All of this revolves around completely
3 prospective design, full details done.

4 You can't simulate a trial that you don't have
5 the details for. And it's a really therapeutic way to
6 create the protocol itself, is to ask a statistician to
7 simulate it or a computer scientist to simulate it for
8 you.

9 If they don't know how to do it, you don't
10 know the design yet. So it's a really important part,
11 and the various questions -- I agree with John
12 completely, Dr. Scott, that it's a case-by-case
13 scenario.

14 Some scenarios we've done 300 nulls. Some
15 scenarios we've done eight, because of the particular
16 situation, and that the trial aspect of it in there.
17 Now, that makes it harder for the agency for sure.

18 It would be really nice if the agency would
19 create a pilot program and investigate several
20 simulated trials over the next year or so. It's a
21 beautiful idea. So I look forward to that, and the
22 exploration of the role of simulations in this. Karen?

1 DR. K. PRICE: I think it's Cyrus.

2 DR. BERRY: Cyrus?

3 DR. SCOTT: Dr. Mehta has slides, which I
4 think --

5 DR. MEHTA: How do you move forward? I just
6 have a couple of slides on simulations in frequentist
7 trials and a couple of trials on simulation in Bayesian
8 trials and then one slide on the computational issue
9 that John brought up.

10 So in the frequentist setting, I think
11 solutions are valuable for verifying asymptotic
12 results. Asymptotic results exist, and for example in
13 time-to-event trials, you will have -- you know the
14 asymptotic properties of the log-rank statistic. But
15 in small samples, it might not hold. You know very
16 well what happens in nominal and binomial trials when
17 there are a nuisance parameters. So it's very -- it's
18 valuable to verify.

19 But if no analytical results are available,
20 then it's essential that you simulate. For example,
21 power, and then the type one error of a response-
22 adaptive trial. You wouldn't be able to get that

1 analytically and would have to simulate. And similarly
2 for more complex designs by the arm trials with some
3 type of adaptation and also multiple endpoints, if you
4 want to know power, you may need to get that through
5 the simulation.

6 Now, one more type one error control by
7 simulation, it's not straightforward. Adaptive
8 designs, multi-arm designs, multiple endpoints, as was
9 just mentioned by Scott, they are complex null spaces
10 that cannot be exhaustively explored.

11 And so you -- but fortunately, at least in the
12 frequentist domain, we have very good tools. These
13 tools have been developed over time, closed testing,
14 combination of P values, preserving conditional error
15 rates and independent increments.

16 These are tools that have been developed in
17 the frequentist domain which do control the type one
18 error in the strong sense, and so they -- I'm not
19 really a case for no simulation. But you don't need to
20 worry so much about this more complex null space
21 because it's taken care of by these tools.

22 Now, Bayesian is a much different issue. I

1 have not as much experience with Bayesian methods as
2 Scott does, but I have some experience.

3 So I think a simple case that you just have a
4 normal delta, mean and standard deviation of one. And
5 the goal is to determine if this delta is greater than
6 deltas -- than some null delta naught. Then the
7 Bayesian inference retrieved this delta itself as a
8 random variable and it puts sort of a criterion for
9 success, which is this probability -- this posterior
10 probability that the delta exceeds delta naught, given
11 the trial data and given some historical data, should
12 be good, should be greater than some gamma.

13 And then you can simulate -- you have to
14 simulate that, that probability of the success
15 criterion and under various assumptions about delta,
16 how often will this success criterion actually hold.

17 And in particular, you want to simulate it
18 under the null space which is in this case delta
19 naught. How often will this success criterion hold if
20 you simulate under the null space, and you'd like that
21 to be bounded by less than alpha.

22 No, so DSIM is the data from the simulation

1 and D0 is the data from the historical trial. Now if
2 you use a flat trial, then the Bayesian and frequentist
3 results should be similar.

4 The issue is what happens if you want to
5 borrow data and it's not from a flat trial. Then you
6 have sources of bias. And there are two sources of
7 bias. One is a selection bias, and that is like
8 publication bias.

9 It's something that Professor Goodman also
10 hinted at in his morning session, that well, you know,
11 I've got all this prior data. And if this prior study
12 was positive, I'm going to bring it in as my prior.
13 And if in fact I didn't have a prior study that was
14 positive, then I won't bring it in.

15 Now, so that can be a source of bias. So
16 there was a notion of only bringing in -- borrowing
17 prospectively. That is to say, the trial -- the
18 previous trial is still ongoing, and you don't know its
19 results. And then, you may or may not have this
20 problem of a selection bias.

21 There are ways of contamination, which is that
22 the control of type one error, it may be difficult

1 because the control arm of the prior study is worse
2 than the control arm of the new study, and so that
3 gives a break to the new study, or the treatment arm of
4 the prior study is positive, but the treatment arm of
5 the current study may not be, and both of these sources
6 can inflate the type one error.

7 Now, so there have been ways of trying to
8 avoid these biases. And one of them is this power
9 prior method for controlling the alpha. This was
10 proposed by Abraham and Chen, and what it does is it
11 handles the heterogeneity between the current and
12 historical data through a power -- through raising the
13 likelihood of the prior to some power, A_0 .

14 And so this A_0 , so you see the posterior is
15 part of the -- or a proportion to the likelihood of the
16 new study and the likelihood of the old study raised to
17 a power. And the extent of this power A_0 determines
18 the amount of borrowing that you can do.

19 If this A_0 is zero, you cannot borrow at all.
20 If A_0 is one, you can borrow everything, and you can
21 choose in between.

22 And then the question is how do you choose

1 this A0. There is an approach suggested by Hadad. I
2 actually won't have time to go into it, but another
3 option is to just pick a fixed A0 and then use that for
4 controlling the type one error. And it sort of
5 estimates the heterogeneity between the historical data
6 and the trial data.

7 We did simulate this method of Hadad to see
8 what would happen on the different levels of
9 contamination. So you see these two tables. One is
10 where you have heavy discounting and the other where
11 you have mild discounting.

12 And each row is representing more and more
13 contamination in the sense that the group, the new
14 trial has a zero delta, no more treatment effect. And
15 the previous trial has treatment effects. So no
16 effect, effect with a mean of two and effect with a
17 mean of four.

18 And we did simulations to see that under all
19 these different situations, the type one error can be
20 controlled -- or slight, almost controlled. Actually
21 the alpha here should be 0.025, but the -- you can get
22 close to it unless there's heavy contamination, in

1 which case, you know, you might get type one error of
2 an almost 10 percent.

3 My last slide is about computational issues.
4 If you're going to use these methods, you have to do a
5 lot of simulation. And again -- and at least in the
6 Bayesian setting, that might be computationally
7 intractable.

8 This is a nice table that was published by
9 Martin Posh and colleagues in 2011. It says suppose
10 that the true type one error -- the true type one error
11 of the test was 0.026. Then how many separate
12 simulation runs would it take on average to get a
13 simulated type one error of less than 0.025.

14 If you only have 10,000 -- if you have
15 simulation runs of 10,000 then one -- on average, one
16 in every four will incorrectly bring you below 0.025,
17 when the true at this point is 0.026.

18 Is you have a simulation runs of 100,000, then
19 about one in 43 times will it happen that falsely your
20 simulation goes below 0.025 when the truth is 0.026.

21 And of course if you say I can simulate a
22 million times, then it would be all right and you'll

1 have about 8x10⁹ before you get a wrong answer. Thank
2 you.

3 DR. K. PRICE: Great, thank you so much.
4 Thank you, John, for a great introduction to this topic
5 and for bringing out many of the important potential
6 hurdles, as well as the challenges that we have, but
7 with an eye toward action and toward identifying
8 solutions. Appreciate that. Thank you for the other
9 discussants, as well.

10 And what I want to do is take a little bit of
11 a different approach. I think not so much answer the
12 questions, but maybe just talk a little bit about some
13 of the things that are on at least my mind, and folks
14 in industry's mind on how we may be able to move
15 forward together and that we're excited to move forward
16 together on this.

17 First of all, as I mentioned this morning, I
18 think it's important that we remind ourselves that
19 clinical trial simulation to some may seem as a very
20 heavily statistical activity, PK/PD activity, and it
21 certainly is. Statistics features very heavily. But
22 it is strongly a cross-functional endeavor.

1 And what we have seen many times, and has been
2 mentioned I know by Roger and Scott and others on the
3 panel, is the tremendous amount of unexpected benefits
4 that we are able to come to through that cross-
5 functional dialog that ensues when we simulate trials.

6 And it has been argued, and I had planned to
7 also indicate that really any trial can and should be
8 simulated. At Lilly, we do simulate, or at least
9 endeavor to simulate every trial that goes out,
10 regardless of whether or not it has a close form
11 solution, in large part too, look at those unexpected
12 things.

13 As was mentioned, intuition doesn't always
14 play out. And so, we're able to see areas where the
15 design may break down, and greatly improve that design.
16 So just something I want us to keep in mind as we go
17 forward, is the cross functional nature, and I'll come
18 back to that before I conclude.

19 Also many of the designs, obviously as we're
20 talking about today, require simulation. And so, what
21 I wanted to do is think about it in three main points.

22 And the first thing is that we can do this.

1 We must do this, and we're ready to do this. And so,
2 when I talk about we can do this, what I mean is we
3 have tools. We have knowledge. We have examples. So
4 we can do this.

5 Sometimes we probably get in our own way, and
6 get a little caught into the details and concerned
7 about things that we can overcome. We have, as I
8 mentioned, tools. We have knowledge. We don't have a
9 tremendous amount of experience, and that's what this
10 pilot program is so well-suited for. But we should not
11 let that get in our way.

12 And we certainly need to improve on the tools.
13 But I think that it's through the experiences in the
14 actual application and just moving forward and just
15 doing this that we're going to figure out where do we
16 really need innovation in terms of the tools. Where do
17 we need innovation in terms of the methods and so
18 forth?

19 So we can do this. What we really have needed
20 though is a pathway for communication. So what has
21 happened historically, and we don't want to spend a lot
22 of time talking about the past, but learning from the

1 past is that we might conduct a lengthy simulation
2 study. And by the time we have an opportunity to have
3 a conversation, it's well into time for the study to be
4 conducted and maybe too late to address concerns from
5 FDA's perspective.

6 And so, having avenues and clarity on those
7 avenues for communication will be vitally important.
8 And I know that is a component of the pilot pathway, or
9 the pilot project.

10 But we really do want to make sure that we
11 have clear clarity on that, as well as a timely
12 communication and understanding of if there are
13 rejections for the pilot, which just may be because of
14 other similar things have been proposed, there's
15 clarity on that to the company so that we don't revert
16 to interpret that to be some negative view of the study
17 and have a pathway to continue that development.

18 So we know that innovative designs are going
19 to need to continue even outside of the pilot program.

20 We must do this. I think that patients demand
21 it. We're all patients at one time or another, and as
22 we talked about, to get to the truly innovative design

1 and the best thing for patients, we're going to have to
2 do this.

3 And along this line, I think this is where as
4 I was getting at earlier, sometimes we get in our own
5 way on this and want to be careful that in order to do
6 this is bringing the cross-functional groups together.

7 As statisticians, we can get into the
8 technical details. There was a conversation earlier
9 about regulatory scientists who certainly can be
10 slowing things down in some sense. But I know some
11 really great ones, and they can be some of the biggest
12 advocates, and could really be essential to helping us
13 more this forward.

14 And so, I think that bringing everyone
15 together in these conversations will be important.
16 Ensuring that we have medical reviewers onboard and
17 that are part of these conversations so that they're
18 onboard, and there's not a perception that this is only
19 one group that is supportive of these approaches will
20 be key.

21 And finally then, we're ready to do this. I
22 just wanted to reiterate that we're excited from an

1 industry perspective to collaborate together. We want
2 to look to develop best practices together. I think
3 there are attempts at doing this. Let's look for ways
4 and understand better how specifically can we do that.
5 Can we leverage the scientific working groups?

6 Can we do other -- have other meetings, or
7 other conversations to develop those best practices,
8 the timely communications, the other ways that we can
9 improve these, the ability for us, help us understand
10 what it is that you need.

11 Help us to understand what we can give you,
12 and how we can do that in a standard manner so that
13 you're able to more efficiently and effectively review
14 simulation results and ultimately approve these
15 designs. Thank you.

16 PANEL DISCUSSION

17 DR. PRICE: Thank you for those insightful
18 comments. We will move to question one. And again, we
19 may need to be adaptive, but we'll see how it goes.

20 Question one, regarding the scope of type one
21 error probability simulations, should all
22 mathematically possible parameter values for which the

1 drug is ineffective be included or only values that are
2 in some sense clinically plausible? How is clinically
3 plausible defined, agreed to?

4 So a couple reminders. Please lean in when
5 responding. Please turn off your mics when not
6 speaking. And we'll begin with Dr. Emerson.

7 DR. EMERSON: So I -- you know, it is
8 impossible to do everything. But it is not impossible
9 to use good statistical theory to look to say where the
10 biggest problems lie and that that should be done to
11 make certain that you do that.

12 The null space that was mentioned about
13 saying, oh gee, you know, x is equal to y , but what
14 equal to what, is not really as interesting to me
15 personally as wondering about whether we're interested
16 in a strong null or a weak null.

17 And that's very, very important to me,
18 personally, is the idea that yes, if under the null do
19 we really believe the treatment does nothing, and
20 therefore we should simulate from the exact same
21 distribution, or we should simulate from distributions
22 where if we're testing means, the means are equal, but

1 other things change, or if you're testing hazard ratios
2 as returned from proportional hazards analyses.

3 If the average hazard ratio under the
4 censoring distribution that you've used is the same,
5 and, you know, they -- I focus a lot of this time-to-
6 event. We do so many things in cancer based on time-
7 to-event.

8 But you really have to worry about early
9 differences versus late differences, and a lot of these
10 making decisions very, very early when there might be
11 an early difference, maybe in the wrong direction,
12 maybe in the right direction. We really have to
13 understand how that is there.

14 And also understanding how, you know, mean
15 variance relationships then show up at under the weak
16 null is very, very important. And so, it's really
17 quite a big space, but trying to find some sort of
18 smooth parameterization of this huge space becomes
19 important.

20 And ultimately, you do have to stop that. You
21 know, what's clinically plausible? That there needs to
22 be something, but it's what's clinically plausible, not

1 just to the investigators at hand, but to the greater
2 population of the people who have to be convinced.

3 DR. PRICE: Dr. Harrell?

4 DR. HARRELL: All right. First a couple of
5 quick comments on Cyrus' presentation. The last method
6 you presented for borrowing is really double-dipping,
7 and is not a proper prior. So it's not a proper
8 Bayesian analysis.

9 And then, the Bayesian and frequentist, when
10 you have a non-informative prior, are only equal in a
11 very special case. And that's where the sample size is
12 fixed and there was exactly one look at the data.
13 Otherwise, the Bayesian and frequentist are only the
14 same if you don't -- if you do not control the type one
15 error with the frequentist approach.

16 But more to Scott's point, I think I'm glad he
17 mentioned the strong and weak null. And the whole
18 debate about whether we should be using null hypotheses
19 needs to always be revisited. And there's a great
20 debate in the philosophy of science about whether
21 hypotheses lead to advancing science versus asking
22 questions. And there's a difference in those two.

1 That debate's worth reading about.

2 And we have some famous statisticians, such as
3 John Tukey and also Cohen has talked about this, that
4 the null hypothesis is never true. So just get it out
5 of your mind that there's exactly zero effect of a
6 drug.

7 And so, when you're doing a simulation to use
8 something that's artificial, it has real implications
9 on what happens. And one way it's artificial is even
10 if you believe the null hypothesis can be exactly true,
11 which I do not, you have to also realize you're making
12 another big assumption in the simulations which is
13 you're entertaining that there is no possibility that
14 the drug does worse than the control.

15 And so you're -- the option that delta is
16 negative, the blood pressure actually gets higher with
17 the new blood pressure drug, is not entertained. And
18 so that's just one of the ramifications from doing
19 simulations at delta equals zero.

20 DR. PRICE: Dr. Ashby?

21 DR. ASHBY: I mean, what's going through my
22 head is which of these are fundamental questions and

1 which of these are kind of transient questions because
2 we're feeling a way, and this is all new stuff.

3 I mean, I'm sort of thinking 10 years down the
4 line, what you'd really want to see is probably some
5 shared agreement of software. And it seems to me
6 there's then two types of questions that you'd say,
7 first of all, are these the right simulations. And you
8 might have some agreement between regulators and
9 sponsor about whether they're right.

10 And then secondly, whether they're technically
11 correct, but rerunning them in different software. I
12 think we should be looking for technical solutions too.

13 But you can't possibly go over all space. But
14 I'm slightly worried that going down this line of
15 questioning, I think we have to, sort of takes away
16 from what was the most sensible thing to be doing. Is
17 it really checking out the questions, the
18 characteristics we need to understand? And I'm more
19 concerned with getting the right set of questions.

20 So even when you start them at type one, it
21 kind of forces you into certain sorts of designs and
22 simulations, some of which are relevant, some of which

1 aren't. So I think, you know, you almost want some
2 interim guidance while we're finding our way. But I
3 suspect the world in 10 years will look quite
4 different.

5 DR. PRICE: Thank you. Dr. Goodman?

6 DR. GOODMAN: Sure. Thank you. Now, this is
7 more a question. It's either a question or a comment.
8 Very often when I see the simulations, they don't
9 always take into account the aspects of the design the
10 clinician might have insight into.

11 And I think in particular I think of the
12 temporal drift in the control group, which in
13 combination with adaptive randomization sometimes --
14 I'll defer to Scott -- can introduce problems if you're
15 adapting strongly and then all of a sudden your control
16 group is doing better over time.

17 The other is clustering within sites. And so,
18 my question is as these -- very often that these
19 clinical features of the study or of the procedure, the
20 patients aren't incorporated into the simulations. And
21 the question is how to make sure that they are, that
22 that input is there, because the clinicians don't know

1 what questions to ask.

2 They can't look at the model and figure that
3 out, and even know that it's missing. So it's really
4 up to the simulators to be able to elicit those
5 features that are not necessarily encoded in just the
6 null hypothesis that would particularly interface with
7 the design of the trial, particularly if it's adaptive.
8 That would cause it to be misleading.

9 So this is sort of a question to those who do
10 this for a living. It's also an issue for the FDA
11 because they have to know how to ask these questions.

12 DR. PRICE: Any response before we move to Dr.
13 Lewis? Dr. Berry?

14 DR. BERRY: Sure. I agree completely. And
15 it's the -- to elicit that and simulate, for example,
16 time variation and does the control vary. And it can
17 be a problem if your control goes -- you randomize less
18 and it was built up at a period where it's different.
19 Could absolutely be a part of that.

20 And so, understanding from the design what are
21 potential weaknesses or parts that could go away and
22 the clinical possibility of them is the interaction

1 that has to happen whether it's ahead of time or once
2 you've submitted and the FDA asks for such things.

3 The FDA may have further insight in other
4 trials that are running, and they've seen things that
5 then they could ask can you add this, can you add this
6 to it.

7 One thing we've come up with on this front
8 that's been a challenge in submitting is we don't
9 submit designs we're not running. So we submit only
10 the design. Here's how it behaves. But we don't show
11 the work in which we decided that was the design, and
12 we didn't do this fixed trial. We didn't do adaptive
13 randomization because maybe it has this issue or that.

14 And so, that's a hard thing, and sometimes
15 we're asked by the agency show us designs you didn't
16 decide so I can agree that this is better than those.
17 It gets a bigger deal, and it can be confusing at
18 times.

19 DR. EMERSON: Just, you know, a couple
20 comments on that. You know, some of the temporal drift
21 that you talk about conceptually could be dealt with
22 with analytic methods, and therefore you do that,

1 although it raises small sample issues, which small
2 sample issues have lots of things in terms of both
3 heavier tails, in terms of they're caused by imbalance,
4 caused by also mean variance relationships that cause
5 greater problems, and the covariate adjustment with
6 small samples. Then, that also is a bigger thing.

7 But, you know, some of those will pick out
8 that you handle the temporal adjustment correctly in
9 the adaptive randomization providing you've got blocked
10 randomization and you adjust for that.

11 DR. PRICE: Dr. Lewis?

12 DR. LEWIS: So a couple points. With respect
13 to the question actually posed, I think we're all
14 agreeing that one should not try to build what I call
15 statistical Maginot lines. That's protection against
16 threats that don't actually exist, such as the patient
17 suddenly becoming immortal.

18 So I think the key is when we're communicating
19 in teams, why it is we're willing to give up this false
20 goal of analytic control. I think we need to point out
21 that these design decisions have real implications.
22 These are real tradeoffs.

1 If you limit your simulation for type one
2 error control, if you will, to those things that are
3 clinically plausible or at least worth worrying about
4 even if you don't find them that plausible, which is a
5 broader category, that allows you to focus on the real
6 threats to success of your program. And that's where
7 our intellectual and computational effort should be
8 focused.

9 I do think it's important that the clinicians
10 or the scientific domain experts who view the
11 simulations and give input on the advisability of the
12 different designs learn to understand those things that
13 threaten the success, as Dr. Goodman's pointing out,
14 and this is a mutual learning experience.

15 And as Karen Price pointed out, you often get
16 insights into the weaknesses of your designs through
17 simulations that you wouldn't have otherwise. And I
18 think it's imperative that all of us work to suggest
19 the kinds of questions be asked, like how sensitive is
20 the design to temporal changes, to cluster effects and
21 to those sorts of things.

22 But the main point I'd like to make here is

1 that there is a group that's ultimately going to be
2 tasked with the oversight role when the trial is run,
3 the data safety monitoring board or the DMC.

4 And one of the things that is critically
5 important is that the DMC understands the range of
6 assumptions over which the design's performance has
7 been simulated and when what has actually happened
8 falls outside of the domains that have been simulated.

9 Because the -- obviously no matter how much we
10 think we know about a disease, occasionally things go
11 terribly, horribly, differently. And the DMC has to
12 understand when the design is performing or being asked
13 to perform in a domain in which its behavior is well-
14 understood or has been simulated. I should avoid that
15 term, or when they need to worry that what they'd been
16 told about its type one error control or other
17 characteristics actually doesn't apply anymore because
18 the event rate is very different or the timed
19 information is very different or the cluster effects
20 are very different.

21 DR. PRICE: Dr. Irony?

22 DR. IRONY: I just wanted to talk about the

1 importance of working with the clinicians, and actually
2 with the FDA reviewers.

3 You know, this is a pilot study. But as we
4 get more and more experience with the simulations, as I
5 got some working with Scott in the center for devices,
6 you will know about these cases.

7 For instance, what happens when you vary the
8 accrual rate? Now, that can be crucial. You know, in
9 your first trial you maybe didn't think about that, but
10 you will go, well, what happens when the control group
11 starts to become better because the standard of care
12 becomes better or that stats will become worse because
13 you start to recruit patients that are worse off.

14 So all these things have to be worked in
15 conjunction with the FDA because their reviewers will
16 have experience as the clinical pilot is in industry.
17 We will require more experience. So all these
18 plausible scenarios and critical scenarios will be
19 developed and can be developed in certain -- you know,
20 with time.

21 DR. PRICE: So we'll have Dr. Mehta, followed
22 by Dr. Bretz, and then we'll move to question two and

1 we'll have further discussion.

2 DR. MEHTA: Thank you. I think that the issue
3 of borrowing data for your trial is a really important
4 issue and should be thought through carefully.

5 You know, how -- I understand Frank Harrell's
6 point about double-dipping. The issue is how are you
7 going to not contaminate your actual trial, but when
8 you bring in data, and this is actually what happens
9 when sponsors submit their designs, at least to the
10 center for devices, where this has been allowed.

11 So I presented a method that was proposed by
12 the MDIC in a public meeting. I haven't developed this
13 method. But you have a choice. You can say, well,
14 there are -- FDA sometimes says we give you a fixed
15 discount. You can take 30 percent. Either take it or
16 leave it, That's the kind of attitude.

17 Now, then that places the sponsor at a risk,
18 and it also places the regulator at a risk. It places
19 a sponsor at the risk because if the new drug is
20 positive and the historical, when it becomes available,
21 is negative, he's going to force to take 30 percent to
22 pull down his affect.

1 It's a risk to the regulator because if the
2 new drug is ineffective and the historical drug is
3 positive, that's going to boost up the delta. So there
4 has to be some kind of a dynamic way to allow borrowing
5 or else you should say we don't allow -- we don't allow
6 borrowing.

7 And maybe there are better ways to decide
8 without introducing biases. But I think that's
9 something that needs to be thought through and
10 discussed.

11 DR. BRETZ: I guess I'm not sure what the
12 difference between question one and two are. So I'm
13 trying to address both.

14 And I think I'm hearing multiple conversations
15 going on. And that makes the conversations
16 particularly interesting, I guess. But starting this
17 what we mean by a null space, Frank, if you mentioned
18 that you don't believe in the null hypothesis, you're
19 referring to two-sided null hypothesis. But what about
20 one-sided. And I would only think about one-sided null
21 hypothesis.

22 To me, that is important because if you think

1 about the null space, and then from a multiple testing
2 point of view in the closed test procedure, the strong
3 versus weak element control, then it kicks in in a
4 multi-arm trial, and you would have to think about
5 simulating all combinations of effective and non-
6 effective arms and the effect sizes.

7 If you think about an enrichment design, all
8 combinations of treatment effects and the subgroup and
9 the overall population. And if you think about
10 adaptation routes, depending on surrogate safety,
11 secondary endpoints, all these effect sizes would have
12 be to included if you think about the strong type one
13 error rate control. So this is one comment about the
14 null space.

15 Then I'm hearing another conversation which is
16 quote natural, Bayes versus frequentist, and maybe
17 overlaid or underlying that a type one error rate
18 control is necessary at all. And I don't think we have
19 the discussion today here. But that's why I like the
20 initial comment -- was it from you John or Lisa, that
21 simulation is not Bayesian versus frequentist.

22 It's -- and I like what Scott said, it's an

1 integration problem and I agree fully with that.

2 And if you think about just a quantile of a
3 standard normal distributions, the 1.96, we get it by
4 Monte Carlo. We can also get it by simulation, and no
5 one would ever have any problems because it's a very
6 defined simulation pattern, right, problem. It's a
7 well-defined integral, and we can solve it efficiently
8 or in this case inefficiently with Monte Carlo
9 simulations.

10 If you think of it by variate probability
11 where you have a nuisance, like the correlation
12 parameter, it is still tractable. It is a well-defined
13 integration problem because now you can go through the
14 grid different correlation values and you can kind of
15 understand what is your least favorable configuration.

16 That's quite possible numerically if you use a
17 very fine grid. But then, I think transparency is an
18 important topic when you -- when it gets more
19 complicated designs and more advanced problems. And if
20 you are thinking about how to define, if you -- I'm
21 hearing about accrual rate and historical data, control
22 rate changing, what is then the integral.

1 Probably you cannot write down the integral in
2 a closed form anymore. So you can simulate the trials,
3 and it remains somewhat an integration problem. But
4 it's somewhat a black box what actually your
5 integration problem is.

6 So this transparency I think is important, and
7 if -- I think one step ahead on -- if you think about -
8 - which is not a topic directly related to simulations,
9 but if you think about transparency of analytical
10 calculations, if you think about this deep neural
11 networks where you have hundreds of layers and
12 thousands of parameters, it becomes incomprehensible
13 what such an algorithm is doing.

14 So where is the boundary of transparency
15 versus then accepting algorithms for which you can't
16 follow anymore what's doing. So I see there's some
17 relationship. What's the necessary degree of
18 transparency in terms of the assumptions, of the values
19 being simulated or power of the simulation program.

20 If you want to evaluate it, I think these are
21 all interesting questions, I think very difficult
22 questions from as far as I'm concerned.

1 DR. PRICE: So we'll move to question two.

2 And I think question two has two parts.

3 How should error rate simulations be conducted
4 when formally borrowing prior information such as in a
5 Bayesian framework, and what does type one error mean
6 in this setting? Should we consider other error rates
7 instead?

8 And just looking at our time, if someone also
9 wants to respond to question three, what are some
10 practical suggestions for implementing trial
11 simulations. Feel free, and I see quite a few cards.
12 So Dr. Price?

13 DR. K. PRICE: Thank you. So I am going to
14 sort of combine two and three I think in this response.
15 So foundationally, I think we can just think about
16 error rate simulations generally, and how best
17 practices, and then talk about some additional
18 components that might be relevant in a Bayesian
19 framework, some additional pieces that would need to be
20 included.

21 So in terms of best practices, obviously you
22 need to have a really good simulation strategy that's

1 laid out ahead of time clearly articulating the
2 objectives, how will virtual patients be generated,
3 methods for ensuring that how -- what you intended to
4 generate was actually what was generated, methods for
5 how you analyze the data, things around have your
6 simulations converged, and there are graphical ways
7 that you can do this.

8 I would argue that one area we could improve
9 is our ability to graphically think and look at
10 summaries of simulations. Maybe there are some
11 interactive tools that could be developed to help look
12 at the simulation properties.

13 And then of course with -- if you have a
14 prior, what is that choice of prior, maybe exploring
15 some alternative options to show prior posterior
16 sensitivity, looking at convergence of the prior and
17 things of this nature.

18 So I think that there are -- there are some
19 references that can be included here where people have
20 talked about best practices, some of these coming from
21 the adaptive design working group years ago, some
22 coming more recently from Bayesian scientific working

1 group and others as well. So I think building on those
2 would be really important.

3 The one last suggestion that I think is very
4 helpful, and I've heard some others mention this, is
5 sometimes just looking at examples, like specific
6 clinical trials that have been simulated, and how this
7 plays out.

8 You know that's something, Scott, you've shown
9 in the past. And so, those types of things, always
10 looking at maybe certain edge cases or where weird
11 things happen so that we can have a conversation about
12 why that happened. Those types of things seem -- would
13 be good. Thank you.

14 DR. PRICE: Dr. Berry?

15 DR. BERRY: So this is a great question, and I
16 swear if -- in a weird way, I enjoyed John struggling
17 with this question and physically grappling with it
18 because it's really in a situation -- and I understand
19 Cyrus' point about borrowing information.

20 But in a situation where is deemed reasonable,
21 the data is deemed reasonable, that this is a good
22 thing to do for drug device biologic development,

1 you've already started with a leg up. There's a reason
2 to bring the data in, to go back and simulate from a
3 null and say, aha, the chance of approving this drug is
4 11 percent because I'm using data that already gives it
5 a leg up. It's a weird type one error because we've
6 already said we actually don't believe it's very
7 likely, you know, that even within some small delta of
8 that.

9 Now you can say okay, well let's go back to
10 before that data was observed and then simulate that
11 data being generated and then go and what about that
12 whole process? But it's hard to go back and
13 retrospectively generate what data could've been there.

14 If you're in a situation where you believe it
15 was cherry-picked, I don't think anybody here thinks
16 it's reasonable to use that data, that we're doing
17 multiplicities and bad science, and I don't think
18 anybody would be in that situation.

19 There are more complicated scenarios where
20 you're in an antibiotic situation or borrowing from a
21 previous trial and the control. You inflate type one
22 error when you borrow information even on the control.

1 Every single arm study has type one error of one in
2 different situations. But we allow them to happen
3 because we have a certain comfort with them.

4 So I think we should simulate different,
5 quote, unquote, "type ones" and understand the
6 unlikeliness of them or the behavior of that, but not
7 live under this framework that you have to be 0.025 or
8 less.

9 Otherwise, you would've never borrowed the
10 data in the first place, and understanding what is
11 reasonable in that scenario is a very common thing.
12 And Telba made reference to this. We've done this with
13 Telba several times before. And it changes the
14 conversation of the balancing of these errors as
15 opposed to the control at a certain level.

16 DR. PRICE: So we'll move to Dr. Lee and then
17 Dr. Emerson, and then we'll open the floor up to the
18 audience.

19 DR. LEE: Thank you. So I'd like to give some
20 comment on question number three, what are the
21 practical suggestion for implementing trial
22 simulations?

1 Well very simply, make the tools available,
2 okay, to people, and then there are some -- you know,
3 make sure that it's easy to use, and, you know, it's
4 well-documented and it's reproducible. And actually
5 Karen brought up a very good point, is that you need to
6 provide some graphical assessment so that people can
7 see, you know, how things work.

8 And for me, the eye-opening thing is when I
9 start to learn about how Bayesian method works and how
10 simulation, you know, can be conducted. People asked
11 me -- some people asked me during the break. You know,
12 I mentioned briefly about the software developer at MD
13 Anderson. And let me just say it again. If you Google
14 MD Anderson software, download our software online,
15 okay, or even go to trialdesign.org, you know, you can
16 get those freely available. I don't know if it's out
17 of the line or not, you know?

18 If there's Internet, you can just type
19 trialdesign.org and there are many tools available, you
20 know, from learning the Bayesian method for both binary
21 endpoint, continuous endpoint and time-to-event
22 endpoint or design trials, give you the stopping

1 boundary, you know, of say Bayesian toxicity monitoring
2 or efficacy monitoring and then give you operating
3 characteristics. And even you can actually run the
4 trial using some of these method, and you can actually
5 also in some cases, after you design the trial, it can
6 give you the template that provide the statistic
7 consideration section in the protocol

8 So anyway, my passion in academia is that try
9 to make the tools freely available to people so that we
10 can learn and we can improve, or in some cases, you
11 know, we can debate the choice of the prior and what's
12 the impact of the prior, et cetera. But it's all
13 there, okay?

14 So as long as the tool, you know, is
15 available, and is reproducible, and we can -- or, you
16 know, agree -- you know in some case, we can agree to
17 disagree, right? And but again, the thing is make it
18 transparent, make it -- you know, kind of useful,
19 reproducible, then we can make improvement upon it.
20 Yeah.

21 DR. PRICE: Dr. Emerson, did you have one
22 final comment?

1 DR. EMERSON: So, you know, in talking about
2 how we implement these simulations -- and Scott made
3 reference to the guidance's, you know, less well-
4 understood methods.

5 And I guess some of my contention is actually
6 what's less well-understood is actually the statistical
7 methods interacting with the adaptive methods rather
8 than just the adaptive methods themselves, is that
9 there's less room to not understand the statistical
10 methods you're using and still have it be valid.

11 And the idea that particularly our methods are
12 often presuming such things as we're using sufficient
13 statistics at all times in their adjustment and there's
14 no other information in the data.

15 And, you know, Roger made a very good point of
16 saying, well, simulations -- we have to really -- it
17 has to be pre-specified for us to simulate this. But
18 to then take these simulations and believe that they'd
19 ever carry forward to fully adaptive, not pre-specified
20 is very dangerous because there can be additional
21 information that's never been considered in that
22 setting.

1 In simulating this, one question particularly
2 for simulating Bayesian methods, you know, I don't know
3 whether I'm -- you know, after Bayes estimators or mini
4 max estimators sometimes, and realize that as you take
5 a prior, you're averaging over lots of individual
6 alternatives.

7 And when is it better to maybe sort of do a
8 tipping point analysis of saying here is a fixed
9 alternative that we behave less well in, and then later
10 you can average in to say yeah, but I don't really
11 believe that that much, rather than always averaging
12 over those. So it has some issues.

13 And then, as Cyrus pointed out, you know, to
14 be really certain what the type one error was, it can
15 be prohibitive. And so the question is how do you
16 decide what's there. And I'll just say what I tend to
17 do is I take our standard frequentist methods that
18 nobody blinks at and say what really is the type one
19 error in those situations and how high can it go.

20 And recognize that on the type one error, if I
21 take my simplistic world of a binary decision space and
22 a binary parameter space, the Bayes factor is the power

1 divided by the type one error. It's multiplicative.

2 And so, what sort of multiplicative increase
3 in our type one error will be accept? And if you just
4 take the standard chi-squared statistic that we take
5 all the time and don't worry about it, it's -- we don't
6 have to pick out 0.026 versus 0.025.

7 You know, we'd feel fairly comfortable with
8 0.027, 0.028 and adopt those standards and just say
9 yeah, it's -- we don't need that precision. We just
10 need to be a standard that people can operate on and
11 define what the level of precision we need to be
12 certain we're okay.

13 DR. PRICE: So we have time for comments or
14 questions from the audience. Dr. Louis?

15 AUDIENCE Q&A

16 QUESTION: Just a comment. Tom Louis, from
17 Hopkins. Sitting here listening, I really got
18 impressed by the power of simulation really as a
19 catalyst. Even if you were to never simulate, the
20 conversation that's happened for the last hour or so
21 just wouldn't happen if you couldn't imagine simulating
22 and have a discussion range widely about things that we

1 couldn't do analytically.

2 And so, I'm not saying we shouldn't simulate.
3 We absolutely should. But it's a little bit like the
4 bootstrap. Discussing what you would do is almost as
5 informative as doing it. And so, I really think
6 simulation's role in getting a conversation going in a
7 way that's hopefully biologically and statistically
8 complex is important.

9 And then another comment, just sitting here
10 reminded me of a conversation I had with Brad Efron
11 about 10 years ago when he said Bayesian's get all the
12 glory, but frequentists do the hard work. And the
13 simulation exercise is pretty much a frequentist
14 activity.

15 QUESTION: Jonathan Smith, Adaptive Plus. I
16 want to -- first of all, let me say that my comments
17 are really in relation to frequentist designs where
18 there's no adaptive randomization and we are saying we
19 have to control -- have strong control for type one
20 error.

21 The first comment is that there are many more
22 situations where we could actually use a numerical

1 integration rather than have to use simulation. And
2 that's quite often plausible, up to maybe six
3 dimensions, perhaps even more.

4 Then if you are using simulations, I think
5 that it -- this may be a couple of strategies that are
6 useful to try and get to the maximum.

7 The first is perhaps start off with a fairly
8 wide grid across each of your factors. Try and find
9 the area where -- or areas where the maximum type one
10 error lies. Perhaps use Scott's idea of modeling to
11 try and hone in on that region. And then, once you've
12 got closer to that region, then run your simulations,
13 maybe with 10 million, 100 million.

14 Another option would be to consider maybe
15 you've got five factors that impact your type one
16 error. Rather than looking at a complete factorial
17 approach to your grids, maybe instead of -- I don't
18 know, if you've got five levels of each of your
19 factors, instead of looking at that, you could start
20 out with a factual factorial, maybe 125th of the 55
21 factorial, which is only 25 different cases. And
22 that's going to give you a lot of information. So

1 those were just a couple of comments. Could I make one
2 more, or --

3 DR. PRICE: Briefly.

4 QUESTION: Sorry. One more comment, a
5 slightly different topic, and that's the follow-up from
6 Frank's comment about whether we need to consider type
7 one error under situations where an effect size could
8 be in the opposite direction.

9 And I think that in the subgroup situation,
10 that maybe is the one place where that often comes up,
11 and we've certainly seen situations with -- where a
12 biomarker negative subpopulation does have a negative
13 treatment effect. Okay. Thank you.

14 DR. PRICE: Since we do not have any
15 additional questions from the audience, I'll return to
16 the panel because we have a couple more minutes. Dr.
17 Mehta, I had actually skipped you because we were going
18 to the audience. Did you have a comment to make?

19 DR. MEHTA: No.

20 DR. PRICE: No? And does anyone else on the
21 panel? Dr. Harrell?

22 DR. HARRELL: I think it was Scott that

1 addressed this about having a fixed, unknown parameter
2 you're simulating from. Was that you that just hit on
3 that a few minutes ago?

4 DR. EMERSON: Sure.

5 DR. HARRELL: Well, I don't know which Scott
6 it was.

7 DR. PRICE: Scott.

8 DR. HARRELL: It was one of the Scotts, maybe.

9 DR. BERRY: What's your prior probability was
10 he or me?

11 DR. HARRELL: Yeah. So the thing I wanted to
12 mention is the -- when I think about that issue, I
13 think about what is the purpose of Bayesian inference,
14 is to -- is to take whatever the world is throwing at
15 you and be able to gain knowledge about what that thing
16 was.

17 So you're trying to -- you're trying to make a
18 prediction or an estimate. You're trying to recover
19 what was not known and to make it more known. So in
20 that way of thinking, the way you would do a simulation
21 is you would have a whole variety of unknown values and
22 you would ask the Bayesian procedure to what extent

1 could you recover those unknown values, whatever they
2 were.

3 And that's actually much different than doing
4 a simulation that sets the unknown value to a constant
5 and finds out some operating characteristic, Bayesian
6 or frequentist. If you're trying to recover that
7 constant, you could never recover the constant.

8 You never would, no matter -- unless your
9 sample size was infinite. But those two ways of
10 simulating are much different, and I -- the Bayesian
11 one to me is more natural because I'm trying to recover
12 whatever it was that was generating the data.

13 DR. EMERSON: So I think you are responding to
14 me, and we'll discuss whether it was well or not.

15 The problem that I have is so often I face
16 post hoc interpretations of data that are radically
17 different from what the interpretations had been
18 beforehand. And it's impossible to, you know, in any
19 prior anticipate something that you never expected to
20 be the case.

21 And so, all I was advocating is that finding
22 the limits of, you know, point priors, if you will, as

1 well as what an average effect is, is something
2 worthwhile because as I was just remarking in a sidebar
3 to Frank, is that I have been on DSMBs as many times
4 where the treatment effect turned out to look harmful
5 at a magnitude that they were looking for it to be
6 beneficial as I have found that have materially turned
7 out to be that beneficial.

8 And nobody started the trial thinking it was
9 harmful. And if you elicited priors forever, nobody
10 would've given you that prior. And so, by trying to
11 find those limits, think of it as a tipping point
12 analysis. That's additional information, and then at
13 the end you can say how unlikely you think it is.

14 DR. HARRELL: Just one slight rejoinder. I
15 think most people would use a prior that would allow
16 for that to happen.

17 DR. EMERSON: But populations of priors are
18 what matter. So I don't like consensus priors. And in
19 fact my -- it is a polling. We're trying to go our to
20 the population of scientists and see how many we've
21 convinced. We're not trying to see if we've only
22 convinced the average person.

1 And so, it is relevant to me also to say I
2 don't have to prove things to everybody. But have I
3 proved it to 95 percent of scientists, 90 percent of
4 scientists, and that also helps.

5 DR. PRICE: Dr. Permutt?

6 DR. PERMUTT: I want to go back to this
7 question of how big a space and can we limit ourselves
8 to clinically plausible values.

9 And you all design trials, and you've
10 addressed it appropriately from a point of view of
11 trial design. But let me ask you a question as a
12 regulator that maybe you can advise me on.

13 After the trial is done, we have a lot more
14 information about the nuisance parameters than when we
15 started. As a regulator, can I confine myself to the
16 values of the nuisance parameters that are plausible a
17 posteriori, and not necessarily worry about possible
18 configurations of parameters that have by now already
19 been more or less ruled out?

20 DR. PRICE: Dr. Berry?

21 DR. BERRY: So I brought this idea up, and I'm
22 sitting next to Dr. Meurer, and we have a trial, a 10-

1 arm cooling trial after cardiac arrest. We don't know
2 how long to cool, so 10 different arms, inverted u-dose
3 response, Bayesian primary analysis of whether or not
4 cooling actually helps, even though we don't have a
5 zero cooling arm. Really quite hard to analytically
6 understand the characteristics.

7 It depends on the distribution of modified
8 rank and scores. Are they more towards zero? Are they
9 more towards six? We simulated a wide range of these,
10 and then we created a complete plan prospectively that
11 we submitted to the agency. This was the center for
12 devices.

13 This is how we're going to simulate it after
14 the fact. We're going to condition on what we observed
15 for these nuisance parameters and re-simulate it,
16 because we had to do this grid search for type one
17 error.

18 And we're going to plugin those values, re-
19 simulate it, and what we're going to bootstrap the
20 actual values of the patients, ignoring the arm that
21 they came from, to just further explore this type one
22 error.

1 And we're not going to then adjust the final
2 criterion, but we might report that the trial had 2.54
3 percent type one error. We believe we've covered the
4 space. But this gives us additional after the fact
5 simulation of type one error where we plug in nuisance
6 parameters that are now known.

7 DR. EMERSON: Or at least now estimated. So
8 that they -- and you know, realize -- and again, when
9 you look at standards and what we do -- I mean, this is
10 standard sort of maximum likelihood idea of you take
11 the estimate of the nuisance parameters and then you
12 just look at what the variability is conditional on
13 that.

14 Now, we know however that that doesn't work
15 entirely, and we know that bootstrapping can't work,
16 but maybe double bootstrap can. And we have to worry
17 about the fact that always our alternatives are
18 counterfactuals, right?

19 We're saying gee, I observed a difference of
20 10 in the means. Could this data come from where --
21 when the difference was really zero? Well, if I was
22 that far off on the mean, then how far off was I on the

1 variance? And the central limit theorem says
2 concentrate on the first two moments, because we blow
3 apart all other information in the data.

4 And so, thinking about what the variances
5 might do under these various alternatives. So the most
6 I can come back to is sort of the thing of saying well
7 we're sort of back to standards here, aren't we? We
8 don't ever know the exact truth, and people can -- a
9 mean variance relationship is never identifiable
10 because it is a counterfactual.

11 It's saying that the data -- you know, if our
12 data is wrong in some sense, then it can be wrong on
13 what that variance would be under something else. But
14 we can come up with standards, and we can come up with
15 standards that may not be perfect for the problem at
16 hand but that are on average okay.

17 And so, I do tend to worry about -- again,
18 it's all just do tipping point analyses with
19 everything. But I look to say how bad does it have to
20 be? How bad does our current data have to be before I,
21 you know, can't trust this at all?

22 And then you sort of go forward. The more

1 that the nuisance parameters are not totally nuisance
2 and are really more correlated with what your effects
3 are, the more trouble you're in.

4 But the other comment is focusing on what's
5 plausible, there's all definitions of what's clinically
6 plausible. So while I just did both, you might tell me
7 that you don't think it's plausible that the
8 treatment's harmful, whereas I'll always say oh, yes it
9 is.

10 But I'm not usually going to put hazard
11 functions that are step functions. They're going to be
12 fairly continuous, and I'll restrict myself to
13 continuous hazard functions on my data.

14 DR. PRICE: So we're going to move into our
15 break. I encourage panelists who I didn't get to, to
16 have offline discussions during the break, and we'll
17 reconvene in --

18 MS. BENT: 15 minutes.

19 DR. PRICE: -- at 2:45.

20 (Whereupon, the foregoing went off the record
21 at 2:35 p.m., and went back on the record at
22 2:49 p.m.)

1 DR. PRICE: So we will move into our final
2 session for today. We are being cognizant of the
3 weather, so we will do our best to end no later than
4 4:15, and if we are told that we need to push that up,
5 we will.

6 So first I would like to have my two
7 colleagues, who are joining this panel to introduce
8 themselves, starting with Dr. Johnson.

9 DR. JOHNSON: Laura Lee Johnson, Office of
10 Biostatistics in CDER.

11 MS. KRAUS: Stefanie Kraus. I'm a regulatory
12 counsel with the Office of Regulatory Policy in CDER.

13 SESSION IV: COMPLEX INNOVATIVE DESIGN PILOT PROGRAM
14 PRESENTATION

15 DR. PRICE: Thank you. So the final session
16 will focus on the complex innovative design's pilot
17 program. The pilot program will have many goals,
18 including an increased awareness of the value of
19 complex innovative designs in a wide range of
20 therapeutic areas and increased learning and sharing,
21 both internally at FDA and externally to FDA.

22 I could name other goals, but I think we're

1 all gathered today with the anticipation that use of
2 complex innovative designs will further enhance drug
3 development, which ultimately translates to benefit to
4 patients, and our overall public health.

5 The purpose of this session is to engage in
6 discussion and obtain input on the pilot program from a
7 broad range of stakeholders. I will only give a high
8 level overview of the pilot program as found in PDUFA
9 VI.

10 Today's discussion will be used to further
11 inform our thinking on various aspects of the program,
12 as well as implementation of the program.

13 Next steps for the FDA will include a Federal
14 Register notice announcement of the pilot program as
15 well as development of a CID website, CID being complex
16 innovative designs, with all pertinent information.

17 So under PDUFA VI, the FDA will conduct a
18 number of activities that confirm our commitment to
19 advancing the use of complex innovative designs.

20 The activities include development of staff
21 capacity, conducting a pilot program, again a focus on
22 this session, convening a public workshop, such as

1 today's meeting, publishing draft guidance and
2 developing or revising relevant manuals of policies or
3 procedures and standard operating policies and
4 procedures.

5 The pilot program is designed for highly
6 innovative trial designs for which analytically derived
7 properties may not be feasible. And simulations are
8 needed to determine trial operating characteristics.

9 Sponsors may submit designs to the program,
10 and those selected will have the opportunity for
11 increased engagement with regulatory staff through two
12 meetings.

13 FDA will select up to two proposals per
14 quarter. The agency will use the designs as case
15 studies for continuing education and information
16 sharing.

17 In terms of the increased interactions, FDA
18 will grant a pair of meetings consisting of an initial
19 and follow-up meeting on the same design to occur over
20 a span over approximately 120 days. The meetings will
21 be led by the statistical review components within CDER
22 and CBER, but will be multidisciplinary.

1 So there are a number of elements of the pilot
2 program that we're currently working through and we
3 welcome discussion on these points today from the
4 panel.

5 The elements include eligibility or selection
6 criteria for the program; timelines, for example,
7 timelines for submission of proposals, for selection of
8 proposals, for review of proposals and for feedback;
9 submission expectations, for example, what are some of
10 the key elements for the proposal versus the meeting
11 package and are they the same; disclosure, so a unique
12 aspect of this CID pilot program is the FDA's ability
13 to publicly discuss example designs to provide clarity
14 upon the acceptance.

15 Before granting the initial meeting, FDA and
16 the sponsor will agree on information that may be
17 shared publicly; communication, this could include a
18 communication strategy between FDA and sponsors of
19 selected proposals, as well as strategies to inform the
20 broader audience.

21 So before I go to our two reactants, I will go
22 over the discussion points. The FDA will select two

1 proposals quarterly for entry into the pilot program.
2 The proposals will need to capture sufficient details
3 to facilitate an understanding of the design analysis.

4 Discuss specific elements of the design and
5 analysis that are important for the initial proposal.
6 Discuss types of trial designs that should be
7 prioritized for selection into the pilot program and
8 discuss factors that might inhibit or encourage
9 submissions for the program.

10 So I would like to ask our first discussant to
11 provide remarks, and that will be Dr. Lieberman.

12 DISCUSSION

13 DR. LIEBERMAN: Thank you very much. So I
14 think we've heard a lot here about flexibility and
15 creativity. And the pilot will definitely require some
16 flexibility, creativity, mutual understanding, patience
17 on especially the sponsor side and transparency in
18 decision-making, both on the FDA side and the sponsor
19 side, as well as communication, very clear and open
20 communication constantly.

21 The thing -- maybe before we go to some of the
22 timelines, and I leave to my other speaker some of the

1 other topics, but before I go to some of the timelines
2 and submission materials, I think it's important to
3 emphasize that even though this will be statistical
4 meetings, it would be nice to understand the role of
5 the clinical reviewers, and so their acceptance of the
6 study designs because it's not just statistics, but
7 it's the endpoints. It's the selection of the
8 populations. And all of these factors will influence
9 the simulations, right?

10 And then, if it's a study involving
11 diagnostics, will CDRH be involved? Will they be part
12 of the meetings, be able to at last say yes, the data
13 that will be generated from this study will also
14 support a filing for a diagnostic. So I think all
15 these will be important.

16 And then, we talk about timelines. You want
17 to think of the flexibility because every sponsor has
18 their set of own metrics of what is fast and how fast
19 they want to move and what are the risks they're
20 willing to take, and different types or kinds of
21 developments.

22 So sort of it's hard to say that one size will

1 fit all. And what I mean by this, some sponsor may say
2 well, we like to as fast as possible go forward after
3 the end of phase meeting. So when we reach our
4 agreement, one month or two, we'll ready with our
5 protocol we're running.

6 This may be all very well. But then where do
7 you accommodate the 120 days between the meetings and
8 the timelines? Other sponsors might say okay, we're
9 not rushing. We're going to take more time.

10 So if we're going to look at this, somebody
11 says yes, we're going to apply like six months, way
12 before the end of phase meeting, and start the whole
13 process. But will there be enough information at
14 endpoints?

15 Will there be enough information on the
16 populations you want to select? Will there be enough
17 information on the safety data to make the right
18 decision about all the simulations and the right study
19 designs?

20 Well, maybe the statistics will be hemmed out.
21 But then if the parameters change, it's a risk to the
22 sponsor if things change. So then there's the

1 flipside, let's wait. Let's wait with all the
2 materials. When we're really ready, we submit more or
3 less at the same time as we ask for the end of Phase II
4 meeting.

5 Okay, well that means that the timelines will
6 push us and we're going to have to look at -- we are
7 going to be far after what we normally'd like to do,
8 two months after end of phase meeting, ready to go with
9 a final protocol. So I know these will be the
10 considerations that the sponsor will take.

11 So sort of when you think about it in
12 summarizing, I think it will be nice to think that
13 there's going to be a window that the sponsor could
14 submit their information, and just don't be strict
15 about it. Oh, it has to be right at the time of the
16 package for end of Phase II meeting, or it has to be x
17 weeks before or after, but put a window around it.

18 When we looked at it through the bio company,
19 we said, you know, it could be anywhere between 60 day
20 ahead to almost -- to a few days beforehand. And then
21 that will sort of define what is really in the
22 submission.

1 If it's close to the package, then the sponsor
2 can reference a lot of the information in the package
3 because that will help the clinical reviewers
4 understand the study better.

5 If it's way before the package is ready, then
6 maybe they need to be more information, not just about
7 the study design, not just about the statistics, but
8 also a little bit within the context of the whole
9 development program to allow more sort of a better
10 perspective on the material.

11 It would be nice to understand, you know, what
12 is the timeline for getting response to the
13 application. Could it be a month to 45 days,
14 especially if there has to be negotiations about the
15 disclosure of relevant material?

16 So sort of say, you know, after two weeks if
17 there is no issues about disclosure, there's just --
18 the sponsor will know. You will know the answer in an
19 additional two weeks. But if we have to discuss
20 disclosure, it might take another month.

21 The other thing is sort of, okay, after the
22 acceptance, what is the time? What is -- and part of

1 it is can we preschedule the meetings at risk ahead of
2 time or what is the feasibility of scheduling a meeting
3 once the acceptance happened? Could it happen within a
4 month? Is it even feasible, both for the agency and
5 the sponsor? It may not be.

6 So maybe there's a way of sort of thinking
7 ahead of time of how do we don't have these wide spaces
8 between the times we make a decision. Oh, now it's
9 going to take us two months to schedule a meeting. Can
10 we be flexible of how we think about this?

11 Then the sort of -- the next step would be,
12 you know, the meeting between the two statistical
13 meetings. I would expect that the 120 days is really
14 for the statisticians at the FDA to run the
15 simulations.

16 So if it's a heavy simulation project, yes.
17 But if it's not, is there any feasibility to sort of
18 making the meeting 90 days or less, so negotiating
19 that, depending on the scope of what needs to happen
20 between those two meetings.

21 And then, how do we sort of, you know,
22 communicate through the whole process? It would be

1 definitely good both on the sponsor side to have,
2 especially if it is heavy statistics, if there is
3 interesting topics, somebody from the sponsor being
4 really the key contact person, but also have someone on
5 the FDA being the contact person for the study so there
6 is clear communication.

7 I would also envision that the packet, that
8 the submission is different than the sort of meeting --
9 material meeting presentations. But that maybe does
10 not have to be sent like weeks ahead, but maybe just
11 two, three days before the meeting. And that would
12 include, I assume, all the details of the statistics,
13 all the simulations information that will be then
14 discussed at the first meeting.

15 And the same thing if there is a review of the
16 statistical sort of design on the agency side prior to
17 the second meeting, it would be good for the sponsor to
18 get sort of overview of what happened, at least few
19 days before the second meeting so that they can look at
20 that react, versus coming to the meeting and here are
21 all the problems that we found with your design, right?

22 So sort of allow that flow of information. So

1 that's why that 120 days is probably critical to allow
2 for this to happen. So it might be hard to do. And of
3 course, I would envision that any documentation, any
4 simulation results that that would be submitted in the
5 standard form.

6 I believe there were some of -- in the
7 previous session sort of ideas of what the reports
8 could entail, so that would be another thing. And I
9 think that I might stop here and let me friend
10 continue.

11 DR. ZHONG: First, I would like thank the FDA
12 and our colleagues from the industry and also from
13 academia who come here to have this discussion.

14 The FDA this initiated this innovative
15 clinical trial pilot program. Actually shed a light on
16 the new era of drug development and gave a lot of
17 confidence to the sponsors.

18 As a lot of people pointed out early on,
19 there's a lot of misconception either in the industry
20 or somewhere. It may or may not be in the agency, but
21 somewhere. Maybe because of lack of issue with the
22 opportunity for innovation, right?

1 So first I would like to make a statement
2 there, thank you. And secondly, I have to be fully --
3 I have to fully disclosed that Gracie and I are
4 coordinated, and that's why she did not touch all the
5 points there, and she -- we can spell out on what we're
6 going to talk about.

7 And third, I mean, I agree to you -- make a
8 transparency that the points I going to talk about
9 actually coming from some consensus from the bio group,
10 also some from the pharma workgroup as well. It's not
11 purely my personal belief. It's some consensus form
12 there.

13 So first let me touch on the entry criteria.
14 For the entry criteria, I mean we completely agree with
15 agency that I mean the whole purpose here -- actually
16 the pilot program is to promote public learning, like
17 in -- and promote statistical innovation and all
18 innovation in health.

19 And the type of designs that Lisa early on,
20 presented actually kind of hit the nail on the head.
21 That's the kind of design that we need to see, okay?
22 Even though as Lisa point out, maybe statistically it

1 may not, so in a way, but regulatory, it is innovative.
2 That's the point I make early on. That's the
3 opportunity for us to bring more awareness on the
4 openness at the agency and to the whole industry to
5 kind of bring the innovation to product development.

6 And also, some speakers early on also said
7 let's focus on those kind of designs that used to be
8 labeled as not so well-understood designs. Yes, and
9 we're all in agreement there.

10 And those innovative design that the agency or
11 the industry have less experience with, even though it
12 could have been used in one or two indications, or by
13 one or two other companies or divisions. But just
14 because of misconception there, it's good to take those
15 trials into the pilot program.

16 And then, the third is focus on candidate on
17 pre-clinical trial stage. People try to define it as
18 have they impact on drug application, like the DRA,
19 NDA, like focus on those first. We all know that a lot
20 of innovative designs have been used in early trial
21 designs, and FDA never discouraged those. We all
22 understood that. But I mean, the issue is could we use

1 them to establish the evidence to inform regulatory
2 decision on drug approval? So this is area that we
3 would like to focus on.

4 And lastly, the entry criteria should be like
5 a -- I mean, like sponsors of the applications should
6 be amenable for public discussion, to encourage public
7 learning, learning at the agency, at industry and
8 others in the statistic community as well.

9 And of course, talking about disclosure, it's
10 not like we're going to disclose everything. I mean, I
11 think the feedback from the companies -- I mean, is
12 that what we should consider is that -- I mean, is only
13 disclose information that is necessary to promote
14 public learning instead of disclose everything, right?

15 I mean, we all heard from agency that, well,
16 disclosure must be a negotiation between the sponsors
17 and the agency, and then the -- but when we talk about
18 the -- there needs to be a certain element that is to
19 be disclosed, right?

20 Most companies are more open to disclose on a
21 design element, such that mostly will likely to be
22 statistical aspect of those kind of elements there.

1 So when we disclose things like product,
2 please do not disclose those things. You can use drug
3 A, drug B instead of exactly which product is, or even
4 a disease.

5 A lot of companies are not comfortable with
6 disclose which disease the company is targeting on. So
7 those kind of information is not necessary to say. But
8 I'd also like endpoints. Endpoints, you don't have to
9 disclose the definition endpoints, but you can disclose
10 if it's confused endpoint, ordinal endpoint or like
11 cardinal endpoints. You can disclose these information
12 like that.

13 And then in terms of statistics, like sample
14 sized or maximum sample or expected sample size, like
15 the power determination. Maybe we don't talk about
16 power. But the false positive rate or false negative
17 rate, all of those things. I mean, and then the
18 simulation, I mean, we talk a lot about simulation.
19 And the simulation is a thing that we all need to
20 learn.

21 And in terms of simulation, I mean we're
22 hoping that we can disclose as much as possible, but

1 has to be compiled with sensitivity and confidentiality
2 of the companies. So that's about the disclosure. I
3 mean there's a -- I mean the bio group actually submit
4 a recommendation on the disclosure. But I'm not going
5 to go through the whole thing, but I picked up the
6 highlight there on it.

7 And then for the communication -- this
8 communication is also something that's very critical
9 for the success of the pilot program and for the
10 encouragement of the companies, sponsors to participate
11 in the pilot program as well.

12 So we kind of think that this would be good if
13 the agency could identify certain elements, working
14 with different working groups and sponsors to certain
15 elements to disclose on a website, some -- like a
16 website or in a certain form so that, I mean, all the
17 companies who wanted to participate in the pilot
18 program will have the opportunity to know what the
19 status is.

20 I make one suggestion is that in order to
21 promote public learning, I mean, the entry criteria
22 there that we would like to look into all different

1 types disease area and still focus on one disease area,
2 focus on looking all the different disease area, and
3 also don't focus on only one trial design type, but
4 focus on different product design choice.

5 Yeah. So that's what we'd like to have, and I
6 also want to point out, I mean, the bio group actually
7 have a list of the elements that -- who I recommend to
8 the agency that we would like -- usually the companies
9 in consensus would be able to discuss on like what kind
10 of information can we disclose on a website or some
11 public forums, allow the transparency to the public.

12 PANEL DISCUSSION

13 DR. PRICE: Thank you. There was a lot in
14 both of those comments. We are going to open the
15 discussion up to the broader panel, beginning with Dr.
16 Lewis.

17 DR. LEWIS: Okay. Thank you. A couple of
18 just comments about the characteristics of the
19 selection process are things that one might want to
20 consider. One has to do with the diversity of
21 sponsors.

22 Obviously it's important that traditional for-

1 profit sponsors be represented in the program. But as
2 was mentioned earlier by Dr. LaVange and others, some
3 of the work that we're seeing in master protocols is
4 driven by things like patient advocacy groups.

5 And one of the things that the agency may be
6 able to do to lower barriers, to research efforts in
7 some diseases, and the multidrug-resistant bacterial
8 pathogens is one that is near and dear to our heart, is
9 to support the design efforts of these patient advocacy
10 or other nontraditional sponsors to develop protocols
11 or master protocols that have some indication that they
12 would be acceptable to support regulatory decision-
13 making because that's a -- the uncertainty in that
14 regard is a barrier to sponsors then being willing to
15 submit their compounds for testing in those platforms.

16 A second has to do with the likely nature and
17 complexity of the simulation code that would ultimately
18 be required to validate the design. One of the
19 questions we get asked very frequently is do you have
20 examples of publicly available code that people can run
21 to really learn what it takes to write a simulation
22 that is realistic enough to inform decision-making.

1 And I think there's unfortunately relatively
2 few examples of that in the public domain. So within
3 the diversity of proposals that would need to be
4 represented in the program, it would be nice that if
5 there was at least some in which when we anticipated
6 that the code be able to be publically released and
7 would be written in R or some other widely available
8 format so that we could help to develop expertise in
9 the broader community to do those kinds of simulation.

10 And then the last, which I'm afraid is maybe a
11 little contradictor to the comments of my colleague, is
12 the importance of concreteness. When examples are
13 anonymized, they lose a lot of the power that they
14 have. A lot of people are looking for very specific
15 examples of something that was a successful design
16 effort.

17 And so, I would hope that at least a subset of
18 the proposals that are accepted into the program are
19 developed in a context in which they can be as concrete
20 as possible with respect to the clinical disease
21 endpoint and other considerations because this is an
22 area of clinical trial design where the -- those

1 clinical details are supposed to inform the design
2 because the design is intended to be customized to
3 those details.

4 So when you anonymize them, you break the link
5 between the very information that is intended to inform
6 the design and the design itself, and that will lessen
7 the value of the examples.

8 DR. PRICE: Thank you. Dr. Chan?

9 DR. CHAN: Yeah. Very good comments provided
10 in some of these discussions. And I just wanted to add
11 couple things. One is that related to the elements
12 obviously we talk about some clear layout or simulation
13 plans.

14 And I think part of that is how having a clear
15 layout and the simulation plan under code to allow
16 whether it is FDA reviewer or third party actually to
17 do a peer review, or even better, to do a validation of
18 the code. So those definitely needs to be part of the
19 elements.

20 But then in terms of the study design, I was
21 thinking whether FDA actually also would willing to
22 entertain maybe just on the program level, not just on

1 the study per say, because sometimes you need --
2 actually when you're thinking about a drug development
3 program, there's several aspects that actually from one
4 study or another study, they involve a lot of
5 simulation or trying to do the monitoring to help
6 select the dose and things like that.

7 So I wonder whether FDA would be open to
8 consider sort of a serial study as one -- or a program,
9 how that pan out.

10 And the third comment or question is in terms
11 of communication time. I notice to you -- submit a
12 program and FDA have an interaction review, but for the
13 transparency -- for the public to understand, I wonder
14 how long it would take for the FDA to actually share
15 the study design, even though the study may still be
16 ongoing.

17 But there's certain elements can start to be
18 shared throughout the community so that the next batch
19 of the program can be balanced along those lines.

20 DR. PRICE: So I don't know that we have
21 answers to those questions. But they're definitely
22 points that we will consider. Dr. LaVange?

1 DR. LAVANGE: So I'm not exactly answering
2 this question, but I just wanted to make a few general
3 comments about the program as we envision it.

4 So first, I wanted to give Estelle Russek-
5 Cohen out there in the audience some credit because she
6 was really the brains behind this pilot program during
7 the PDUFA negotiations, and is particularly the part
8 about being able to talk openly about the designs so
9 that better information about what FDA will accept or
10 not accept you know is out there.

11 Second, we'll -- may get into this today, but
12 it'll be better explained when the Federal Register
13 notice comes out announcing the pilot. But we did
14 envision at the time, and probably FDA still does, that
15 there would be different you know -- the disclosure
16 wouldn't be the same for every design.

17 So it may be that nothing about the drug or
18 the sponsor or even the disease needs to be disclosed.
19 It may be just the elements of an adaptation, or
20 something else.

21 On the other hand, if there is use of a
22 patient registry, then you'll have to disclose

1 something about the disease. But you know this would
2 not be just opening up the entire development program,
3 or even the protocol.

4 It's not a full disclosure or protocol. It's
5 really just being able -- I mean put yourself in FDA's
6 shoes and think about what would be most beneficial to
7 the world of directed element for us to disclose.

8 Well maybe it's the fact that we are seriously
9 considering a design with this particular adaptation at
10 these particular times, based on this information,
11 these decision-making criteria, this level of evidence,
12 or this way to simulate the operating characteristics
13 and so forth.

14 So you know, it's not full disclosure of
15 everything, and I won't say anything else, Stefanie.
16 But I think that's important that this is a -- what
17 would be disclosed or what needs to would be on a case-
18 by-case basis, and we're not talking about in most
19 cases opening it all up.

20 And then, you know, third, I think it's very
21 important, and somebody has said this already today
22 it's up to the sponsor. If they -- they don't have to

1 partake in the pilot, and that doesn't mean they can't
2 propose something innovative. So you can still propose
3 a very innovative design and choose not to go through
4 the pilot.

5 The idea of going through the pilot is you get
6 a little bit more regulatory interaction, hopefully you
7 know pretty fast, which is -- Gracie made that a very
8 important point. And you're contributing to the body
9 of knowledge, which advances science. So you know it's
10 a good thing to do, so just wanted to make those
11 points.

12 DR. PRICE: Thank you. Dr. Ashby?

13 DR. ASHBY: I think I'm probably answering
14 point two more than point one. Regarding -- so I think
15 the first thing is that you need to be careful about
16 the range you accept, because once you start going
17 public and talking about them, people say oh, well
18 that's what they mean by adaptive designs. The FDA
19 will accept those ones, but not those ones.

20 So I think we need to be transparent about the
21 selection process, but secondly, a careful choice
22 across a range will send the right messages.

1 I guess if it was me, I'd go for -- if I was
2 in the regulatory side, start off with kind of the
3 easiest one you can, because just how to do the
4 conversation, who comes to those meetings is going to
5 take time, and then grudgingly get more complex.

6 And the thing I would really like to see done,
7 but it may be too complex for a pilot, is actually that
8 the work is put where adaptive studies are most needed,
9 at chief of the public health, and to me you -- at last
10 one area is in watching infectious diseases, where if
11 you have a pandemic, and you want to be learning really
12 fast, so that in real-time you get back. And I've been
13 involved, and Berry Consultants have been involved in
14 European package which is trying to get to that.

15 And to me, the public debating getting those
16 studies setup so that they are ready to go, and so that
17 you've got public buy in and you've done all the
18 thinking would be well worth the investment. And I
19 wouldn't start there for the first quarter, but if you
20 haven't got one at all, that kind of thing, I'd be
21 quite disappointed.

22 And then my final point is please make sure

1 that patients -- the patient voice, public voice, are
2 involved in this, partly to get it right, and partly
3 because of trust. But I think that that -- getting
4 through the pilot, making sure that you've got that
5 embedded from day one will pay dividends in the long-
6 run.

7 DR. PRICE: Thank you. And Dr. Price?

8 DR. PRICE: Thank you so much. Just a couple
9 comments primarily on discussion points two and three.
10 Some of the type of trial designs I think that would be
11 helpful are -- and we're also maybe per some of the
12 disclosures that John was talking about, inferentially
13 seamless types of designs, and borrowing methods,
14 designs that have some form of formal borrowing, basket
15 platform type of designs, many of these things that
16 we've discussed today would be spot on with the types
17 of things that again, have been done, but maybe not
18 routinely. And so, we want to have more interactive
19 discussion on how to do that.

20 Some of the factors -- and this is through a
21 variety of conversations I've had as well as with some
22 of my internal colleagues, what would be important to

1 help encourage, or not to inhibit a clear and simple
2 process for submission of the pilots. If we get to a
3 pathway where having a long drawn-out conversation
4 about disclosure and what would be disclosed, that
5 would cause some concern I think.

6 I mentioned this before, but just to
7 reiterate, it would be important I think to have
8 clarity on the reason if it is rejected. I think it
9 would be a natural kneejerk reaction to say okay,
10 whoops.

11 That's maybe not allowed, but we know that it
12 may actually be that this is now the third you know
13 adult borrowing for -- or pediatric borrowing from
14 adult data, so that's really why, but clarify on why it
15 was rejected and a pathway for continuing to allow that
16 design to move forward, because it's important. And I
17 think clarity on when and how the FDA will be
18 communicating learnings, as well as routinely -- and
19 updating that knowledge.

20 So this is going to be an adaptive thing,
21 itself. So learnings on -- we talked about -- I liked
22 the points about the time. There may be a window. You

1 may learn over time what timing seems to work well, and
2 so having knowledge of that will be important.

3 And it would also be great to know if there
4 are certain types of designs that you had hoped to see
5 but you're not seeing, and communicating that I think
6 would help sponsors to say okay, let's now look at
7 where in our portfolio we might have an opportunity to
8 come forward. So you might get some experiences that
9 way. Thank you.

10 DR. PRICE: Dr. Emerson?

11 DR. EMERSON: I guess one aspect that I would
12 want to see, were I doing this sort of thing -- I'm
13 not. But is the process that you go through of what
14 the initial submission was, and then what additional
15 things FDA wanted to see for this documentation. What
16 questions were not addressed in the initial submission?
17 What things had to be addressed and that sort of thing?
18 It's this process.

19 The word that's sort of missing from
20 discussion point one to my mind is documentation.
21 You're talking about the design. You're talking about
22 the analysis, but what's the documentation of the

1 design and analysis that you'd wanted to see so that it
2 was understood?

3 You said you needed to have the details, but
4 it seems to me that this is a process of trying to
5 gather information about how to in general present
6 adaptive designs so that the FDA can understand them,
7 or regulatory agencies in general, and what the sponsor
8 would want to go with.

9 I guess I don't -- you know from the start in
10 a lot of this thing see that the clinical trial that's
11 submitted ever has to be conducted really, so that
12 there is a concept of if a sponsor doesn't want to
13 divulge too much of what they're actually doing, but
14 wants to participate in this program.

15 It can be, you know, under not quite false
16 situation, but some aspect there just to gain that
17 information because that's the process that I would
18 think that we're trying to identify the most.

19 DR. PRICE: So some of that, Dr. Emerson,
20 could become a part of the selection eligibility
21 criteria in terms of realistically planning to move
22 forward with the study. So I'll move onto Dr. Zhong.

1 DR. ZHONG: I would like to respond to the
2 comment that Dr. Emerson made. It kind of relates to
3 question number one, this documentation, yes? For
4 clinical trial design, it could in an initial
5 submission, and definitely we -- there's some elements,
6 like -- just like what we need to do, when we submit
7 and initial hypothesis or synopsis.

8 It's not just a very high-level concept. We
9 have to understand the patient population endpoint, a
10 subpopulation group, and post selection rationale
11 criteria, so on, so forth, like those high level
12 things. And then more details on the statistical
13 element design, elements of the trial, the trial design
14 elements.

15 So that's why you select this kind of trial,
16 and what's the rationale behind use of that, and for
17 the trial endpoint. And those should be described in
18 the documentation, right?

19 And then for decision criteria, and we will
20 need to have some decision criteria, also described
21 there. There's -- but not talk about simulation. It's
22 a hard decision too, based on simulation to talk about,

1 all right?

2 And this particular method to analyze data and
3 also make it through a decision, those things should be
4 described in the documentation, and also the level of
5 substantial evidence. So here we have this and for the
6 other, we'll talk about another choice on disease in
7 small population, right?

8 The evidence, it may or may not be the so-
9 called the 5 percent offer level anymore. So we all
10 have to open mind and think about how to assess the
11 level of evidence based on the risk-benefit ratio. I
12 listened yesterday in the rare disease workshop, and
13 they discussed how to treat a patient who had a rare
14 disease and no options. It's also a risk.

15 So we assess -- like I mean what evidence we
16 need, then please look at the risk-benefit there.
17 Yeah, I'm not talking about lowering the ball, lowering
18 the criteria to get the job approval, all right? But
19 we just have to assess the level evidence, it's not the
20 five percent rule anymore.

21 And ideally, I mean to move the science
22 forward and the documentation also contain like a

1 simulation plan and the evaluation of the important
2 operating characteristics. So those things, I believe
3 that we should have in the document.

4 So, but to the point number two, and here we
5 think about the -- so maybe not point number two. So
6 like in point number three, what factors might inhibit
7 or encourage the submission for the program?

8 I feel like listening from Dr. Chan, we
9 haven't disclosed certain information, but cannot like
10 hide all the information. The agency can understand
11 that. But I would like echo my colleague's point, like
12 if we disclose too much, that could be a factor to kind
13 of inhibit the submission through the pilot program,
14 and would not allow us to achieve the kind of promoted
15 innovation to the agency.

16 And also I mean the buy-in from the agency and
17 those who are review divisions. And I think the
18 horrible things that we spend months discuss this in a
19 way to innovate design, but when we go to the phase
20 meeting stage, or even latest stage, or else that
21 review divisions said no, we don't accept this design.

22 But this could be huge factor there, that can

1 inhibit the submission there. So some kind of pre-
2 specified enrollment in other division, review
3 divisions into this review process, and could really
4 help encourage the submission there. And also the
5 guide -- career guidance is -- we're not asking for
6 guidance for everything, but certain guidance still
7 needed, even the guidance for the analysts require for
8 this submission. It's needed.

9 I mean, I go back to simulation section and I
10 fully understood that -- I mean there's no criteria for
11 acceptance there. But I think that would be good that
12 the agency could give some guidance on what a
13 simulation plan should contain at high-level, right?
14 What operating characteristics the sponsors should
15 include in the simulation plan? So some guidance there
16 would be helpful for sponsors. I will stop here.

17 DR. PRICE: So thank you. And Dr. Emerson,
18 just to go back to your question -- I did want to make
19 you aware that during the -- as we've been discussing
20 the pilot program, one thing that we are considering is
21 an active IND, so that also would guarantee that a
22 company does intend to move forward with the design.

1 DR. EMERSON: But my point is if that's a
2 barrier for disclosure, is that serving your goal? If
3 the goal is to learn how to specify adaptive designs in
4 a way that we can move forward and learn something that
5 both.

6 It seems to be both industry and the FDA needs
7 to devote resources to solving that problem and you're
8 never going to do it if everything has to be you know
9 proprietary information, and what aspect of this
10 process, of submitting, thing like this.

11 Where do you even envision that the results of
12 the clinical trials will enter into this? It really
13 seems that this is an approval process and -- in what's
14 going forward, and there's no mechanism whereby the
15 results were there.

16 So is it really crucial that the clinical
17 trial will be done, or is what's crucial is you know
18 modeling after -- I would say industry would model it
19 after something they're wanting to do, and in that
20 process you present.

21 Now people sitting around this table have
22 experience, coming up with documentation of adaptive

1 designs and the like. But what we want to do is get
2 that out into the public domain and remove all of those
3 barriers.

4 So, so far I haven't heard anything that says
5 doing the clinical trial is crucial and we'll provide
6 the information at the end.

7 DR. LAVANGE: So this is all hypothetical
8 because the program hasn't been announced, but the
9 discussion during the PDUFA negotiations, and Gracie
10 correct me if I'm wrong, really had to do with -- okay.

11 The way it evolved was there was some
12 discussion on the FDA side that sponsors were
13 withholding protocol ideas, study design ideas,
14 assuming that the FDA wouldn't take them. And we also
15 felt a little strapped that we couldn't talk about some
16 of the more innovative proposals for protocols we'd
17 seen because things took a while.

18 And then, on the sponsor side, the feeling was
19 that the more complicated designs took a lot of
20 regulatory interaction because when you get into
21 simulations you know just one protocol review -- I mean
22 it takes a bit of back-and-forth, you know?

1 This is not what the FDA wants, or we need
2 more simulations, or we need this, or we need that.
3 And so there was a desire for more regulatory
4 interaction. And so, we came up with the pilot idea
5 mutually to offer increased interactions on a pilot
6 scale, because resources at FDA are limited and
7 reviewers are often fairly strapped for time.

8 So could we give -- could we pilot this?
9 Could we try to give more interactions on a complicated
10 design? And in exchange we can at least talk about the
11 design so that people are aware that we are accepting
12 or engaging about the protocol?

13 So we -- this is just the first step. I mean
14 I agree that what you want is good, but we're sort of
15 taking the first piece of this. So this would be a
16 protocol review. This is not an NDA submission. The
17 trial is not finished. This is a protocol review, and
18 we're trying to enhance that process. Is that a fair
19 statement?

20 DR. EMERSON: But it is the abstraction of
21 this whole process that one, what we've heard is saying
22 gee, how do you parameterize these innovative complex

1 designs? How do you parameterize the simulations that
2 you do? What are the areas of uncertainty that the
3 regulators have, and how do we get that back?

4 And it seems to me that that's what's crucial
5 in this pilot program, is to say that that
6 communication, the back-and-forth that you have, that's
7 where most the education's going to come from.

8 I mean the question is, is what did we not
9 know to supply to the FDA, and what after the FDA asked
10 a question that they suddenly decided, yeah that was a
11 stupid question. We didn't really need to know that.
12 You know that information is crucial for being too
13 (indiscernible).

14 Now I'm making this up, but you know the --
15 you know there. You have an SGR. Are you an SGE or is
16 it -- Frank are you an SGE or are you a --

17 DR. SCOTT: I'm SGE and Maria.

18 DR. EMERSON: Okay. So but it's the idea of
19 saying can you take in people who are some -- you know
20 neither academic nor FDA, but trying to abstract it and
21 then hit upon what that abstraction of this process is
22 that's acceptable for release to both the sponsor and

1 the FDA to -- you know where you have some people who
2 are dedicated to trying to describe a common framework
3 on what that educational system is.

4 Otherwise, what this seems to me is this is
5 you're encouraging people to submit things that will be
6 in a silo and nobody'll ever find out about.

7 DR. LAVANGE: So the purpose of the public
8 disclosure was to not do that. But that doesn't mean
9 the pilot's going to answer everything. And so, I
10 think we probably thought or envision that in this
11 process you would have more public discussion at
12 professional meetings about certain designs.

13 You would -- I mean I have sat in meetings
14 where sponsors have put up on the screen all these
15 different types of adaptive designs that some of which
16 are not complicated at all and said this is what the
17 FDA doesn't like because they call them less well-
18 understood in their 2010 guidance, and I wanted to say
19 no, no. You know we didn't mean that.

20 So you'll have more open discussion of designs
21 at public meetings and so forth. You will have -- I
22 don't know white paper, something will come out of this

1 about how to submit simulations.

2 I mean, I think there will be lots of things
3 that will happen as a result of this. I think we're
4 just trying to move the needle initially in this way,
5 but I -- everything you say is a good thing to happen.
6 I'm -- I don't think this pilot can make all that
7 happen, but maybe it'll be the start is just my
8 opinion.

9 DR. PRICE: You've stimulated discussion and
10 Dr. Lewis wants to respond as well.

11 DR. LEWIS: Yeah. And just -- I just want to
12 apologize if I seemed to make it appear as if I was
13 saying everything in the program had to be fully
14 disclosed.

15 In my mind, the -- one of the strengths of the
16 proposal is the number which looked like two per
17 quarter, which by my math is eight a year. And that
18 allows for some diversity in the types of sponsors, the
19 degree with which it's definitely gonna be run, the
20 degree with which you can negotiate public disclosure
21 of the communication and the iterative process, et
22 cetera, et cetera.

1 So in my mind, I think the panel has
2 identified a whole bunch of positive attributes of
3 types of projects that might be accepted into the
4 program, and the goal is to have as many of those
5 attributes represented over the population of projects
6 as opposed to presented in every one.

7 MS. KRAUS: So a few points for consideration
8 on disclosure. Companies like government agencies can
9 tend to be fragmented in terms of the statistical
10 staff, the clinical staff, the regulatory staff, the
11 legal staff.

12 When you're considering about applying for the
13 program, you prob want to have had those conversations
14 with your regulatory staff and legal staff to make sure
15 that everybody's on the same page about how they feel
16 about disclosure so that we don't get a design that we
17 really like, and then people go back to their
18 regulatory folks and legal folks and say you can
19 basically disclose nothing about this.

20 The other point that was raised about
21 disclosing or requiring to disclose too much as being
22 an inhibiting factor, I would encourage you to think

1 about what too much means under specific circumstance.
2 You can approach it from the perspective of well you're
3 asking us to disclose too much, or this is too much, or
4 you could approach it from the perspective of let me
5 assume that I'm going to disclose almost everything
6 about my trial.

7 What do I want to hold back and why do I want
8 to hold that back? What's the interest that I'm trying
9 to predict in that process? And that may help you
10 realize that maybe some things that you think is too
11 much information really isn't too much information.

12 DR. PRICE: Thank you. Dr. Marchenko?

13 DR. MARCHENKO: I just wanted to know that of
14 course level of confidentiality will always vary from
15 sponsor to sponsor, and you will need to decide if you
16 select this program because sponsor doesn't want to
17 give you enough information to incorporate
18 confidentiality.

19 But what I do think would be important is to
20 make sure that the least therapeutic area is announced
21 because right now the perception is that those complex
22 adaptive designs can be used only in oncology, or rare

1 diseases. And I think this is what the -- we would
2 like to break too, because there many other therapeutic
3 areas where those type of designs are applicable.

4 At the same time, I do want to agree with
5 everybody's here that you are not trying to lower the
6 standards. It doesn't mean that right now in every
7 therapeutic area we are going to use external control
8 because it's not going to be the case.

9 I think what Scott said -- I think it was
10 important with regard how you're going to present the
11 argument. Like from my perspective, it would be
12 important that you would put initial design at least
13 comments provided by agency, comments address the -- by
14 the sponsor or by society writ large, so that it would
15 be step wise process, not just here's the final design
16 and that's what they would consider to be a good
17 design. We need to understand why.

18 And what was discussed -- and then it's
19 probably a question more for you. When I first read
20 this program, I thought we were talking about
21 confirmatory trials, here. But the more we discuss it,
22 I realize that you're practically encouraged to be in

1 any kind of a design, even the interesting phase II
2 design, which sponsor is willing to share. Is that the
3 case?

4 DR. PRICE: So I think in its initial
5 inception it was envisioned it would be more towards
6 the confirmatory space.

7 We are open to innovation, but I will say
8 during the initial inception, it was considered in the
9 confirmatory space. Dr. Berry?

10 DR. BERRY: So Olga sort of asked my question,
11 but I'll ask it again. Are you looking to show this
12 scenario where you receive say an adaptive design
13 report, simulation code, the results, and people get to
14 see your reaction to that? Or are you trying to go a
15 step backwards and have an interaction?

16 And how do you create that design? Did you
17 simulate multiple things? Did you compare them? Did
18 you approach that? Do you want to get into that
19 building of an adaptive trial and get eyes on that, or
20 just this point of what happens when somebody submits
21 an adaptive design and get eyes on that?

22 DR. JOHNSON: So in many ways it's a little

1 bit of both because realistically you can't really do a
2 good job of the first one without an understanding of
3 the second. So I don't -- I would not expect -- it's a
4 pilot, I should also, you know -- always the emphasis
5 that part of this is that there will be a learning
6 experience and a 360 structure here. It's going to
7 happen.

8 But it's -- you can't -- I would hope that
9 what would happen here is that something doesn't come
10 in. And it's just a yes or no stamp, right? There
11 should be iteration and discussion and that happens
12 across every single type of design that we see,
13 typically.

14 So I would expect it to go that way, but many
15 times you have to understand like what were you
16 thinking? Did you think about this? So I do expect
17 there will be some back-and-forth, but again it's a
18 pilot. That may change, and it'll really depend also
19 on what comes in, but I would say you can't do the
20 first without the second.

21 DR. BERRY: Yeah. It would be great to see
22 some of that. And just a warning, I tend to be

1 somebody who is less concerned about operational bias
2 and outside information.

3 At some point you may need to not disclose
4 anything about a phase III trial that could give people
5 information about how the trial's going, based on
6 knowing the gory details of the actual simulated trial.

7 DR. PRICE: Dr. Meurer?

8 DR. MEURER: (Off mic.)

9 DR. PRICE: That's okay. You haven't said a
10 lot so -- you haven't spoke a lot so I wanted to give
11 you an opportunity.

12 DR. MEURER: Okay. Very good. So I guess I
13 would like to I guess put in a plug for academic
14 sponsor investigators, as a potential population for
15 this program since I've collected a few IDs and IMDs as
16 -- in that role.

17 I think that that also in terms of having the
18 goals, of having a very open and transparent protocol.
19 It may be easier in the academic space, particularly if
20 it's repurposed existing approved drugs and new
21 disease.

22 QUESTION: Do they have to pay the PDUFA fee?

1 DR. PRICE: No.

2 DR. MEURER: Not for an academic sponsor
3 investigator.

4 DR. PRICE: Not for an IMD.

5 QUESTION: No, but to be a part of this
6 program?

7 MS. PRICE no.

8 DR. MEURER: So I guess I'm interested in
9 thoughts on I guess that population, for this. I mean
10 obviously, you don't even know how much excitement
11 you're going to have about this, but that may be a
12 population that could benefit from this process and
13 would have an incentive since it would be government
14 funded in the end to be doing very transparent work
15 that could be seen by everybody.

16 DR. PRICE: Thank you. Dr. Mehta?

17 DR. MEHTA: Thank you. I think it's going to
18 be very helpful when you actually make the announcement
19 if you have some concrete examples of what types of
20 designs will qualify for this program.

21 As this is going to be very complex designs,
22 like this umbrella or basket type, or the simpler types

1 of adaptive trials, just to classify as not well-
2 understood, such as just sample size re-estimation, or
3 population enrichment, or some -- drugs, dose
4 selection.

5 Even for these simpler types of adaptive
6 trials, there are companies wherein the regulatory
7 departments concerned that they will -- that they won't
8 be acceptable to the FDA.

9 So I would strongly recommend that you
10 actually list some examples in your announcement of the
11 types of designs that could qualify for this program.

12 DR. PRICE: Dr. Harrell, followed by Dr.
13 Zhong.

14 DR. HARRELL: One partial way to address some
15 of these issues, especially Scott Emerson's issue, is
16 to have a dry run with a hypothetical development, and
17 hypothetical, clinical trial, that you could -- or a
18 group could make up that sort of typifies a lot of the
19 issues that you're going to see in real trials.

20 And then you have some sort of national
21 webinar with lots of participation where you actually,
22 in a crowd, start designing the adaptive trial. And

1 then you start gathering the general issues that come
2 up, that Scott was asking about, abstracting those.
3 It'll help the abstract.

4 DR. ZHONG: So I'll respond to Scott and
5 Stefanie a little bit on the disclosure. And the post
6 pharma and IO was in had members from the working group
7 for that the applications, should be amendable to
8 encourage popular learning. We're not going to try to
9 hide from the public.

10 So I want to make it a bit clear on what -- I
11 mean the group do not feel comfortable to disclose.
12 For instance, I mean it -- like the indication, like
13 the group doesn't feel comfortable with that, might be
14 similar action more towards structure right?

15 Then, even sometimes in the sponsor name -- a
16 lot of sponsor do not feel comfortable with -- more
17 company, one compound per disease. You disclose the
18 name of sponsor, it could be a disadvantage to the
19 company as well.

20 And study group are an sample analysis that
21 performs on that status. So those are the things that
22 these sponsors did not want to disclose.

1 The most important thing on the study designs,
2 and other companies actually are willing to use these
3 study parameters. So I just want to make a little bit
4 clear there.

5 We are not trying to hide anything there. I
6 mean the -- most of the company would like to
7 participate in the pilot program, of course benefit
8 company itself, but at same time also promote public
9 lending, and promote innovation in statistic and
10 clinical environment, so --

11 DR. PRICE: Dr. Lieberman?

12 DR. LIEBERMAN: Thank you. So one thought
13 about some of these -- how to disclose some of the
14 information that everybody's asking for, so instead of
15 talking at a conference about one specific design that
16 was observed.

17 The other one could be like quarterly, or
18 biannual updates of here are the types of therapeutic
19 areas that the designs will peak there. Here are the
20 types of sort of discussions that we had, and it
21 wouldn't be tied to any specific design, but sort of
22 summarized the issues that came out, the responses that

1 we were getting, sort of -- and put together.

2 So then everybody here is like you all got
3 mention that it's not just the rare disease and
4 oncology, but it is different therapeutic areas you
5 will see it as, but also you'll see the variety of sort
6 of responses and interactions, but not tied to one
7 specific molecule.

8 MS. KRAUS: So -- introduce myself again.

9 DR. PRICE: They'll be connecting.

10 MS. KRAUS: Oh, apparently the people on the
11 adobe can't tell who's speaking, so this is Stefanie
12 Kraus, Counsel at CDER.

13 I wanted to pose a question to the panelists,
14 based on the disclosure discussions we've had, which is
15 when we get to the point of the disclosure discussions,
16 so presumably something has been said in the initial
17 application, we like the design, and we see that there
18 is at least some opportunity for discussion, how do you
19 envision those discussions going?

20 What we had not envisioned was that this would
21 be a negotiation among lawyers, but a negotiation among
22 scientists, so that we have an agreement on what we

1 feel is necessary to learn from these designs, and move
2 the science forward.

3 So I throw out for you how you envision those
4 going. Yeah?

5 DR. LEE: Maybe first suggestion would be that
6 the sponsor in their application sort of provides. And
7 she said that I helped her.

8 What I basically did, I took a protocol that
9 was adaptive protocol, and I stripped all the
10 information about the molecule, the therapeutic areas,
11 the type of the endpoints, just maybe coded that this
12 was type in vent endpoint, but I didn't say that it was
13 survivals and others, and said this is the statistical
14 section. This could probably be shared anywhere with
15 anybody, and the sort of types of adaptations.

16 So sponsors could in their application start
17 with that, and just put this. Here's how its
18 statistical analysis, or the synopsis: We strip the
19 things that we don't want to disclose. Hear that --
20 how it look like, and that being the sort of point is:
21 Is that enough? And then maybe a little bit scientific
22 discussion. Could we add a little more?

1 DR. PRICE: Dr. Lee?

2 DR. LEE: Well I'd like to make a general
3 comment first. That is we often know less than what we
4 think we know, okay? And if I count on anything today,
5 I think learning is kind of the keyword, and we try to
6 learn more, try to be adaptive, try to improve on what
7 we -- how we do things.

8 Going back to this -- therefore I think it's
9 great to have this innovative design pilot program,
10 okay? And to move things forward in terms of applying
11 better and more efficient designs.

12 But one thing more clear is that: How does
13 this program works in terms of the -- in the drug
14 approval pathway or the process? Because if it's
15 already faced design, then it's less controversy,
16 right?

17 But we heard this that is initially when it's
18 planned is for confirmatory study. And we wish to
19 understand this, it's not a MDA, okay?

20 So we know that, for example, in oncology that
21 we have this accelerated approval, you know, based on
22 indication, but need to be confirmed later for the

1 advocacy. So I'm not quite clear how does this pilot
2 program fit in, in terms of the drug approval process?

3 DR. PRICE: So I'm thinking this through. Any
4 of my industry colleagues want to help? Raji's going
5 to help.

6 DR. SRIDHARA: So you know this has nothing to
7 do with the approval process. It's an IMD that we are
8 talking, or maybe even a pre-IMD, and all we are
9 talking is about the design.

10 We haven't seen the results yet. Where is the
11 approval decision coming in there? I don't think based
12 on a design we are going to say this can only give you
13 accelerated approval, or this can only give you a full
14 approval, or what have you.

15 So I think approval is a totally different
16 issue. All we are talking is we have a good design to
17 answer the question that you want to answer. And how
18 are you doing it?

19 The -- that's what is being done. And the
20 other thing I -- if I can take couple of comments --
21 can I make? Okay.

22 The first thing is: I think all of you must

1 realize that all the trials, all on clinicaltrial.gov.
2 So once an IMD is there, it has to be reported there.
3 And I think of what more are you going to include in
4 this pilot that you're going to disclose? Maybe more
5 details about your design aspect and about the
6 simulations.

7 And simulations are -- you know without your
8 drug product there, and therefore probably there should
9 be a little bit more openness in putting this forward.
10 You could think of you know either there was a talk
11 about how do we put this out, or what have you?

12 I think it we're not putting the disease in
13 there, it's very hard for anybody to understand because
14 the endpoints are quite different and why you decide
15 and design is okay in one disease versus it cannot be
16 okay in another disease.

17 There are very many factors that go into it,
18 and so not having the disease in the background may not
19 help always. You can always come back and say I don't
20 know. Okay, time to move to the endpoint, but what
21 time to event is you're talking about? Is it getting
22 rid of an infection? What time it takes, or versus a

1 survival? There are very many different studies, so I
2 think we have to look into that.

3 Some parts are present at how we should -- how
4 we can put this out about the protocol or what have
5 you.

6 And I want to think, and you know give us your
7 opinion if this should be done somewhat similar to
8 biomarker qualification program that we have, where we
9 do have a website where one of it is qualified is put
10 in there, and should we have a website where a trial
11 which goes through the pilot, and the accept the design
12 of the study can be put in such a way. What do you
13 think about it? Is it too much?

14 And again, you know this has been on what you
15 have already in the clinicaltrials.gov, and the age
16 ability portion, and a -- I'm thinking that probably it
17 cannot be static because if you're already have a
18 design that's already in the pilot program, and it's
19 made public, then another one coming with a very
20 similar or close to the same design, do you really want
21 to consider that?

22 So these are some of the things. And I think

1 from a sponsor point of view, you are to say when is it
2 appropriate to announce this to the world, or to say
3 okay, we can share. We are comfortable sharing at this
4 point. Maybe when you put it in the
5 clinicaltrials.gov, or after you have enrolled X number
6 of patients, you feel comfortable? Okay. Our trial is
7 running now. We don't mind putting this out.

8 So some of those things probably you know as
9 sponsors, you might want to think about. Thank you.

10 DR. PRICE: And I would just add if -- I had
11 to think about your question. It's not exactly a -- I
12 think an easy answer to the question, but in the --
13 just because a sponsor is maybe not in the pilot
14 program, that does not preclude an innovative design.
15 And where would that protocol, or where would that
16 design fit in the approval process?

17 So it's similar considerations, and some of
18 that really is up to the sponsor in terms of where are
19 they in their development program.

20 So I think just looking at the time, and
21 seeing that we have someone at the mic, we'll go ahead
22 and move to our audience participation, and we'll take

1 the person at the first mic.

2 AUDIENCE Q&A

3 QUESTION: So as I listen to this discussion
4 on -- by the way, I'm Angela Johnson with CTI
5 Consulting, and also Texas Tech University.

6 As I listen to this discussion I think of the
7 many different types of sponsors we work with, some
8 being very small biotechnology firms and some being
9 very large. Then you've also talked about academic
10 groups and also patient advocacy groups that come in.

11 With these first pilot trials, is there an
12 interesting in going towards the platform route and
13 sort of a follow-up question to that is: If so, does
14 that favorite in the favor of one type of sponsor, and
15 maybe even discourage say small biotechs from taking on
16 these adaptive approaches, saying this is just for
17 larger programs. This isn't applicable for me.

18 How do we make this equitable where smaller
19 programs are also being brought in and saying yes, FDA
20 is going to facilitate and have conversations with you
21 about innovative designs when maybe you have a smaller
22 pipeline.

1 DR. JOHNSON: Actually I could talk about
2 that, but I think we're very pressed on time right now,
3 so it might be better if we just go ahead and listen to
4 all the comments and move forward.

5 DR. JOHNSON: So thank you for your comments.
6 We'll keep noting them down.

7 DR. PRICE: So we'll go to mic two.

8 QUESTION: Hi. This is Dr. Liu from Bowling
9 Green, department of statistics. We achieve learning
10 form both positive and active cases. Sometimes I think
11 we learn more through the -- I understand there will be
12 incentive for sponsor who participate in the program
13 and who are actually selected.

14 I'm just wondering if there will be any
15 incentive for the sponsors to also share the
16 rejections? You know you will basically select eight
17 cases, and maybe you will reject 40 cases.

18 DR. JOHNSON: So we'll take that into account.
19 Thank you.

20 DR. PRICE: First mic? Step --

21 QUESTION: Okay. I had a couple of -- some
22 questions. I actually think clinicians want more

1 detail than the statisticians do when -- is it on?

2 PANELIST: Yes.

3 QUESTION: Maybe I'm short. Okay. So Roger
4 made a good comment. I think clinicians hone in on
5 certain details that they think really has to be there,
6 and the statisticians tend to see oh, it's oncology
7 with time to event. That doesn't mean you know the
8 kind of cancer, whatever.

9 But I can see the pilot program playing around
10 with different approval rates, retention rates, dropout
11 rates as part of a discussion. Because sometimes it
12 will work for that kind of cancer, and sometimes it
13 won't. And therefore it doesn't really get down to the
14 particular company's actual solution, and overall
15 survival is something we all understand.

16 So there could be situations in which it's not
17 a narrow indication. In fact, I think as part of the
18 power program, we might want something that's not too
19 tight because we kind of hope it's going to stimulate
20 drug development.

21 And so therefore, it ought to apply in more
22 than one little, narrow indication. But a lot of

1 things depend on what comes in and when. That's it.

2 DR. PRICE: Thank you, and we'll go to mic
3 two.

4 QUESTION: Hi, I'm Katie (ph). I'm one of the
5 clinical leads here at the FDA and I'm working in CBER.
6 And part of why I wanted to work here is because of the
7 innovation. I think the science is really exciting,
8 and I think this panel's been fantastic.

9 Three practical suggestions for the care and
10 pleading for your medical officers as we go through
11 this process. One, I wanted to echo a comment I heard
12 this morning about being transparent about the why,
13 stating up front what's the rationale. So if I
14 understand why a sponsor wants a novel trial design,
15 it's a lot easier for us to agree on what. So just
16 being really candid about that upfront.

17 You know we anticipate the biggest threat to
18 the success of our product is this. We want this
19 attribute in our trial to try and protect. Well now we
20 can have a conversation.

21 And the second thing is show don't tell. So a
22 couple times I've had interactions with sponsors where

1 they're telling me what they want to do. I think I
2 want to agree with them, but I can't tell exactly what
3 they want to do. And I'll say send me an example.
4 Send me a case report form with fake data. Show me how
5 you want to score it and I'll look at it and say yeah,
6 that'll be fine.

7 So simulations are good, but in this setting
8 where it's really novel, you know an example, a choose
9 your own adventure. Okay, if we encounter this state
10 of knowledge A, we anticipate our trial unfolding in
11 this way.

12 If we encounter state of knowledge B, we
13 anticipate our trial unfolding this way. It's just
14 sort of qualitatively describe different outcomes,
15 depending on the scenarios you might encounter I think
16 would really help to have a good discussion.

17 And then third is the assumptions. So you
18 know I don't understand probability, but I don't need
19 to to understand how a randomized control trial works,
20 because I've had enough practice with them, but I
21 understand the assumptions that we tend to bump into on
22 whether or not the clinical scenario is likely to be

1 robust to those assumptions.

2 So the packages have to include some
3 discussion of the assumptions you're making and why you
4 think they're going to be robust in the clinical
5 scenario so that we can comment on whether or not this
6 makes sense. Thanks.

7 DR. PRICE: And the next person at this second
8 mic before we move to the first?

9 QUESTION: Hi. This is Bob Beckman from
10 Georgetown. And I just had a simple question following
11 from the question about how this connects to drug
12 development. And the answer was given that this might
13 all be in the pre-IMD, or IMD setting, but I was kind
14 of I guess this is a two part question.

15 First of all, I thought and I wanted to
16 confirm, that it could also be available for a novel
17 confirmatory trials, and if that's the case then I
18 wondered whether a company that was willing to present
19 novel confirmatory trial, if they went through a long
20 interaction as part of the pilot program, and arrived
21 at a mutual acceptable, confirmatory design, could they
22 -- could that result in something that was equivalent

1 to a SPA?

2 DR. PRICE: So the spot has a lot of elements.
3 So I'm hesitant to say yes or no. We really hadn't
4 considered that. But I will say one part of the SPA
5 that would not be attractive in this setting, in my
6 mind, would be the time line.

7 An SPA is a special protocol assessment that
8 has a very short timeline, and we're talking about
9 fairly complex issues that will require significant
10 time.

11 But if you're talking about an element in
12 terms of just having some form of agreement, one would
13 hope that if we reach a mutually agreeable design, that
14 it would move forward.

15 That being said, that does not necessarily
16 mean that the drug will be approved. You know you
17 could do this great design, and it turns out your drug
18 just doesn't work.

19 QUESTION: Right. Well that's true for SPAs,
20 so --

21 DR. PRICE: It is. So we'll go -- thank you.
22 We'll go to the first mic.

1 QUESTION: Thank you. Ruthie Davie (ph) from
2 Metadata Solutions. Knowing that you may not have time
3 to respond today, I just want to plant a seed for a
4 thought later. And that is whether the agency would
5 consider sort of hypothetical project, and I'll give
6 you an example to explain what I mean.

7 So imagine there is a therapeutic area where a
8 sponsor typically works with single arm trials, and
9 going forward they'd like to use some sort of external
10 control for those trials.

11 Would you consider a project that looks at a
12 randomized trial, creates a historical control there,
13 and sort of validates the creation of that historical
14 control so that it could later be used in future drug
15 development programs?

16 So the actual project is kind of hypothetical
17 based around that randomized control trial. It's
18 probably completed and removes a lot of the problems
19 with revealing information.

20 DR. PRICE: Thank you for giving us something
21 else to consider. And our last public comment or
22 question?

1 QUESTION: Thank you. This Connie Latinagara
2 (ph) from Eli Lilly and Company, and I want to thank
3 you for -- panel members for all the great discussion
4 so far.

5 We've heard a lot of technical topics as well
6 as operational topics, today. And my question is: How
7 do we envision handling you know all of these topics?
8 Is it something that FDA is wanting to tackle
9 themselves, or is it something that could be
10 collaborated in nature, since we do have you know
11 existing working groups, as well as taskforce with
12 industry and pharma?

13 And what I mean by working groups is you know
14 the adaptive design working group that have you know
15 various complications so far, as well as the Bayesian
16 scientific working group who have you know past work,
17 as well as ongoing work to tackle some of the topics
18 that we discussed today?

19 MS. KRAUS: Along those lines, just to remind
20 everybody that we have a docket that's open, that's in
21 connection with this public meeting. So if there's any
22 points or comments you still want to make, or have us

1 consider anything, that docket is open through April
2 20th, and you can find the docket information on the
3 agenda.

4 CLOSING REMARKS

5 DR. PRICE: So thank you all. This has been
6 very helpful, and a very insightful discussion.
7 According to the agenda, I am to give concluding
8 remarks. These will be extremely brief so we can all
9 get out and get safely to our homes. And I wrote a
10 couple things.

11 So we started the day with the Swiss Army
12 knife, and in my thought process on the Swiss Army
13 knife was one size does not fit all, which was a theme
14 that we heard yesterday at the rare disease workshop as
15 well.

16 So there may be objectives and questions of
17 interest that may be best answered via a simple, yet
18 appropriate design, and there may be study objectives
19 and questions that will require a Swiss Army knife that
20 may entail a more complex design and analysis.

21 These complex innovative designs may entail
22 adaptations, and may require simulations. The designs

1 may be based in frequentist methodology, or Bayesian
2 methodology. Regardless of the methodology, the
3 discussion today suggests that pre-specification is
4 important in terms of modifications and adaptations
5 that one might make.

6 General broad themes that I heard were the
7 need for transparency, clarity, education,
8 collaboration, including the cross functional effort,
9 and communication.

10 Dr. Lee stated, and I wrote it down because I
11 really liked it: education, innovation, and
12 implementation.

13 So the education will be needed across
14 disciplines within the FDA as well as among external
15 stakeholders. A step toward educating in our opinion
16 will be the complex innovative design pilot program,
17 which will allow continuing education and information
18 sharing.

19 This discussion today is not the end, but a
20 part of the process of moving drug development forward,
21 for again, the benefit of the patients and the overall
22 public health.

1 The pilot program is a part of moving forward.
2 However this does not preclude innovative designs
3 outside of the pilot.

4 And Dr. Price, who -- we are not related, but
5 I like that last name -- Dr. Price said we can do this.
6 We must do this, and we are ready to do this for
7 patients and for public health.

8 So again, I'd like to thank you audience for
9 your participation. I would like to thank our
10 panelists who came again, from near and far. We have
11 panelists from the west coast. We have panelists from
12 Europe, so this has just been a great discussion.

13 You've only seen a couple of FDA
14 representatives today, but this really has been an
15 effort among many of my colleagues, as well as many
16 offices within CDER and CBER.

17 I'd also like to thank Dr. LaVange for --
18 while she's at the FDA, kind of laying the framework
19 for this and moving us forward -- and for Dr. Estelle
20 Russek-Cohen, who did the same as director of CBER, of
21 the office of biostatistics at CBER.

22 I hope I have not forgotten anyone. I usually

1 do not like to name people, because inevitably I am
2 going to forget someone. So that being said, thank
3 you, safe travels to everyone.

4 (Whereupon, the foregoing adjourned at 4:15
5 p.m.)

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I, KeVon Congo, the officer before whom the foregoing proceeding was taken, do hereby certify that the proceedings were recorded by me and thereafter reduced to typewriting under my direction; that said proceedings are a true and accurate record to the best of my knowledge, skills, and ability; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this was taken; and, further, that I am not a relative or employee of any counsel or attorney employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.



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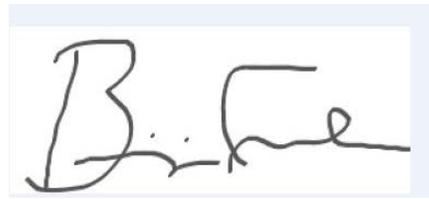
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4/2/2018

Darcy Rogers

A handwritten signature in black ink, appearing to read "B. Graham", is enclosed in a light blue rectangular box. Below the box is a horizontal line.

4/6/2018

Edited by: Benjamin Graham

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