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CONFIDENTIALITY OF INTERM RESULTS

IN

CARDIOVASCULAR OUTOCME SAFETY TRIALS

PUBLIC HEARING

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Food and Drug Administration

White Oak Campus

10903 New Hampshire Avenue

Building 31, Room 1503

Silver Spring, Maryland

M E E T I N G R O S T E R

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C O N T E N T S

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P R O C E E D I N G S

MS. HILLS: My name is Indira Hills. I'm a Regulatory Project Manager in the Office of Translational Sciences here in CDER in the FDA. I want to welcome you all to the FDA. Thank you for your participation and your attendance, and I really would like to thank the panel and the speakers for their contributions today.

Since this is a Part 15 hearing, I would like to go over some ground rules of what a Part 15 hearing are. We at FDA are here to listen and ask clarifying questions. You're here to state your position and comments. The hearing is informal in nature and the rules of evidence do not apply. No participant might interrupt the presentation of another participant at any hearing for any reason. The presiding officer, who is Dr. Lisa LaVange in this case, and other FDA penal members may ask a question of a person during or at the end of their presentation. No person attending the handing may question a person making a presentation.

FDA may recall the presenter for additional

questions at the day assuming time allows and the presenter remains available.

Public hearings under Part 15 are subject to FDA policies and procedures for electronic media coverage for FDA's public administrative proceedings. Representative of electronic media may be permitted, subject to certain limitations, to videotape, film, or otherwise record FDA pubic administrative proceedings including all of the presentation of today's speakers. We are also recording the sessions. The hearing will be transcribed and copies of the transcript will be available through the docket and will be on our website within 30 days of today.

Please note that each speaker was given the amount of time that they requested and the time slots are available on the agenda of the time when they will be speaking. There are additional minutes allocated for FDA panel members to ask clarifying questions. If a speaker goes over their time, the time allowed for questions will be reduced accordingly. If a speaker ends early, we intend to move on to the next speaker. Given the full agenda, we request that each speaker

keep within their allocated time to allow us to follow our schedule.

If you did not register to do an oral presentation and would like to do so, you can do that at the open public comments section at the end of the hearing. Please see me during the breaks if you would like to do that. In the interest of accommodating as many speakers as possible, we can and will extend the comment period longer if needed. Please note that means we may go beyond 5 o'clock this afternoon.

This hearing is not your last chance your comment. The docket will be open until October 11, 2014 and we strongly encourage all interested parties to comment. Please see the *Federal Register* Notice for details on that, and we will be reviewing all comments very closely.

Our agenda today consists of the opening remarks, introduction and charge given by our presiding officer, Dr. Lisa LaVange, followed by the FDA presentation by Matt Soukup, and sessions arranged to allow for a series of speakers to address the questions posted by the Agency in the *Federal Register*

Notice, then public discussions and comments will follow.

Now, I will go over a few housekeeping items. I would like you all to take a moment to put your mobile devices or cell phones on mute. Wifi is available as FDA guests' wifi; that's the network. The password is "guestaccess," all lower case, one word. Food is on your own expense. It's outside of this room, the kiosk just outside of -- well, it was going to be beyond the registration table. Bathrooms are also outside of the room, down the hall to the right, then to the left. Taxi information is available at the registration table for those who need it.

And for the audience comment period, I ask you to you to use the aisle microphones, please, since the session is being recorded. Please state your name, your affiliation, your questions or your comments.

As I'm responsible for all the guests here today, I ask that you stay within the Great Room, Building 31 area. Don't go wandering off.

I would like to now introduce Dr. Lisa LaVange. She is the Director of the Office of Biostatistics in the Office of Translational Sciences here in CDER in the FDA. Dr. LaVange joined the FDA in September 2011. As Director, she oversees approximately 175 statistical reviewers and staff members involved in development and application of statistical methodology for drug regulation. I give you Dr. LaVange.

DR. LaVANGE: Thanks, Indira, and good morning. Welcome to today's Part 15 hearing on confidentiality of interim results in cardiovascular outcome safety trials.

The purpose of today is for us to hear from the audience consisting of sponsors, regulators, researchers, healthcare providers, patients, and other representatives of organizations that have an interest in this area. While FDA approves drugs that have been shown to be safe and effective, there is also an interest in studying rare events such as cardiovascular outcomes as a post marketing requirements. Sometimes, as in the approval of

diabetes drugs and weight loss drugs, this requirement is met by continuing a study that was begun prior to approval with approval-based on data from the interim analysis. The study continues to more fully characterize the safety profile of the drug in the post-market setting. This has proven to be a bit complicated both for sponsors and for regulators, the challenge being how to preserve the integrity of the trial by keeping interim results confidential while still releasing enough information for patients and physicians to know how to treat patients with the drug that is now on the market.

And the FDA also is -- we are committed to transparency when we approve drugs, but we are also concerned about preserving the integrity of the trial. So we've had many conversations internally. We've had some conversations with some of you outside of the agency at different public meetings, and we thought we would convene this Part 15 hearing so that everyone could state their case and their concerns, and then we can possibly address those today.

As Indira mentioned, the format is for you

to speak and we have approximately 12 or 13 presenters I believe. We were able to grant everyone the time that they requested to speak. We have time after each speaker for the panelists to ask questions to the speaker, and then there are times before lunch and also at the end of the day for any other comments that the audience -- anyone in the audience would like to make, so we welcome you to do so.

I have printed here and they were also in your agenda in your packet the questions that we hope to address today, though we didn't organize the speakers by question. So this is the overall purpose and it is to hear from all of you about appropriate handling of interim results in ongoing studies, particularly cardiovascular outcome studies.

And the first question explains the setting: When a trial to evaluate cardiovascular safety of a new treatment is ongoing at the time a drug is approved, and where results from the trial contribute to the approval decision, do stakeholders agree that disclosure of detailed analysis (such as point estimates of hazard ratios and their associated

confidence intervals) could undermine the integrity of an ongoing trial and jeopardize its continuation potentially eliminating or substantially delaying the Agency's ability to obtain needed long-term safety information? So this is a general question to hear if there are some who may not think we have a problem or maybe we're looking at the problem in a different way.

And then underneath that question, there are three follow-ups:

One, exactly what interim findings, if disclosed, would represent the greatest risk to trial integrity or jeopardize its' continuation? Two, can partial disclosure of interim findings at the time of approval, essentially disclosing only that the standard for approval has been met, offers sufficient protection of trial integrity and also provide healthcare practitioners with the essential information they need to inform use of the drug?

So this gets at -- the first part gets at what do we really not want to disclose and the second what do think it would be okay to disclose.

And then the first follow on is, if the

detailed interim results were disclosed at the time of approval and the ongoing study was discontinued, do the questions about its integrity or difficulty in continuing to the planned end of the trial, is it feasible at that point to conduct a new trial as a post marketing requirement that would fulfill the original study objective?

And then the last question is a bit more open-ended: Are there other alternative trial designs that would allow for disclosure of interim results on safety risks at the time a product approval while also allowing for further information to be obtained post-market? So we are asking if you have any ideas of things that we may not have thought about.

With that, I'd like to introduce Dr. Matt Soukup. Matt is a Team Leader in the Division of Biometrics VII, which is the Division that oversees safety analysis and review both pre and post-market. Matt has been involved in, I believe, every trial that we have run in terms of the design and analysis from our end to satisfy the requirement sent out in our diabetes guidance published in 2008 for establishing

post safety -- cardiovascular safety of these drugs, and he is going to share some of the details about it.

And I forgot to introduce the panel, so before we go to Matt, I'd like the panelists to go around and introduce themselves and I'll start with Kevin on this end.

DR. PROHASKA: My name is Dr. Kevin Prohaska. I'm the Medical Officer in the Office of Good Clinical Practice responsible for medical policy (inaudible).

DR. CALIS: I'm Karim Calis. I'm a Senior Clinical Analyst in Office Medical Policy.

DR. ARCHDEACON: Hi. I'm Patrick Archdeacon. I'm a Medical Officer also in the Office of Medical Policy, CDER.

DR. CHAKARAVARTY: I'm Aloka Chakravarty. I'm Director of Biometrics VII which is Office of Biostatistics, CDER.

DR. SOUKUP: Good morning. I'm Mat Soukup. I'm a Team Lead within the Office of Biostatistics.

MS. HILLS: Indira Hills. You guys already met me.

DR. TEMPLE: Bob Temple. I'm Deputy Center Director for Clinical Science.

DR. JENKINS: Good morning. I'm John Jenkins. I'm the Director of the Office of New Drugs in CDER.

MS. SAGER: Nancy Sager. I'm the Director of the Division of Information Disclosure Policy.

DR. ROSEBRAUGH: Curt Rosebraugh, Director, Office of Drug Evaluation 2.

DR. GUETTIER: Jean-Marc Guettier, Director of the Division of Metabolism and Endocrinology Products.

DR. LaVANGE: All right. Thank you, and now I'll turn the presentation over to Mat.

DR. SOUKUP: Thank you, Lisa, and good morning. My presentation really is just to kind of give you a landscape and framework for how this two-stage approach has been utilized to understanding risk as we use it in the Office of Biostatistics. And I'll pay a little bit of attention to some of the statistical implications. Some may be relevant here for the topic and some may be a little bit more, but I

think they're worth reiterating.

So first, in terms of the background and really the general framework for how this two-stage approach for understanding risk is done is we have a stage one where the goal is to rule out a relative increase of risk of which I'm defining here as delta one. And then in stage two, what we have is we have a different risk margin of delta two, so where the goal and objective there is to rule out an increase of risk of delta two.

Some notes in terms of this framework is that we're using the same end point essentially for the evaluation of the risk in stage one as stage two, and we're defining delta one and delta two as a predefined risk margins. Some will refer to it as a non-inferiority risk -- or non-inferiority margin, but I think we tend to prefer the terminology of a risk margin.

In terms of the relationship of delta one and delta two is we know that delta one is larger than delta two, and what this implies is that we're requiring a more stringent amount of risk to be ruled

out in stage two than in stage one.

Some general comments on type one error, and not really focused on in the meeting here but I did want to kind of bring this up, is that we do view these two hypotheses in stage one and stage two to be analyzed at distinct points in time when you're powering under the same set of assumptions. And because of that, we allocate a type one error rate of .05 to each stage in the testing framework. And as a general note, if you plan on testing the stage two hypothesis where you're trying to rule out delta two, at the time of the testing of the stage one hypothesis, this does require a multiplicity adjustment of alpha two, and I'll show a little schematic of how that would be applied in a little bit.

In terms of where this framework has been utilized most commonly, it is as specified in the type 2 diabetes guidance from 2008 for understanding cardiovascular risk. And within that guidance, we do specify the delta one and delta two to be 1.8 and 1.3 respectively. Here it has a ratio as being our effect

measure and that's typically the methodology that we commonly employ within that area of assessment.

So now looking into an example testing procedure just to kind of give you an idea of how this two-stage approach is used is I have the number of events listed as the x axis here and the critical value used for your stopping boundary as the y axis. And the first stage in stage one, and this is applying to the type 2 diabetes guidance, is if you're trying to rule out a 1.8 relative risk, then this particular group sequential type approach is straightforward. It's an O'Brien-Fleming spending function, and tests are going to occur at 50 percent and 75 percent of the planned number of events you need. And that you can see as our spending function there. So relatively straightforward in terms of statistical procedures.

The stage two then is this is if we consider the same amount of information being utilized is now if we're looking at the 1.3 risk margin, the number of events here is going to be much larger than what we used in stage one. And I've basically put in there that there would be three interim analyses at 25

percent, 50 percent, and 75 percent of the total information. And here, the 20 percent, you can see that would be tested at the time of testing of the stage one hypothesis. So there is an ability to test in this particular framework. This isn't the only framework that can be used and we've seen many different ones, but this is kind of -- it tries to lay out how stage one and stage two are utilized kind of in unison when rue looking at the same amount of information generated.

So now I'll briefly kind of talk about sample size. We look at this as event-driven information trials or a set of trials. So we have our sample size calculation here which I won't go into, but I think the key point that I want to emphasize here is how the risk margin does impact the number of events and some of the reasoning for why this two-stage approach has been utilized.

So in this slide, what I'm showing here is the relationship between the risk margin and the number of events required. In this, the risk margin range is from 4 to 1.3. So you can see as the risk

margin becomes more stringent, more events are needed. And specifically, if you want to see exact numbers, if you plug it into the formula, before, this is what we see. Here, for the diabetes guidance for 1.3 when powering at 90 percent assuming a relative risk of 1, so there's no effect, and then looking at a two-sided type 1 error rate of 1.96, 611 events would be needed; whereas if we look at the 1.8 risk margin, which would be the stage one objective, 122 events are needed.

So from this, in terms of information size, looking at stage one risk and stage two, is that we know that the number of events to rule out delta one in stage one is a fraction of the number of events to rule out delta two in stage two. And on the previous slide, as you can see, it's really 20 percent of the information would be collected at stage one of the stage two hypothesis in the type 2 diabetes setting.

So what we have to realize in this particular framework is that any findings, if in stage one, should be considered relatively unstable. They should be interpreted with caution because they would be subject to wide confidence intervals. And I have

pointed out here that we know that the maximum value of the point estimate can be as high as 1.26 and still meet the 1.8 risk margin in the type 2 diabetes framework setting. So some people would maybe be considered with the 1.26 but statistically, we have to acknowledge that that can happen and still meet the boundary. So that's why our stage one we do consider it to be relatively unstable at the time of completion.

Another point to note and a little nit unrelated to the sample size calculation but to acknowledge that treatment exposure, what we understand in stage two relative to stage one is that we have a lot more exposure to treatment in stage two than we would at stage one. So we understand more chronically used drugs with longer term exposure to the drug, so we are able to understand that more in stage two than what we could be able to understand at stage one.

So now just kind of getting into some development approaches. Some will be relevant to the conversation here today, some not so much.

Essentially, we've seen four to date proposed by various sponsors and I'll cover each one briefly. The first one here is the -- in stage one, what is done is phase two-phase three trials primarily designed for efficacy are combined through meta analytic approaches, looking at the safety endpoint of interest to rule out the delta one in stage one. And then after stage one, a dedicated cardiovascular outcome trial or other outcomes trial would be used to rule out the delta two risk. So these are really done in sequence, the outcome trial coming after the meta analysis.

Approach two is also really a sequential type approach through time where trial one, which would be an outcome trial, can be used to look at the risk to rule out delta one on its own. And then in stage two, that information is combined with another separate trial that's conducted after trial one is complete and that's used in a meta analysis to rule out the delta two.

Approach three, which is really kind of the conversation that we're getting into today is where

it's a single trial that is used. It's powered for delta two, so it's powered to rule out the more stringent amount of risk. And an interim analysis of that trial is done to rule out delta one. After that has been successful, that trial continues to accrue events and the testing -- and the trial continues to enroll, to recruit and to observe additional events to meet the delta two in stage two.

Approach four is somewhat of a synthesis of approach one and approach three where sponsors would want to use information from their phase two-phase three trials but also use information from an outcomes trial which they initiate earlier in their development program. So they do a meta analysis of the phase two-phase three trials plus an interim analysis of the outcomes trial one here to assess delta one. That outcomes trial then is continued to accrue events throughout the development after approval and that is used for ultimately ruling out delta two.

So in terms of the "interim analysis" of stage one, and I'm using interim analysis in quotes here for the following reason, is determination to

stop for ruling out delta one, it does not result in a trial termination. Rather it results in an ability to file an NDA or BLA application. That trial would continue to accrue events to rule out delta two which it is ultimately powered to do.

So this is a little bit unique to other interim analyses that we see for efficacy; mainly, if you meet a stopping boundary, the trial is terminated. Here a trial is not terminated when it met its objective. Rather it continues to accrue events to look at the more stringent risk margin. And because of this, this has been a unique framework in that it requires additional levels of blinding of the stage one data. DSMBs are in place for all the trials that we have seen to date. They remain blinded per charter and that process is well-established and we've seen it quite frequently.

Where it's unique here is that now because the interim analysis meeting the objective triggers the submission to the Agency, this requires the sponsor to actually have the results of that interim analysis in their hands to prepare a study report, to

submit the information to the agency for review. So there are people within a company that do need to have access to the information to file the application to us. And part of this is it's not just high level summary results. This would be the full data that we would request as an agency so we can review, so this would include electronic records containing patient information, patient listings, and all of the necessary details we need for Agency review of the application. It's a little bit unique in that sense.

So just kind of wrap up. Really, this two-stage approach has been a flexible approach to allow sponsors to file an NDA or BLA submission with a fraction of the necessary information with further assessment of that risk done in stage two. In terms of this type of approach, it's created some unique statistical challenges, I think, operational challenges outside it -- really, how the products are developed and that, I think, is what created the challenge in this and how a type one error rate is controlled.

But the focus here today really is on how we

maintain blind the stage one data and what do we do with that, I think, has been an issue we've struggled with as an Agency and this is what we're here to listen to you about. And again, this is broader blinding of a DSMB. This is -- it's a little bit bigger and little bit more complex of an issue in blinding.

And that's all I have. Thanks.

DR. LaVANGE: Thanks, Mat. So to just add a couple of comments to Matt's presentation, we are talking about a unique situation today. The FDA issued a guidance about data monitoring committees and that came out, I believe, in 2006. But that guidance makes it clear what our expectations are in terms of interim analysis results of most studies not being shared with persons that have any kind of executive power to alter or change the study. And this is reiterated in our adaptive design guidance in 2010 so that in the normal scheme of things, large studies with interim analyses are set up to not share details of interim analysis results with sponsors. Rather just the decisions or recommendations or

recommendations for the DMC. And our first speaker will probably talk about this as well.

At the same time, the FDA reviewers also are not privy to interim analysis results in a normal setting. So in a large study, the study proceeds, the interim analysis are conducted, the DMC reviews the results, shares the recommendations with the sponsor but not the data or the details, and that data does not typically come to us. The only reason it might is if there is a serious safety concern that we need to know about because it could affect other trials that are running at the same time.

So while we are exposed to safety data on an ongoing basis, we are not delivered or we are not recipients of detailed interim analyses in the normal setting of clinical trials. So this is a very unique paradigm where we're making an action on interim data, we see the data at the FDA in great detail and do our thorough review because we need to do that to approve the drug but the study may still be ongoing. And then likewise, as Mat said, the sponsor gets the data because an application has to be submitted, and there

are ways to put firewalls up and so forth, and we'll hear about some of that today.

But I just wanted to set the stage for this not being your usual phase three trial. It's a little bit different paradigm and that's why we're giving so much attention and time to it.

So any other comments from the panel about Mat's -- anybody want to say anything before we start?

(Whereupon, no response; no questions posed.)

DR. LaVANGE: Okay. So we'll go ahead then with our first speaker, Professor Tom Fleming, and his slides are up. And Tom, if you would come to the podium. Tom is a Professor of Biostatistics at the University of Washington. He has published not only a book about data monitoring committees and interim analyses but also several papers, a couple of them recently and possibly spurred on by this particular paradigm. And you have a fair amount of time.

DR. FLEMING: Thank you, Lisa. In terms of disclosure, over the past 12 months, I've served as chair or member of more than a dozen data monitoring

committees and the sponsors for these committees are listed here. In terms of my time today, I'm here as an independent academic. And in terms of travel expenses, I've provided for all of my own expenses for travel from Seattle.

I'm very appreciative of this opportunity to speak with all of you today. I've often stated that FDA are among my heroes because of the importance of the influence and contributions to protecting and improving the health of the nation and the world.

What I would like to do today is build on very nice introductory context provided by Lisa and Mat talking and to address the specific questions that the FDA has put forward. I'd like to begin though by discussing a bit the principles and issues around the importance of maintaining confidentiality. So if we begin by talking about the mission of a data monitoring committee, it might be stated as being two-fold, first and foremost to safeguard the interests of study participants but to also preserve the trial integrity and credibility to enable the clinical trial to provide timely and reliable insights to the broader

clinical community. And we might refer to these as individual ethics and collective ethics, and both are certainly very relevant, the second though particularly relevant to the issues that we're going to be discussing today.

In essence then, there are some fundamental principles are important in assisting the DMC in achieving its mission. The DMC will often need to use judgment in its review of totality of data. And when you think of a judge, you want them to be knowledgeable, so the DMC should have multidisciplinary representation. And you want them to be unbiased and so membership in the DMC should be independent, free of significant conflicts of interest.

But another fundamental principle is the DMC should have sole access to interim results on relative efficacy and safety of interventions. The United Kingdom NHS Health Technology Assessment Program commissioned the Data Monitoring Committees Lessons, Ethics and Statistic Study group called "DAMOCLES" to investigate existing processes of monitoring

accumulating data and to identify ways of improving the DMC process. In 2005, then they issued their report and DAMOCLES concluded that there is near unanimity that the interim data and the deliberations of the DMC should be absolutely confidential and breaches of confidentiality are to be treated extremely seriously.

There are several sources of insight that led DAMOCLES to this conclusion. One of these was evidence from NIH cooperative group studies. The NIH cancer cooperative group, the North Center Cancer Treatment Group, began to have data monitoring committees in place in 1977. The Southwest Oncology Group didn't begin to have DMCs in place until 1984, and so there was discordance between the two over a period of seven years where interim data were shown only to the members of the DMC during those seven years for the North Center Cancer Treatment Group. But in interim data were widely disseminated on a six-month basis every six months by the Southwest Oncology Group during those seven years.

To get a sense and insight about the

importance of maintaining confidentiality, there were 10 major trials that were conducted during those 7 years by each of those cooperative groups and they were well-matched by being adjuvant trials in colon cancer, breast cancer, and lung cancer. In the 10 trials that were conducted by the Southwest Oncology Group, there was a ramping up of enrollment and then due to prejudgment, there was trickling away of that enrollment over the period of the trial in 5 of the 10 trials. This was, for those of you that remember our experience in research in the 1970's and early '80s, this was not an uncommon experience.

But in the North Center Cancer Treatment Group where results were kept confidential, none of those 10 studies showed that declining accrual rate over time. When this review was done, there were 9 of the 10 trials that were completed in both settings, but there were two of the studies that had been conducted by the Southwest Oncology Group where there was not active termination of the trials because they had answered the question the study was designed to address. There was passive termination because the

precipitous drop in enrollment rate made it impossible to achieve the completion of the trial. Well, back in those days, it was great for our CVs as we released the results regularly, we could publish the results ever year.

Well, there were two of the studies that were completed in the Southwest Oncology Group where early published results were very inconsistent with what the final results showed. Based on these and other data, there is considerable evidence that maintaining confidentiality does reduce the risk of prejudgment in turn, reducing the risk of having declining enrollment rates, altered adherence, early release of misreading results, or inability to complete trials. Maintaining confidentiality maintains the commitment to capturing outcome data.

There's another interesting benefit as well. If one is conducting a clinical trial that is intended to be confirmatory and not just exploratory, it's extremely important to have pre-specification of the primary and secondary endpoints and pre-specification of the analyses that will be used. If data are --

once data are available, it's very problematic if emerging data would, in fact, influence the definition of those primary analyses and endpoints. This is important because this pre-specification provides a sampling context that enables the p values, at least regarding the primary and secondary endpoints, to be interpretable, and it avoids the fitting of noise that could lead to random over estimates in the estimates of treatment effect, random high bias.

Yet during the conduct of a trial, there may be emerging external data, and that emerging external data could be very relevant to what we had pre-specified as the primary analyses in the ongoing trial.

That emerging external data can be used to refine the design, the analysis plan of the ongoing trial as long as the people making that decision remain fully blinded to the emerging data in the ongoing trial. And as a result, maintaining confidentiality of that interim data has the added benefit that it allows this flexibility to modify the trial design for the ongoing study based on insights

from emerging external data.

I'd like to amplify a little bit here the fact that maintaining confidentiality reduces the risk of early release of misleading results. I was on the data monitoring committee for the committee program Clinical Research in AIDS 002 trial. This was a study that was conducted in HIV-infected patients who'd become intolerant or failures with AZT. Standard therapy at the time was DDI. The question was would an alternative agent, DDC, also be appropriate use in this setting.

Four hundred and sixty-seven patients were enrolled in the early 1990's where the intention was to follow these patients until 243 experienced the primary endpoint of either symptomatic AIDS events or death. And these data were then reviewed after each 25 percent of information occurred, after each 60 events emerged in the trial.

This slide shows the evidence that was seen at the time of these four analyses when each 25 percent of the data emerged. These -- our DMC met then on August 1991, on November '91, February of '92,

and in August of 1992.

The data that we were looking at, the principle outcome data along this axis here at the bottom is the rate of progression to symptomatic AIDS or death, the primary endpoint on DDI relative to DDC. The intention was to determine whether, in fact, DDC was similar to the standard DDI ruling out a margin that it was 25 percent worse, so a design that was conceptually much like what we're doing in our cardiovascular safety trials looking to see whether we can rule out a 30 percent increase.

When the data were first reviewed at the first interim analysis, there were 39 patients with symptomatic AIDS events or death on DDC and only 19 on DDI for an estimate of 2.08, for twice -- the rate of these events were twice as high on DDC compared to DDI. If you did a nominal p value, the p value was 009, the confidence interval excluding that the rate could be as low as 25 percent higher on DDC than DDI.

So while the intention of the trial was to see whether, in truth, they were the same ruling out 25 percent higher, the early analysis said the rate on

DDC was twice as high ruling out that it could only be as little as 25 percent higher. Yet the data monitoring committee, even with the nominal p value of 009 on this important clinical endpoint, did not terminate the trial because it realized the unreliability of interim data.

It was being guided by an O'Brien-Fleming group sequential boundary that was being applied at the analyses after every 60 events. And the boundary basically was built to be very conservative using low p values or wide confidence intervals at these early analyses allowing the final analysis to be conducted at nearly an unadjusted level where globally across all four analysis, one is protecting the two-sided 05, i.e., 2-1/2 percent false positive error rate.

So using the O'Brien-Fleming boundary, the proper expanded confidence intervals that are shown by these orange parentheses indicated that while these data were disappointing early indicating a higher rate on DDI than DDC, the proper adjusted confidence interval indicated the data were still consistent with the potential of having no increase. The study was

continued.

As we moved forward with each 25 percent of additional data, the estimates for the excess of rates of progression to symptomatic AIDS or death on DDC compared to DDI, this estimated excess gradually converged to no difference. At the final analysis, there were 130 events on both arms. The estimate was that there was the same rate of progression to AIDS events and death on the two arms ruling out the rate could be as high as 25 percent higher yielding a positive result for DDC.

These interim data were not only misleading regarding the primary endpoint of AIDS and death, they were also misleading regarding a very important biomarker. In 1990-91, there was considerable belief that the CD4 count was a critical measure of how likely it is that you would have benefit. What we knew is that AZT had a spike in CD4 count. DDI had that same spike. DDC did not. And so not only at this interim analysis was the rate of progression to AIDS and death a clinical endpoint nominally significant of p of 009, when you compared DDI to DDC,

DDI was also superior for the effect on the biomarker of CD4 increase. So we had a smoking gun that gave us an understanding for why DDC was, in fact, inferior to DDI.

We have asked numerous ID docs, "What is the likelihood if these data had been released in August of 1991 that this study ever would have been successfully completed to its final results in August of '92?" The uniform answer we've gotten is essentially no chance that it would have been successfully completed.

I was on the data monitoring committee for a clinical trial that was comparing an angiotensin II receptor blocker against a calcium channel blocker in hypertensive patients who were at high cardiovascular risk. The study was a 5-1/2 year trial, began in May of 1998, completed in December of 2003. Our monitoring committee was monitoring it regularly when we were halfway through, about 2-1/4 years into the trial, we had already enrolled 15,000 patients into the study. And the ARB had a higher rate of death, 25 percent higher rate of death compared to the calcium

channel blocker, and a one-third higher rate of MI and stroke. Even though these rates were based on hundreds of events, the data monitoring committee realized the unreliability of interim data. The study was continued to its completion in December of 2003 at which time at which time there were four-fold as many events. The excess on the death rate on ARB compared to calcium channel blocker had disappeared and the excess on MI and stroke had become only half as large as they had been at the interim analysis, plus the emerging evidence indicated that the ARB had a lower rate of heart failure hospitalization and a lower rate of the biomarker based endpoint on diabetes.

So in both the CPC RA trial and in this trial and in many others that we've monitored, it's very apparent that if the early results had been released, they would have been very misleading for what the final results of the trial indicated.

As I've said, DAMOCLES indicated there is near unanimity that the interim data should be absolutely confidential. Formal statements of concordance to this have been issued by many

authorities.

The NIH has a policy statement for data and safety monitoring where they've indicated confidentiality must be maintained during all phases of the trial including monitoring, preparation of interim results, review, and response to monitoring recommendations. Usually, only members of the DSB should see interim analyses of outcome data.

The World Heath Organization has indicated that DSMB should ensure confidentiality and proper communication to enhance the integrity and credibility of the study.

From a regulatory perspective, EMA has indicated a critical point in all DMC activities is to ensure the integrity and credibility of the ongoing trial. Thus, the DMC and the sponsor are responsible to have appropriate policies in place to ensure the integrity of the study. As an example, policies to avoid the dissemination of interim study results prior to unblinding have to be in place. FDA has indicated the interim data and the results of interim analysis should generally not be accessible to anyone other

than DMC members. Sponsors should establish procedures to ensure confidentiality of the interim data.

So to then address these important issues that have been put forward today by FDA, a key issue is what information can be released that preserves the essence of confidentiality and in turn preserves the integrity and credibility of a clinical trial. I think to answer this it might be good start with a setting that's very familiar to us which would be a superiority trial.

So to give an example of this, I'll mention another trial that I served on the data monitoring committee, and that was the normal hematocrit trial in end stage renal disease where in essence, the standard intervention there, which was use of standard doses of erythropoietin stimulating agents gave partial normalization of hematocrit. The trial was designed to compare that standard dosing of ESAs to high-dose ESA that would be expected to more completely normalize hematocrit, to determine whether such a strategy would favorably impact the primary endpoint

of the rate of deaths in MIs.

The sample size calculation indicated that the trial was powered to provide very high power for a 25 percent relative reduction in the rate of death MI using the high dose against the standard dose where we were preserving the standard two-sided 05, i.e., 2-1/2 percent false positive error rate in the setting where the hazard ratio was one. This required a trial where 742 patients would need to be followed to the death MI event.

The data were analyzed during time using an O'Brien-Fleming group sequential boundary, and they were analyzed after every roughly 186 death MI events occurred where at the first analysis, the results were significant in there were 4.3 standard error effect; at the second analysis, at 371 events, 2.9 standard errors; at the third analysis, 2.3 standard errors; and at the fourth analysis, two standard errors and collectively, the probability of getting a false positive conclusion across those four time-points would be only 2-1/2 percent.

And in fact, we used a (inaudible)

implementation that allowed for a continuous use of this boundary since the analyses aren't necessarily done at exactly one-quarter of the way.

So what do these boundaries look like in this traditional superiority trial? What I'm showing here along the y axis is the rate of the primary endpoint of death MI on the high dose against the standard dose ESA. The null hypothesis is the relative risk of -- is one. The high dose doesn't provide any added benefit. The alternative hypothesis is that there is a 25 percent relative reduction. So in essence, at the first analysis, at 186 events, the boundary would be hit if the estimated results are 4.3 standard errors away from a quality. And that would be an estimate of about a 45 percent reduction in the rate of death MI.

At the second analysis, it's 2.9 standard errors which would be an estimate of a 25 percent reduction in the rate of death MI. At the third analysis, 557 events, it is 2.3 standard errors which is an estimated effect of an 18 percent relative reduction.

And at the completion of the trial, positivity is achieved if the estimated affect is about a 13-1/2 percent relative reduction. The property of this boundary is if in truth the high dose is no different than standard dose in the rate of death MI, the probability of penetrating this boundary at any point is only 2-1/2 percent.

Similarly, the boundary for ruling out a 25 percent reduction is symmetric. It's shown here in yellow and the probability of penetrating that yellow boundary if you really have a 25 percent reduction is also only 2-1/2 percent, so it preserves the power of the trial.

In essence, even if one knew that this was the monitoring boundary the data monitoring committee was using, if it's released to the public that the data monitoring committee has reviewed these data in the context of this boundary and has decided and recommended the study should continue, that does not provide an alteration of the public's perception of equipoise. So in essence, at the 50 percent point in the trial, the boundary would be hit only if the

estimate exceeded the 25 percent reduction that one was powering for or if there was an indication of results in the wrong direction. If the estimate is anywhere between a null hypothesis of no effect and the alternative for which we have high power, which is the 25 percent reduction, the study would continue.

So unless somebody believed in advance the truth was an enormously large effect or the truth was we're inducing harm, there is no material evidence that's released by indicating that the study has met the boundary considerations or continuation. The DMC recommendation for trial continuation effectively preserves confidentiality.

So with this as context, what information can be released now if we consider cardiovascular outcome safety trials; what information can be released that preserves the essence of confidentiality and in turn preserves the integrity and credibility of the trial for a cardiovascular safety trial? Well, this slide, in essence, shows us the context of what we're doing in the cardiovascular safety trail. The goal in a type 2 diabetes setting is to determine

whether or not if, in truth, we have a new experimental strategy compared to a control regimen; if, in fact, the experimental strategy and the control regimen are the same, looking to see whether we can rule out that the experimental strategy has a 30 percent higher rate of the endpoint, typically, cardiovascular death, stroke, MI.

In fact, it's hoped that in many of these settings, these experimental strategies not only would be the same in the risk of death stroke MI but, in fact, could be better. The goal, in fact, with type 2 diabetes' agents is to provide clinical benefit to reduce the risk of micro vascular complications or macro vascular complications, the latter being cardiovascular death, stroke, and MI. So suppose we were reaching the final analysis of that trial, the 610 events.

If, in fact, the estimated relative rate of events on the experimental to the control is no more than a 10 percent increase if we're in this upper region here, we can rule out the margin of 1.3 and we would have a positive result.

If, in fact, the result not only is more favorable than a 10 percent increase, if it's as favorable as a 15 percent decrease or better, we not only can rule out a 30 percent increase, we can rule out a quality and conclude superiority. If interim analysis are conducted at the 50 percent point or 75 percent point, then these dotted yellow bars here indicate the region over which you could actually terminate the trial and rule out the 1.3 margin.

However, I make these dotted lines because all sponsors I've worked with when I've been on data monitoring committees have said, "If at the mid-point of a trial your estimate is a 20 percent reduction in the rate of death, stroke, MI, don't stop the trial and report simply because we can rule out the 1.3 margin. We're on a pathway where these results, if the results continue, could readily lead us to a potential conclusion of superiority." So the monitoring boundaries to stop these trials for benefit typically have been the superiority boundaries shown here in white. And if these boundaries are penetrated at any time, the study can terminate with a conclusion

of superiority of the experimental strategy compared to standard of care for its effect on the principle end point of death, stroke, MI.

If, however, when we get to the end of the trial, the white boundary is not penetrated but the point estimate is better than 1.1, in the range from 1.1 to 0.85, the study would successfully rule out the 1.3 margin. If at any point the red boundary is penetrated, harm would be established. That is what might be called stage two or step two that Mat was talking about in his presentation.

Stage one or step one is what occurs when we have the first 122 events where one is determining whether or not one can rule out the margin of 1.8 which, if successfully done, could lead to a DMC recommendation to release the data to the sponsor for purposes of regulatory filing. This is achieved -- ruling out 1.8 is achieved at 122 events, as Matt had pointed out, if the point estimate for the relative rate of the primary endpoint, death, stroke, MI on the experimental of the control is 1.26 or more favorable. We would argue that releasing this information -- by

the way, make this a dotted line because it's solid in the sense that these data would be released to the sponsor, but it's open in the sense that the trial would then continue ultimately to determine whether one could rule out the margin of 1.3.

If one simply reports -- if the sponsor or the Agency simply reports that the data at the 122 events does allow us to rule out the 1.8 margin, i.e., in essence, that the point estimate is 1.26 or better, as in the case of the superiority trial, I would argue this doesn't disturb equipoise to the public. The point estimate, for all the public knows, could be .8 in which case there is considerable likelihood that the study would not only rule out inferiority margin of 1.3, it might even be superior; the point estimate could be 1 in which case there's still a considerable likelihood of achieving a non-inferiority conclusion. The point estimate could be 1.2 in which case it's still possible that non-inferiority could be achieved but with a much less likelihood of that outcome. So there remains considerable equipoise in the public as to the principle question the study was designed to

address even if at that point, it's indicated with these data that one can rule out the 1.8 margin.

The FDA asks what interim findings, if disclosed, provide the greatest risk to trial integrity and continuation, and in particular, what disclosure of point estimates and confidence intervals potentially undermine the integrity of ongoing cardiovascular safety trials. Well, to set the context for this, let's return for a moment to the classical superiority trial setting.

If, in fact, in the superiority trial that we were talking about in the end stage renal disease setting, if one didn't simply state that the O'Brien-Fleming boundaries for termination weren't crossed, if one released the fact that the point estimate was .8, a 20 percent reduction, that would be substantial insight giving the public a considerable sense that, in fact, with a 20 percent reduction, if that's maintained at the next analysis, there only has to be an 18 percent reduction for termination, superiority could be claimed and certainly a considerable likelihood that superiority would be met at the end.

On the other hand, if a point estimate was given that was only a five percent reduction in the primary endpoint while with this estimate it's still possible to hit the margin, the boundary for benefit, that likelihood would be considerably less. Revealing the point estimate in the superiority setting would be very informative about the final outcome and hence would be harmful to trial integrity.

What about now in the setting of the cardiovascular safety trial. Similarly, if we were to reveal the point estimate as being .8, that would give a considerable sense that the trial is quite likely to achieve non-inferiority, may even, in fact, achieve superiority, Whereas, if we revealed that the point estimate was 1.2, that, in fact, still could yield the potential for achieving non-inferiority but would give a very much more unfavorable sense of the likelihood that that would occur.

It's very important in any trial, particularly in non-inferiority cardiovascular safety trials to establish performance standards. Among those performance standards are standards to achieve

high levels of retention, i.e., low levels of loss to follow-up, standards to hit the target population, to ensure that we have proper generalizability of conclusions, to hit the event rate, to ensure that patients are at sufficiently high risk to give the targeted number of events. These are important standards in superiority trials. They're even more important in a non-inferiority safety trial where it's important to ensure that we're addressing that excess risk is not unacceptable in settings where it's most plausible.

There are other performance standards that are clearly as, if not more, important in an NI safety trial than in a superiority trial. We need timely enrollment because these studies, the post marketing aspect of these studies are being conducted while the product is already widely being used. Adherence and cross-in rates need to be kept low. It's important to have -- by adherence I mean best real world achievable adherence to the experimental intervention. And lack of cross-in to the experimental intervention by those patients that are on the control arm. That's

important in a superiority trial because if that happens, you're deluding the sensitivity of the trial to seeing the superior effect of the experimental arm. But if you, in fact, achieve statistical significance 58:xx, you can say that that's still an interpretable result.

But in a non-inferiority safety trial, if the experimental regimen is not adhered to in a best real world achievable way or if the control patients are allowed to cross-in, then a conclusion of similarity ruling out an excess in risk wouldn't be interpretable because you wouldn't be confident that that, in fact, is applicable to a setting where the experimental agent is being used in the best real world achievable matter.

Well, what happens if the point estimates were revealed to be .8 or 1.2; what happens to these performance standards? If the point estimate is reported to be 0.8, a favorable point estimate, well the product is now being marketed. This is post marketing so there may be a lesser incentive for patients to join the trial since they can get access

to the intervention through public marketing. And for those that are already randomized, there may be a likelihood that the control patients would go off and get publicly available intervention, publicly available experimental intervention leading to a higher rate of cross-in.

If the point estimate is shown to be 1.2, there are many alternative options that patients have in type 2 diabetes. They may be less willing to join a trial where the data that have been revealed indicate an estimated higher risk of death, stroke, MI on the experimental therapy. And for those that are already randomized, there may be an increased likelihood of those patients not maintaining adherence to that experimental therapy. Any of these would have serious negative consequences on the integrity interpretability of the non-inferiority safety trials.

FDA asks, in essence, would essentially disclosing only that the 1.8 boundary has been ruled out provide caregivers the essential needed information while preserving or protecting trial integrity. I believe that there is a considerable

argument that that answer is yes. If one, in fact, releases the evidence that the 1.8 margin has been ruled out, then one knows that the point estimate is in the range of 1.26 or more favorable in this range. That insight that would be conveyed would allow one to be confident that you can definitively rule out a 1.8, that the point estimate that you have, in fact, is more favorable than the 1.3 margin that has to be ruled out, and that with an estimate in this range, it's considerably unlikely that the results, when the trial is concluded, would, in fact, establish harm.

Ensuring integrity and credibility of clinical trials in superiority trials but also very much in non-inferiority safety trials doesn't just happen. It doesn't happen with passive approaches. We need active approaches to ensure integrity and credibility. So in a cardiovascular outcome safety trial, as in any trial, we need a study protocol, we need a statistical analysis plan, we need a well-formulated DMC charter.

It's also very important to have a performance standards document to actively enhance the

likelihood of achieving high performance. These performance standard documents should lay out what are the targeted levels of performance; what is that we hope to achieve, should also then lay out the creative approaches that will be in place to enable us to achieve this, and then should ensure accountability by having procedures in place that would allow for monitoring whether or not we're achieving these standards.

And by the way, it's fully appropriate for performance standards outcomes, outcomes such as the enrollment rate, the adherence rate, the cross-rate, the retention rate, the currentness of data pooled across treatment arms to be available to sponsor. So it's not just the DMC. The sponsor can jointly look for the accountability to ensure that these performance standards are being achieved.

In a cardiovascular safety trial, as Mat had laid out, in a setting where you're actually releasing the interim data to the sponsor for purposes of regulatory filing, there are serious additional challenges to maintaining confidentiality. As a

result, we need to be very proactive in this setting as well establishing in advance the parameters under which those data will be released, the educational procedures and other steps that need to be taken to ensure that we're maintaining confidentiality and proper oversight. And this could be done through the development of a data access plan.

In August of 2012, Dr. Steve Nissen and I sent a letter to FDA and in that letter, we indicated that in current ongoing cardiovascular safety trials where consideration of marketing approval may be based on interim data, access to unblinded data should be limited to a small core group in order to preserve the integrity of the trial, of the final analysis of the ongoing trial.

Within sponsors, a data access management plan should be created to ensure that only members of an unblinded team have access to unblinded interim data with the composition of this team determined from -- with the input from the FDA review division, the DMC, and the trial's academic executive committee. Data supporting the sponsors' submission should be

tightly restricted to the members of the unblinded team until after completion of the fully study. Unblinded team members should not participate in the subsequent conduct, and management of the study until the final database is locked and the trial is unblinded.

So some conclusions regarding the early release of interim data: The first is that allowing the marketing to be contingent on ruling out 1.8. So if one is designing and conducting a trial, a cardiovascular trial, determining whether the 1.3 margin could be ruled out, then using the interim data to serve as t he basis of determining whether or not the 1.8 margin is ruled out does empower sponsors to be able to achieve more timely marketing. This is a major benefit to sponsors and to public health but it comes at the price of ensuring that we're maintaining the integrity of the ongoing trial that requires maintaining confidentiality of the point estimate and the confidence interval.

Achieving these dual objectives is very challenging. I've been very impressed that uniformly

in the experiences I've had that not only has the academic community and the FDA been very supportive and creative, the sponsors with whom I've worked have been consistently also very constructive and creative in committing to achieving this dual objective.

Second principle conclusion is that establishing and monitoring key performance standards is key including the achievement in a timely way of enrollment, getting best real-world achievable adherence, avoidance of cross-ins, and high levels of retention.

And finally, a data access plan is needed to guide access to the 1.8 interim analysis. A key principle is access is provided when the DMC releases these data for the sole purpose of facilitating a regulatory filing. This access is not to, in fact, address or facilitate separate business considerations such as finance raising or establishing partners. And Dr. Nissen will talk in greater depth about his data access plan.

The FDA asks if detailed interim analysis were disclosed at the time of approval and the ongoing

trial stopped, would a new large trial as a post marketing requirement be feasible. In essence, I think this question is asking can the data used to assess the 1.8 margin come from a separate trial from the data used to address the 1.3 margin. I view this to be a special case of the second principle question that the FDA has asked which I paraphrased as follows. Discuss various approaches that would simultaneously on the one hand facilitate regulatory decision-making by providing the required evidence regarding the 1.8 margin and on the other hand still enabling the timely completion of a post-marketing study addressing the 1.3 margin in a manner to ensure its integrity and credibility.

So there are several approaches. These overlap very much with the approaches that Mat indicated in his presentation. One approach would be to conduct a separate trial to assess the 1.8 margin and to seek marketing approval based on those data from the trial that addresses the 1.3 margin. This would be an acceptable approach but it would typically be less efficient. In essence, you'd be conducting

the 122-event trial; then you're starting over, not using the 122 events in generating a new 610 events. Furthermore, if the 122-event trial, in order to give a timely result would typically have lesser duration of follow-up, it's going to require much larger sample size than 20 percent of the size of the 610-event trial, maybe 50 percent of the size. So it's a much less efficient approach. It would yield, as a result, the most timely conclusions about whether we could rule out the 1.3 margin, and it certainly wouldn't minimize the risk of prejudgment.

A special case of this scenario where you have a separate 1.8 trial and a 1.3 trial is where, in essence, and this is one of the options Mat talked about, the 1.8 margin could be addressed by doing a meta analysis of phase two and phase three efficacy trials. This approach not only has these issues of concern, it has a number of additional concerns. Efficacy trials usually have low risk patients. Rather than having a patient population as in a CV safety trial, it would have 20 to 30 eves per 1000 person years. These efficacy trials may have 5 to 10

events per 1000 person years. And typically, patients would be followed only 6 to 12 months, not for years, and so they're very inefficient in terms of the numbers of patients required to yield events.

They're also, while conducted with quality as efficacy trials, they're not conducted with the highly rigorous performance standards for cardiovascular safety trials ensuring in particular that we have best real-world achievable adherence and lack of cross-ins, which are critically important to the interpretability of a cardiovascular safety trial. And because the endpoints of these efficacy trials are the efficacy endpoints, maybe hemoglobin A1C, hypoglycemic episodes, or other biomarkers or endpoints, because cardiovascular outcomes are not the principle efficacy measure, there is often an uneven quality of capturing adjudication of those cardiovascular events.

And finally, there is another issue of concern as well. If we were designing and conducting a superiority trial, we wouldn't allow the results of that trial to be revealed and to use those results to

decide which subgroups of patients we're going to include in the primary analysis. Well, similarly, if one is going to do a 1.8 meta analysis, if you can do a meta analysis of phase two and three trials as the basis of judging whether you can rule out the 1.8 margin, it would be inappropriate to conduct those phase two and phase three trials, see the results, and then thereafter decide which of the trials and how much data from those trials we're going to include in the meta analysis. It needs to be pre-specified before the conduct of those phase two and three trials. And that type of pre-specification is rarely done.

Well, that then leads us to alternative strategies that Matt pointed out where, in essence, we're going to conduct the 1.3 margin cardiovascular safety trial, and we're going to use an interim analysis to determine whether or not we can rule out the 1.8 margin. One approach that's had some discussion is that the data monitoring committee in this setting could maintain sole access and simply report to regulatory authorities whether the 1.8

margin has been ruled out. This approach would meaningfully enhance maintaining confidentiality. But much more discussion is needed about the acceptability of this approach relative to the level of insights required by regulatory authorities when they make their judgments about whether to approve a product.

So that leads us then to the final approach which is if in fact we're going to do the cardiovascular safety trial to rule out the 1.3 margin and we use the interim analysis of those data, if the 1.8 margin is ruled out by that interim analysis, then, as has been done now in a number of prior trials, the DMC would release those data if the 1.8 margin is ruled out to the sponsors unblinded team and to regulators. Under this approach, it's critical that procedures are in place to ensure that interim data are not released to the public, to ensure that we avoid the risk of prejudgment reducing the enrollment, increasing the rates of cross-in, decreasing the level of adherence, that we're achieving best real-world achievable adherence. It's also important that procedures are in place so that we can ensure that the

data are available to the sponsor only to those who are on the unblinded team where the unblinded team has the sole principle purpose of facilitating regulatory filing and that that unblinded team is firewalled away from the rest of the sponsor, particularly the blinded team from the sponsor who now takes on the sole responsibility for the ongoing trial leadership within the sponsor. If procedures are in place to achieve these objectives, I believe that this does provide a scientifically acceptable approach to achieving and obtaining timely, reliable and interpretable results.

I'm very appreciative for the widespread input and collaboration that's already occurred from FDA and from academia and from all of the industry sponsors that I have worked with who have constructively and creatively worked to try to achieve these dual objectives of facilitating the ability to have early filing and yet at the same time, to maintaining the integrity of the long-term cardiovascular safety trial designed to rule out the 1.3 margin. It will be -- however, even with these very significant contributions, it will be invaluable

to all of us to have a clear guidance issued b FDA to guide these procedures, and we're hoping that this process today and subsequent processes will yield or will lead to a clear guidance that FDA will provide. Thanks.

DR. LaVANGE: Thank you, Professor Fleming. Now we might have some questions from the panel and perhaps I could lead off. We have five minutes for questions.

You mentioned the term "public equipoise" or equipoise in the public and you also had a very informative slide that talked about what can break down in terms of enrollment, adherence, cross-ins, and so forth. So the public is a big term, right? You've got people in the study; you've got physicians running the study; you've got the sponsor and related CROs and other agencies involved in the study; you've got other sponsors, the investment community; there are quite a lot of people in the public.

Do you -- are there gradations of equipoise? Clearly, the patients in the study and the physicians running the study need to be kept the most blind, so

to speak, but are there -- can you -- do you break up the public and decide how important equipoise is?

That's my first question, and my second is what can the role of the DMC be in an ongoing study to assess this? The examples you gave for an HIV and the Southwest Oncology Group were terrific, but all the information about what went wrong was not available until the study was over. We have a situation where we put a drug on the market as an approval based on interim data, but then the study has to keep going. So during that period, what kinds of assessments can be made as to whether equipoise is in place or not, and who oversees that?

DR. FLEMING: Yes. So those are certainly key questions. When I talk about maintaining equipoise in the public, what I mean is that we need to have confidence. We in the scientific community, you in the regulatory community need to have confidence that while we've set you a procedure here, while you have a very constructive and creative procedure that facilitates earlier potential filing when you only have 122 events, we must be confident

that the trial -- the principle issue here is ruling out the 1.3 and the trial can be successfully completed. Equipoise and the perception of equipoise is key to that.

And so confidentiality needs to be maintained by everyone who's in the position, the public, the patients that are on the trial, patients who could become future patients in the trial, the caregivers, and the sponsor's blinded team that's involved in conducting the tri al all need to, in essence, have access to information that doesn't alter their sense of equipoise just as in a superiority trial, saying that you didn't cross the O'Brien-Fleming boundary surely leaves you with that sense of equipoise.

I believe in a cardiovascular safety trial indicating the DMC released the data to the sponsor unblended team and to the regulatory authorities allows us also to maintain that sense of equipoise as I've described. So it's not well-defined exactly who gets access, and that's part of what we need the FDA, the DMC and the sponsor and the executive steering

committee to work through in each setting. But it should -- in essence, the principle is it should be the smallest core group possible that is integral to the regulatory filing and those people then need to be firewalled away from everybody else who, in fact, is involved in the continued conduct. That's what I mean when I'm saying equipoise in the global public then needs to be maintained.

You mentioned the data monitoring committee can play a role and, in fact, we can play a role. We do have complete access to data during the conduct of a trial. That means it's not even in a traditional sense of an ongoing efficacy superiority trial. We don't keep everybody blinded. The data monitoring committee is unblended and I've been on hundreds of these. Never once am I aware of any setting in which anybody on a data monitoring committee, even though they have privileged access, has ever led to a release or an unblinding of results. We can do this and the monitoring committee takes on an added responsibility here. Their responsibility is to determine whether or not that 122-even, 1.8 margin is ruled out in which

time they would release the data to the unblended team within the sponsor to share with the regulatory authorities to determine whether approval should occur.

The DMC, though, will continue in its role in protecting and safeguarding patient interests and in enhancing and integrity and credibility of the trial by monitoring the quality of continued conduct of the trial. We need to be advocates for ensuring that there is a data access plan, there are performance standards, and that these are being properly followed. And by following the performance standards, we get indirect insights. As the trial is continuing in the post-marketing phase, is the enrollment rate adequately continuing; are we avoiding having loss of adherence to the experimental therapy; loss at the level of best real-world achievable adherence; are we avoiding cross-ins in the control arm? So we can carefully monitor these. They're indirect measures but they're also informative.

So the DMC plays a key role. Without question, though, regulatory authorities have huge

influence because as much as there has been a widespread commitment by the private sector, by industry and government sponsors and by the academic community to maintain integrity, the FDA has huge influence, favorable, positive influence in providing the insight about how to do this properly and the motivation to do so. So we are clearly relying very significantly on your leadership as well to be able to successfully complete this.

DR. LaVANGE: Thank you. Other questions from the panel? Bob -- sorry -- and then John.

DR. TEMPLE: You may have answered this but looking at the slide that's actually still up, you gave two choices. You can imagine that number one, where we don't get to see the data, is not the most attractive one for us. But if I understand you, you think if you do b properly with all the caveats you just enunciated, that would be okay also?

DR. FLEMING: I agree with both of your comments, Bob. A provides a wonderful option to maximizing our confidence that we're maintaining confidentiality yet we fully understand that it has

significant controversial aspects in terms of how much insight to regulatory authorities need to have. And we very much look to your guidance on whether "a" in any setting would be feasible. Assuming that there a number of settings where it wouldn't be, then the setting "b" becomes a particularly significant alternative approach that now has been, in my experience, the most widely taken approach.

And yes, I agree with what you're saying, Bob. I believe that approach b can be done with integrity. I don't believe that it will occur with a passive approach. I think we have to have a very proactive pre-specified approach of indicating what is the purpose of releasing data; it's solely to facilitate regulatory filing; how are we going to establish who will get access; how do we properly educate them; how do we achieve accountability to ensure that when that access is given that it's not putting at risk the ability to maintain confidentiality with the broader, as Lisa was talking about, for the successful completion of the 1.3. I think it can be done but it takes a very active

approach and here's where I say guidance from FDA on your views about how to do this will be invaluable to all of us.

DR. LaVANGE: Then John Jenkins had questions.

DR. JENKINS: Yeah. Tom, on this slide you have up here, there's also a possibility for something in between. So I would be interested if you could comment on the feasibility, the logistics of the DMC and maybe the CRO who's managing the trial for the sponsor, releasing the data to the regulatory agency but only telling the sponsor that the boundary has been met so they can submit the regulatory application, but the sponsor themselves never see the underlying point estimates and confidence intervals and the data. So is that a feasible approach?

DR. FLEMING: Well, John, that's a great point that I really should have addressed because your pointing out another creative variation that is in between a and b. Again, I've been impressed with the commitment that sponsors have shown to getting this done right, recognizing that it's important to protect

this ability to allow early filling and yet at the same time, there's a strong recognition by them that we need to maintain confidentiality. I'd like to hear more from sponsors but I believe that there is, in fact, a considerable likelihood that many sponsors would consider that an acceptable approach because it enhances their ability to ensure that confidentiality is maintained and I'm sure we'll hear from some of them today. It reduces some of the complexities that they may face in ensuring confidentiality has been maintained.

So if sponsors find this an acceptable approach, John, I would consider it an important variation that you've raised that would still, unlike option a, all the Agency to have full access while restricting that access now only to the Agency.

DR. JENKINS: I think it really helps to address the point you made several times about the data access plan. You kept saying that only the unblended team within the sponsor that's required to be unblended to submit the regulatory submission would have access, but I think that gets harder and harder

to define in smaller and smaller companies. So if the sponsor themselves never see the data but can in some way logistically work it out that the CRO and the DMC can submit that data to the FDA, that would avoid any problems within the sponsor where, you know, an individual may have multiple hats within a small company.

DR. FLEMING: Yes. I go back now 15 years to where data monitoring committee procedures were growing in their frequency of use. This began in 1990 so we're almost 25 years now of having data monitoring committees in place for industry-sponsored trials. DMCs began four years ago in government-sponsored trials.

And when FDA issued their guidance on data monitoring committees, there was indication that the independent statistician, the liaison between the database and the DMC should be outside the company. There was a lot of angst about that when FDA initially issued that saying we're taking some control away from the company, from the statisticians, but there were important benefits along the lines of what you're

talking about to such an approach. Industry has been very creative in implementing DMCs and has come to accept that FDA recommendation as a near standard now that you will have a separate CRO who takes on the responsibility of doing the analyses that are presented to the DMC.

So similarly, if FDA came forward with a guidance saying there are variations for how we can do this but an approach that has particular appeal is where a CRO would be engaged for purposes of getting the data released by the DMC and providing the regulatory filing. As much as that would be difficult, I do envision that it has upsides that if it were recommended by the DMC as a particularly ideal approach that that, in fact, could readily become more commonly used.

But I also say that while you're right, particularly for a smaller company, it's particularly challenging to carry out option b where there would be an unblended team. I do think that because it's difficult doesn't mean we can't do it. And I've been, again, very impressed by the commitment that sponsors

have made to doing the right thing. And if we get a proper FDA guidance as to what would be an acceptable approach when you followed option b, I believe that this can be successfully done.

DR. LaVANGE: Thank you. We're going to hold. We have another question from the panel but we're going to hold it to stay on track and we'll call you back up if that's okay, Tom, before lunch.

So our second speaker is Dr. Robert Ratner and he is the Chief Scientific and Medical Officer of the American Diabetes Association.

And we, Bob, are pulling your slides up. If you can come to the podium, that would be great.

DR. RATNER: Dr. LaVange, thank you very much for the opportunity to come speak to you. I am not a statistician. I've spent 30 years as a clinician taking care of people with diabetes and as a clinical investigator on well over 50 different clinical trials. And one of the important things that Dr. Fleming mentioned in his superb discussion of the statistical approach was the scientifically acceptable approach. There is no disagreement there.

Given my background, let me bring you back to reality and what we deal with on the ground in terms of doing clinical trials and taking care of individuals with diabetes. I have no financial disclosures. I work with no drug companies and have not for the last 2-1/2 years.

2007-2008 was an exciting time. We had data from the ACCORD trial, from the ADVANCE trial, and the VA Diabetes trial suggesting no benefit in tight glycemic control in effecting cardiovascular outcomes. As you can see from the ACCORD trial, there actually was a difference in terms of cardiovascular outcomes, but the study was stopped on an interim basis because of an excess of non-cardiovascular deaths and that's shown here.

Following that, the discussions at the FDA concerning Rosiglitazone really set the stage for these cardiovascular outcome trial requirements and the guidance that came out in December of 2008. I think it's very, very important to keep in mind that diabetes, unlike acute coronary syndromes, is a chronic disease. Death, myocardial infarction and

stroke are certainly important to people with diabetes, but they have 40, 50, 60 years to survive with the disease prior to that time-point. It's also important to realize that if you did the studies long enough, you actually demonstrate a cardiovascular benefit first shown in type 1 diabetes.

In the DCCT/EDIC trail, you can see a 42 percent reduction in cardiovascular events but it took 20 years. In type 2 diabetes, in the UK PDS study, once sees a 15 percent reduction with the intensive therapy but it took 25 years to see those effects.

So what are we currently dealing with? We're dealing with an FDA guidance that has required companies to perform cardiovascular outcome trials on all new drugs for diabetes to prove safety. So there are the five cardiovascular outcome trials with the DPP4 inhibitors. SAVOR and EXAMINE have now been reported out as being non-inferior. You have four studies with GOP1 receptor agonists and you have three studies with SGLT2 inhibitors. You also have one additional study on insulin. Altogether, there are over 100,000 patients randomized to trials for

cardiovascular outcomes in diabetes. These are blinded trials -- 100,000 patients. In addition, you're looking at well over 400,000 patient years' experience. And the first two trials have reported out as essentially being negative. Why?

We've done very, very well in terms of cardiovascular outcomes in this country over the last 40 years. It has been plummeting like a rock and this is all to the credit of academicians and industry working on statins, working on blood pressure control, working on anti-thrombolytics, improved care in coronary units, there's lots of reasons.

But what I want to focus on is what the impact has been in diabetes. In the last 20 years, we've seen a 67 percent decrease in myocardial infarction in the setting of diabetes. We've seen a 53 percent reduction in the incidence of stroke. We're doing lots better.

Well, what's the impact of all of this? Certainly, our patients with diabetes are living longer. That's wonderful. But it has significant impact on that issue of scientifically acceptable

approach, because when you do a study protocol and you do a data analysis plan, you have to calculate your power based on your event rate and the impact of your intervention.

So let's take a look at what happened to ACCORD, ADVANCE and VADT. Here they're looking at cardiovascular outcome trials as their primary outcome, and you're looking at a range of predicted event rates of 2.9 percent per year to 6.7 percent per year. None of them came close. A 16 to 21 percent reduction in the observed event rates simply due to improved patient care. The event rates are falling. That becomes a very, very important consideration. So the ability to show a difference or even the ability to show non-inferiority is dependent on the hazard rate of the outcome, and we're seeing it drop now to below 1.5 percent per year.

In addition, you have to calculate your effect size. What is a rational, reasonable effect size that you're going to say is going to be acceptable? If you're starting at 1.5 percent per year, a 33 percent reduction drops you to 1 percent

per year. Are you going to accept anything less than a half a percent per year absolute rate reduction? And I think it's critically important as we get down to these low numbers that we deal with absolute rates, not relative rates. It becomes very misleading.

The exposure to the intervention becomes very important so that if, in fact, you have an event that occurs over a 20, 30, or 40-year period of time, you have two choices. You either enrich your population with those who are going to have the event quickly or you run a 20, 30, or a 40-year study. Guess which is more practical?

The question of generalizability then becomes critically important.

The confounding therapies provided to participants is important and Dr. Fleming emphasized this, the drop-ins, the drop-outs, the changes in therapy over time.

Keep in mind again diabetes is a chronic, evolving disease. The natural history of the disease is failing beta cells which requires progressive increase in therapy. Those become confounders in

long-term trials. And the number of times the data are interrogated further influences this.

Now I would never argue with Dr. Fleming about his boundaries, but it's clear that the multiple looks problem occurs. The more often you look at the data, the higher the false positive rates. Now you can set your boundaries as he has done so that by the end, you're really trying to minimize that, but you can see how the percent increase in false positive rates goes up with multiple looks.

So why can't we prove CVD safety? The absolute risk of CVD events is falling and, therefore, we need large numbers of subjects. When you start getting to hundreds of thousands of patients in randomized blinded trials to answer the same question, I think one has to raise an ethical consideration. We need to follow them for a long period of time and therapies change so confounding becomes a problem. Again, we're going back to the scientifically acceptable approach and whether or not it's actually doable.

We start too late in the course of the

disease because we're trying to enrich the population for those who are going to have events, but that loses generalizability and, in fact, it loses much of the biology and we lose alpha if we look too often.

We've asked some of the wrong questions and we really don't want to confound the studies further. The questions posed in this hearing pertain to the early disclosure of partial information from these trials prior to their completion. The scientific significance with each examination of the data is clearly a loss of statistical power, so forfeiting alpha further diminishes the probability of finding anything reliable from the studies that are already compromised by falling event rates and lack of power. The answer to the questions is, clearly, the disclosure of detailed analyses would undermine the integrity of the ongoing trial.

Now Dr. LaVange asked a critical question of Dr. Fleming and that's equipoise. How do we really arrive at equipoise? And equipoise for the clinicians, for the investigators, and for the patients are the areas that I can deal with. As an

investigator, equipoise is "this is an important question and I don't know which is the right group to be in and, therefore, I can legitimately recommend to my patients that coming into the trial, regardless of which arm, I have equipoise."

The issue in terms of clinicians out in the real world is "how much information have I heard from a whole variety of sources that's going to influence whether or not I'm going to put my patient on that drug and that's the problem associated with the fall in into the therapy, or am I going to pull them out of the study because what I've heard is bothersome to me and that increases the dropout rate."

From a patient's perspective, the bottom line is every single patient who volunteers for the study is the bravest human being I've ever met because they have no idea what the consequences are going to be and they trust us.

So let's go to some very simple examples of equipoise and confidentiality. Let's talk about advisory committee hearings at the FDA and what impact those have had on clinical equipoise. I had the great

pleasure of being part of the original 2008 panel as an invited guest of the FDA. I was at the 2010 hearing. I was at the most recent hearing as well. Clearly, what has happened with rosiglitazone has severely damaged equipoise. Regardless of what the data are, how they are interpreted has had significant negative impact.

All I would do is refer you to the last rosiglitazone hearing in which the question was raised "Can we do the TIDE trial again?" The TIDE trial was discontinued because it was felt there was not sufficient equipoise and reversed last year. And there was a unanimous agreement that there was no longer equipoise in terms of performing what everybody believed was a necessary scientific trial.

So what I would say is that we have an awful lot of people who have volunteered their time, their health, and their money to doing cardiovascular outcome trials. The last thing we can do is to damage the quality of the trials that are ongoing, and the most we can do is to begin to ask the question about their ethics. Thank you.

DR. LaVANGE: Thank you, Dr. Ratner. Are there questions from the panel about this presentation?

(Whereupon, no response; no questions posed.)

DR. LaVANGE: Okay. I think we're good. Thank you.

Our next speaker is Dr. Walt Offen. Dr. Offen is Global Head of Statistical Innovation, Data and Statistical Sciences at AbbVie, and I believe he's also speaking for PhRMA today. And we'll have your slides up.

DR. OFFEN: Good morning, everyone. As Lisa said, my name is Walt Offen. I'm with AbbVie but I am here this morning representing PhRMA. And for those who don't know what PhRMA does here is they created a limited duration key initiative team is what they call it, LDKIT, and basically, every company, everybody PhRMA member company nominated an individual and we have had conversations. And so what I'm presenting today is a consensus of that PhRMA group.

So a disclaimer just to say that I'm not

here representing myself or my company but rather the PhRMA viewpoints. I was tempted to say just what Dr. Fleming said and then sit down, because you're going to hear a lot of the same messages in my presentation to the points that Tom Fleming made. But there are a few additional ones and I do think there's value in re-emphasizing some of the important points that he made.

The first point here is that we acknowledge that allowing drugs, important drugs to be improved based on the interim data is important and it's a good thing. So it's certainly the current paradigm is far preferable to one where the study would need to be completed and rule out the 1.3 margin before approval. So there have been many -- or at least several cases that were noted by the previous speaker where drugs have been approved based on the interim findings.

Second point here is just as Tom Fleming very eloquently laid out, public disclosure -- and public, Lisa, to your question, really is anybody, I mean just anybody, whether it's patients participating, whether it's the public at large --

public disclosure of detailed results, and detail here can mean simply and does mean simply hazard ratio and the confidence interval, would pose risk to the ongoing trial. They could bias the prescribing behavior of the drug if it's then approved, is on the market, while the CVOT is ongoing and could have additional negative ramifications.

Again, this point was raised earlier but we concur. We recommend that the guidance that was published in 2008 for diabetes drugs should make recommendations on how companies should handle interim data. The slide that had some discussion on Tom Fleming's talk is a good one, the different options, a, b, and then a.1 if you will, the intermediate way of handling this. That should be laid out so there is greater consistency across the various diabetes drugs and obesity drugs that require these cardiovascular outcome trials. And the guidance should state that only limited interim data -- and really, what we mean by limited interim data is simply to say that the 1.8 margin has been met, has been ruled out so the drug is approved, so it's not even really data per se.

Finally here, the PhRMA encourages FDA to engage in an open dialogue on the rationale for requiring a full CV outcomes trial for every single new diabetes drug regardless of biological plausibility, whether that's non-clinical toxicology, toxicity, or clinical signals of risk. I see this as similar to many years ago when the thorough QT studies were required and initially, I think it was required for every drug. And over time, the FDA came to realize that there are cases where such a study is not necessary, and that's basically the message here, is that there may be drugs where these CVOTs are not necessary.

So, what happens if these interim data are disclosed; again, hazard ratio point estimate and the associated confidence interval? And also, this point has not been brought up previously. What about the other cardiovascular safety data? I think those probably also should be kept confidential. In fact, probably all the data from that CV outcomes trial should be confidential, so things like blood pressure and some labs and adverse events that could tip off

the public -- again, could be any aspect of public -- on whether that drug seems to be having or trending towards an increased cardiovascular risk.

So this has been really well-described by Tom but again, if you only have 20 percent of the data, which is what you have, 20 percent of the information at the interim, those confidence intervals are very wide; the data can be very misleading. And something that Tom pointed out that I want to say in a slightly different way that I think is a good point, the HIV example-AIDS data that he showed suggested a non-proportional hazard rate over time. And so what you could have if you picture two drugs in a cardiovascular outcome trial where in the long-term, both have the same increased cardiovascular risk but one of those two drugs, conditional on having cardiovascular outcome is much more likely to have it early, in the early months even, of the trial, the interim data is going to show a hazard ratio that's actually higher -- a higher estimate, biased higher, and if the trial is allowed to continue, you will see those rates come down as the AIDS example that Tom

shared.

There's a risk of modified behavior of the participants and investigators if these data are made available. These points have been made already. New patients may be less likely to enroll or even continue the participation of patients in the trial if those interim results are made known and thus there is a significant risk that the trial will be unable to achieve the primary objective.

Now if that trial -- if the original trial is jeopardized, then a company has to assess whether a new trial is even feasible. There's case-by-case determination. But ethics committees and IRBs may have difficulty in approving such a follow-on trial if they have the results from the interim.

Here I want to make a point that's not directly on the slide. Tom mentioned that one could consider stopping, the paradigm where you have two cardiovascular outcome trials. First one's done to rule out the 1.8. Then you start another one to try to rule out 1.3. I think many of the issues that he raised and that I agree with would still be there for

that second trial because now the equipoise may still be an issue. Everybody knows the point estimates, 1.26 let's say, and the upper limit is 1.79, so it achieves approvability standards but it looks bad. And so now to try to start that second trial, you have those same issues as if you just let the original trial continue.

This is another issue that hasn't been discussed yet but it clearly needs some careful consideration and discussion. This goes beyond just the FDA. You can imagine the FDA and the sponsors may all agree to keep the results confidential, very limited number of people in the sponsor or CROs, but if another jurisdiction, another country that the package the NDA has submitted to decides they don't agree with that and they make the data known, then essentially the data are known everywhere. I mean even without the internet, that would be true but now with the internet, if it's known in one country, it's known everywhere. So this is a potential concern.

So again, we would suggest that we see in the guidance a description of how disclosure of the

interim data should be handled by companies internally and how FDA will handle the public disclosure of the interim data, again, to provide a consistent and predictable framework. Publicly disclose only the -- obviously, any information on the trial design, how many events are required for the trial to be completed and a final analysis occur, all of that is fine. And really, the only data or information that should be disclosed is the fact that if -- assuming this is true, of course -- but if the data show that 1.8 is ruled out.

So we suggest using FDA's approach in this March 12th memoranda which they distributed prior to this meeting. Use that as a model which, again, says the data are unblended to a defined group of firewalled personnel in the company or third-party vendors. I will make the point here that third-party vendors, we consider as, in a sense, an extension of the company because they are certainly paid for their services. And so whether it's internal sponsor people or CROs, that confidentiality and firewall must be in place. And data would be disclosed pursuant to

confidentiality agreements. I agree with what Tom said that it can be done. I know in my previous employer, we had letters that everyone had to sign that made very clear that this confidential and certainly any breach of that would lead to loss of employment, etcetera. So I mean it was made very clear how important it was.

And then finally, we recommend the FDA refrain from publicly disclosing these data based on the interim.

Alternative methods, a couple of thoughts here. One, I made this point earlier but there may be cases based on biological plausibility and previous information either on that drug or perhaps others in the same class that alternative methods could be considered such as real-world evidence, patient registries, sentinel-like claims data databases to assess the safety post-marketing. And again, the second point here is that we recommend tailoring the methods based on the biological plausibility and prior evidence of cardiovascular risk associated with that drug.

Additional considerations: We recommend -- this -- I know this isn't the purpose of this hearing to consider. This is really a hearing assuming that we have a cardiovascular outcome trial with an interim analysis, how do we maintain confidentiality. But nonetheless, we do recommend that guidance requirements -- well, first of all, guidance requirements have increased the development time. Initiating a large cardiovascular outcome trial during phase three development can double the costs. It puts a lot of patients, as the previous speaker indicated, hundreds of thousands of patients that have participated in these trials and so that needs to be put into perspective.

The cardiovascular outcome studies of the anti-diabetic agents to date: So far -- including the record trial, so far they have shown no evidence of increased cardiovascular benefit or harm.

And finally, the footnote shows the reference here but a recent study examining the benefit-risk ratio of the current requirements suggests that focusing on reducing the cardiovascular

risk may not benefit patients overall due to the resulting potential loss or delay in access to new anti-diabetic agents. So it basically is a statement to say we need to look at the benefit and the risk together and not just focus only on cardiovascular risk.

So to conclude, to just re-emphasize the key points, protecting detailed interim assessment of CV safety from public disclosure before the final results are available is in the best interest of the patients, the prescribers, the public, and the sponsors. The guidance that was published in 2008 should be -- should address the type of interim data that may be publicly disclosed and how companies should handle interim data internally using the -- we recommend using DA's approach in that March 12th, 2013 memo as a model.

We recommend considering alternative methods to assess the CV safety post-market and finally, we recommend to engage the stakeholders to re-evaluate when those large cardiovascular outcome trials should be required. Questions?

DR. LaVANGE: Thank you, Walt. Any questions from the panel? Yes, start with John.

DR. JENKINS: Does PhRMA have a position on Dr. Fleming's proposal for a data access plan that limits access to the data to those necessary to submit the regulatory application? He emphasized several times that people involved in the business matters of the company as well as those involved in continuing the ongoing trial should not know the detailed data. So what is PhRMA's position on that proposal?

DR. OFFEN: Yes. We do concur with that. I think having a detailed access plan and not only having an access plan but actually documenting who saw and who needed access to which data. And I think -- I forget who made the point; maybe it was Lisa earlier -- that there are different levels of unblinding. Someone like a statistician who's actually doing all of the analysis of the data, as I said, including adverse event data, everything relating to cardiovascular data, would have access to patient-level blinding -- unblinded, so that would have to be noted. And then others would have access

simply to the hazard ratio and the confidence interval. So, yeah, I think that that makes a lot of sense. It would not be something where we would just say "Yeah, we firewalled" and we don't really know who had access to the data." We need to know they are and have a plan for it.

DR. LaVANGE: Bob.

DR. TEMPLE: You briefly noted that the problem associated with completing one modest sized study and then going on to another is not all that different from looking at the interim results; that is the effects on the subsequent trial seems similar. Tom sort of hinted at that a little but that's important because, you know, Mat presented those as alternatives. And there has been some view that it was better to separate them but you don't seem to think there's all that much difference. I wondered if you wanted to elaborate on that.

DR. OFFEN: Sure. Well, I tell you, not only is there not necessarily not that much difference but I think there is potential harm. If you're doing an interim analysis as we're talking about here, many

of those patients are still, you know, ongoing. In fact, the majority of them probably are still ongoing, and if you terminate that trial right there, you lose a lot of information. You force most of the patients or at least many of them into essentially being censored. You don't know if they would have had a cardiovascular event. And to then restart a new trial -- so that's a negative, a mark against the strategy that says stop the first trial, submit it, you get approval, you can publish those data and then now start a second trial.

The point I made, and I do feel pretty strongly about it, is that if you think in that paradigm -- so let's say the point estimate is 1.26, we'll make it that extreme case, upper limit 1.79, that gets out into the public now. That trial has completed. Now you're trying to start a new trial. You got to get IRB approvals. You got to get patients interested in enrolling. You've got to get the physicians that are participating in the trial to have equipoise. Everything that I think that Tom laid out as a concern of sharing the interim data that could

affect the conduct of the ongoing trial would apply in this situation where you now have a new trial.

DR. LaVANGE: Aloka Chakravarty.

DR. CHAKRAVARTY: Walt, you mentioned disclosure anywhere is disclosure everywhere, and different regulatory agencies have, you know, different considerations into the disclosure rates or evidence rates.

So in your group, did you discuss any recommendations or any considerations based on the global effect of disclosure?

DR. OFFEN: Yeah. That's a good question. We -- to answer the question did we discuss it as a group, no, not -- we pointed out that this is an issue, important issue. But I have to admit while I was sitting over there listening to the previous speakers, the thought occurred to me. And I think this is a consideration that sponsors would have to make is that if we knew a particular country, let's say, and let's say it's even a small country, when we make our submission, they will publish the hazard rates, and so I think this -- it's incumbent on the

sponsor to really think hard should we not submit to that region or that country until the trial is completely over, because it's in the sponsor's best interest -- I mean even -- again, sponsor makes that kind of decision, you could argue, shouldn't have the access to that interim data. And it's a risk to say I'm going to go ahead and submit there knowing they're going to open that data to everyone. It may very well risk the ability to complete the trial if that's done. So that's the only idea I've come up with but I think maybe we need some ICH-level discussions on this and see if we can get agreement from at least the major countries in the world.

DR. LaVANGE: Patrick Archdeacon has a question.

DR. ARCHDEACON: Yeah, thanks. So I think after Dr. Fleming's talk, Dr. Jenkins had pointed out that there is an alternative "c."

DR. OFFEN: Yeah.

DR. ARCHDEACON: I just wonder if you could react to that a little bit but in the specific context of a presentation to an advisory committee. So it

seems as to b would imply that perhaps that this was done -- at least a segment of it would be a closed committee session. Here, it would essentially remove the cardiovascular outcome trials or at least any details of it from being discussed at advisory committee. Is that something that PhRMA has a position on?

DR. OFFEN: Yeah, we do. Well, let me just make sure I understand the question. You're asking me whether PhRMA has a position on the option that was brought up as in between the a and b where the sponsor has no knowledge, nobody at the sponsor has knowledge, it's just the DMC submitting directly to the FDA; is that what you're asking, right?

DR. ARCHDEACON: Right, and I guess -- and I think you answered some elements of that earlier and I'm just wondering right now if you could comment on specifically whether PhRMA has an opinion about whether it is good, bad, or indifferent if a discussion about the details of that trial are removed from the advisory committee meeting.

DR. OFFEN: Yeah. The -- so that's a more

specific question about the advisory committee. Yeah. I would have to believe -- we didn't discuss the advisory committee aspect directly but I would have to believe that PhRMA would say it's the same answer as divulging it to the public. Again, as I said, public can be anything and if it's said at an advisory committee, unless it's closed and so you have -- you know, you limit to how many people see it and they sign confidentiality agreements, unless that occurs, that would not be advisable.

DR. ARCHDEACON: Yeah. I'm sorry. Let me clarify one more time if I can. So since there would be an asymmetry of information between the sponsor and the regulator about this, the CVOT when you're going to the advisory committee, I'm presuming that what would wind up happening is there would probably be no discussion of it at the advisory committee.

DR. OFFEN: Right, okay.

DR. ARCHDEACON: So the FDA, in some degree, after hearing the advisory committee about the risk-benefit in the absence of that discussion would then later weigh their own opinion. Would that be a

concern for industry or not, that FDA would have a sort of a second phase of its consideration that were outside of what was discussed at the advisory committee?

DR. OFFEN: I don't know -- I guess I don't know exactly what PhRMA would say to that, but there is a position to not even go that route. So in other words, the intermediate thing where the sponsor -- nobody at the sponsor sees the data. The DMC sends summary data directly to the FDA. Our position is not -- we're not fond of that and one key reason for that is that to make a submission, the company really needs to look at the whole picture, benefit-risk. So I could see a case where you have a 1.26. It meets the 1.8 barely and a sponsor might see other risk factors, could be other side effects, cancer or something of that nature where they would say we don't even want to submit this. It's over for this compound.

So the position, I feel, is that the information does have to come to a limited number of individuals at the sponsor. And maybe I'm still not tracking your question then. So if -- so given that,

you still wouldn't have it in a public advisory committee, those data. If it is a closed kind of a session, then I think those sponsor people would be there. The ones that are unblended could be at that discussion. Does that -- did I address your question?

DR. ARCHDEACON: Yeah. I think you largely have. I guess I'm just sort of -- as I was following that line of thinking, it had seemed to me one implication of this would be that the FDA would ultimately make a regulatory decision based on some information that the sponsor did not have.

DR. OFFEN: Right.

DR. ARCHDEACON: And I think that's just what I'm trying to drill down to is what the comfort level regarding that is.

DR. OFFEN: Yeah. Generally, not comfortable but I mean every company, of course -- every company can make their own -- there may be some companies that would feel that, in certain situations, that they're fine with it, but generally, no.

DR. LaVANGE: John, did you have a follow-on?

DR. JENKINS: I just wanted to ask a follow-up to my question at the beginning because I wasn't clear because toward the end of your answer, you said something about, you know, you'd have to decide what people in the company would need to have access to data, and you talked about point estimate and confidence intervals.

So can you clarify again beyond saying "we met the boundary" and providing the full data to the unblended team that's going to be preparing the regulatory submission, can you say more clearly your thoughts about whether other people within the company, say the management team, would be aware of the data at the point estimate-confidence interval level or just "we met the boundary?"

DR. OFFEN: Yeah. I think what you're getting at is how limited -- who -- what kind of sponsor personnel are privy or have access to the unblended safety data and what level of data do they have access to. I would generally suggest that management would only know that the -- that we'd met it, that they know that we're -- submission is going

in, the 1.8 has been achieved. They have -- in general, I'm saying management, as like very senior management, have no reason to see the detailed data. Now there will be some individuals in management, maybe a therapeutic area, you know, the head of the diabetes research unit or whatever who would have access.

So I don't know if I'm answering your question exactly but the point is a data access plan would identify who has access to what level of unblinding and why. So I don't think that group has to be extremely large. Much of it can be given to CROs but as I've indicated, I think we still would identify who at the CRO has access to the unblended data and that number should be small. I mean you wouldn't want to give the data to everybody, every employee at Quintiles or something like that. So it would be very limited. Did that help at all?

DR. JENKINS: Yeah, that's helpful. For example, should the people in the company who are responsible for making the business's decision to continue pursuing approval of this drug or to raise

money to complete the trial be aware of anything beyond "we met the boundary?"

DR. OFFEN: I don't think so. I don't they would need to. I think it's those that are putting together the submission to the Agency and other parts of the world that would have to have access.

DR. LaVANGE: Okay. We may bring you back up --

DR. OFFEN: Okay.

DR. LaVANGE: -- for additional questions but we need to move on to Kelly Close from Close Concerns and we'll get your slides up.

MS. CLOSE: Thank you. I was just trying to set this up. I think we are going to put it in presentation mode, might not be possible. Okay, no problem. Well, let me introduce myself. Good morning. My name is Kelly Close and I really thank the FDA very much for the opportunity to present to you today. It's really an honor to present both to you and esteemed colleagues and attendees on behalf of our teams at Close Concerns and at the diaTribe Foundation. So patients really salute and extend

appreciation to the FDA for calling this important hearing and for requesting broad opinions and including the opinions of patients.

Just as a bit of background -- I'm President of Close Concerns which is a healthcare information organization focused exclusively on diabetes and obesity founded in 2002. I have had diabetes for nearly 30 years and this work is of deep personal interest and importance to me. As far as disclosures go, over 100 organizations have scribed to *Closer Look* which is Closed Concerns' b based news service on diabetes and obesity. Over 80 percent of those are for-profit based organizations. Some of those are sponsors who've applied for approval for drugs over the last 12 years. The rest of the subscribers are non-profit and government organizations. And I paid for all my travel here today.

At Close Concerns, our mission is to improve patient outcomes by making people smarter about diabetes and obesity. We attend over 50 scientific, medical, and regulatory meetings ever year. We follow over 80 public companies every quarter, and we're

lucky to converse and regularly learn from some of the most well-known thought leaders in diabetes.

Today's meeting is about interim data disclosure from CV outcomes trials which seeks to balance two opposing factors as indicated on the slide. I think a key question that follows from this rationale is what the risks are to interim analyses of CV outcome trials, and I'm going to talk about this mostly from the perspective of the patient today.

There are a couple of risks to point out and those are on the slide here. The first is just in some cases, interim CVOT data could result in misleading conclusions. And second, interim data disclosure could compromise a trial. So here's a hypothetical example. What would you say upon seeing this interim data from an outcome trial at a one-year mark? "Participants in the treatment group had a 13 percent chance of having a certain adverse event while those in the control group only had a 7.6 percent chance. This represents, obviously, a highly significant odds ratio of 2 to 0." Some researchers might have said, when asked if they would stop the

trial, "Yes, that data looks concerning and could well justify ending the trial." If you said yes -- of course, a lot of you know this data -- you would have stopped the DCCT. The one-year interim data results for retinopathy within the DCCT suggested that intensive therapy to reduce blood glucose caused retinopathy. Now I'm showing this as just an example of what could happen.

As many of you will point out, the DCCT retinopathy illusions could be considered spurious for a bunch of different reasons, right, differences in biology, study objectives, levels of evidence, decision algorithm and more. However, the point is that in extreme cases, deciding on trials using early data could conceivably create a problem by preventing researchers who are working toward valuable decisions that are able -- only able to be obtained over the long term.

And as you can see in this plot, the retinopathy curves in the DCCT didn't begin to separate until year three of the study. And just on a personal note, I would say I actually remember this

study. You know, I had been in the emergency room two or three times a year until the DCCT happened. Then Dr. Jerry Share (ph) at the Joslin Clinic explained to me how my life would change if I didn't take exactly the same dose of NPH and exactly the same dose of regular insulin every morning and every evening no matter what I was eating, no matter what I was exercising, no matter how much stress I had. The DCCT actually had, as all of you know, very, very major differences not only just to type 1 patients but it served as an important model for a type 2 trial to begin.

So interim data disclosure could compromise trial results and it's really -- I get nervous when I think about what could have happened with the DCCT stopping early.

This quote is taken from a March 29th FDA Division Director memo for an SGLT2 inhibitor. And we see in "d", there are now three outcome trials for this SGLT2 inhibitor alone, perhaps partially because the original CVOT was potentially affected by the public disclosure of interim data at the FDA advisory

committee.

As Dr. Fleming said very well -- I don't even really need to go over this slide again but FDA statistical best practices are super clear about the disclosure of interim data from clinical trials. So the following is a direct quote from the 1998 FDA guidance documents, and that notes that the exclusion -- that the execution rather of an interim analysis should be a completely confidential process. These unblinded data and results are potentially involved. And I just emphasize that last sentence. Any interim analysis that is not planned appropriately may flaw the results of the trial and potentially weaken confidence in the conclusions drawn. So whether or not this should be avoided or whether or not the guidance should be refined is a question for the researchers and scientists and advisors at FDA.

And patients really want you to talk about it and figure it out. We know that that is all part of this process.

So with that in mind, what are some of the alternatives to interim data disclosure, or what are

some of the different ways of thinking about it that we think could serve patients? So a few of these are listed on the slide here, and I'm not going to go through all of them in depth because there actually are so many of them but I want to go through a couple.

So, you know, we think as -- we think a lot about benefit-risk as patients and we'd love to tell FDA more about how we feel about. And patient groups are really heterogeneous so it's not like there is just one patient perspective. There are many patient perspectives. But I think many patients certainly would agree, and my colleague, Manu Venkat, is going to be talking about 5,000 patients that we surveyed just last week on some of these questions, but, you know, we think that patients are a very heterogeneous group the way they think about trials and so forth. We also believe that different ways of thinking about drugs probably are impacted by the benefit that the drug brings. Some drugs are "me too" drugs; some drugs have potential to be transformational; and some truly are and look very transformational from the early data that we see.

So approving a drug earlier without CVOT data for certain segments of a type 2 population with lower cardiovascular risk or higher need could actually reflect, you know, the heterogeneity of that patient population. So while there might be valid concerns about potential off-label use in higher risk patients where there are conditional approvals, we still would like conditional approvals to be considered.

And again, if you think, asking patients about how much risk they're willing to take on is really important. They obviously need to be educated and we can understand a number of objections to conditional approvals but given the propensity of professional organizations like ADA, ESD, and ACE and others to encourage individualized therapy, we believe that a one size fits all approval strategy does bear some re-examination.

One strategy we frequently hear is keeping interim data blinded until all, except for an ad hoc firewalled group similar to the data safety monitoring boards that already exist for clinical trials and that

have been discussed quite a bit today already. So here, data disclosure to the public obviously would ideally be minimal; hopefully, that can actually happen, but selecting the group does pose challenges. Some stakeholders might not feel confident in approval granted on the basis of a thumbs up or thumbs down from this ad hoc group. How the media gets involved, leaks, things like that are also a concern.

We also believe that these researchers and clinicians who would be in this group should include those who have some deep knowledge of drug development. While it's very important not to include anyone conflicted, we also would want to make sure that the group included those who really were the most well and most recently informed on drug development.

Solutions that involve barter changes to the timeline, development and approval include to moving to fully pre-approval CVOTs while extending drug patent life to compensate for the resulting delay in possible approval. Imagine something like this. Something dramatic like this probably would require Congressional approval but I still think it's

something that we could -- I think it's still something that we might want to think about. You know, it's complicated but we want to urge more thinking on this just because given the major changes that CVOTs have brought to the field, this is a big deal not just in terms of expense of trials but also time.

Another solution that's already been discussed a little is collecting CV data earlier in clinical development. Of course, phase two trials are typically much smaller so this might not be very practical.

There's another one in here that actually isn't on the screen but that's interest has been shown in large sample trials, and I thought about that because we're going to hear about one of those on September 11th. I'm really eager, as I know a lot of patients are, to see how those proceed. So conducting trials in high-risk subpopulations provides faster, less expensive readout, obviously, than doing longer trials in the general population even though some would say that there are real ethical, clinical, and

scientific objections to this expediency.

With that said, the large sample trial is designed to use the intended general population in a real-world setting, reduce costs, and increase interpretability. We'd be eager for views on this from the expert clinical trialists in the room. So clearly, those are pretty dense sets of options.

What's clear is that there is no absolute win-win. There is not. And we appreciate that FDA, through interim analysis, is trying to make it possible to get data to advisors earlier (inaudible) and the compounds are deemed safe, the compounds that are deemed safe can get to patients earlier.

On the other hand, there's no clear-cut answer how to best do that. Following this public hearing, we'd love it if FDA would call together researchers and scientists and other advisors to discuss this question given the learnings of the last six years as well as the learnings of today.

So, you know, that brings us to one other question which is effectively another risk-benefit question. Are CVOTs, the way they're structured now

in light of the decisions on Avandia, the best way to evaluate CV safety? I fully recognize and appreciate that this is not the forum for any discussion, much less decisions, on anything other than interim analysis, but just a few quick thoughts.

First, it's unclear whether data is generalizable given that particularly sick patients are used. We understand as patients why that's done but it doesn't really change the question and it doesn’t help us understand it any more when we think about who's in the trials. To boot, the trials also have a sizeable number of patients treated over fewer number of years. As patients, we wonder, okay, it's by 1000 patients over 5 years; is that the same as 10,000 patients over 2-1/2 years; is that the same as 20,000 patients over 1-1/2 years and, you know, you could go to infinity thinking about all of this.

Again, we understand why it's done but would love a little bit more explanation from patient perspective when we go into these trials exactly what's being looked for.

Next, we just talk about exposure to the

(inaudible) drug. It might not be long enough given that trials have been seeing higher event rates than actually have been expected when we look at this most recently.

One of the things that the patients are most curious about is, of course, the potential benefit that might be viewed from looking at CVOTs but most CVOTs really weren't designed to show benefit. UKPDS, NDCCT, as we heard from Dr. Ratner, each required 10 plus years of follow-up to show benefit. And I know these are not the best examples. I know there are a bunch of confounding factors, and I do think that the power of big data could be enormous.

And we hope that FDA is able to work with pairs individually and collectively, also to learn as much as possible about questions of safety. And we also hope that it can work with global regulatory agencies even more than it already has.

Specifically, the SAVOR and EXAMINE, two major CVOTs for DPP4 inhibitors, there was a maximum of two years of feedback. Patients would love for there to be longer feedback for those trials but far

be it for us to ask for sponsors to pay for these trials. Perhaps it could be funded by the government, perhaps funded by a consortium, maybe do the fifth, sixth, seventh companies who are doing these trials once safety is established in a certain class, maybe some of the funding there could go to look toward long-term benefits.

We also wonder if it's possible for the FDA to discuss the 1.8 interim (inaudible) thresholds and whether or not they're the optimal thresholds given what has been learned since 2008. We certainly don't want to provide any quotes out there out of context so we're going to move past this slide, but this is from a major KOL in the room who actually said this quote at a recent scientific meeting. I believe it was IDF 2013. FDA has a Closer Look subscription as do many here. If you don't, just let me know and we can email you the full conversation here. We're going to skip over some of these slides again because we want to be able to add some context from how patients look at things.

And so I'm just going to talk for a minute

about -- before we talk about innovation, I want to talk a little bit about what patients hear when we listen to FDA trials and we hear researchers talk about, you know, there are 12 different classes of drugs; why does this have to go that quickly, you guys can wait; right? So, you know, when you talk about that, some patients sort of hear it as reductive, some patients might hear it as insulting.

You know, until relatively recently, virtually all of the 12 classes have had aspects of them that have actually made them pretty hard to use and actually pretty hard to prescribe as well, right, so aspects of them, like hypoglycemia, like weight gain, like edema, like association with congestive heart failure, nausea, problems with bone density, uncertainty about the broader side effects, concerns about potency. This doesn't mean that the risk-benefit to using any of these other drug classes isn't worth it from a patient perspective, but in terms of socioeconomic status, diabetes hits patients at the lower end disproportionately. Many patients have no access to HCPs who can really help them titrate the

drugs, come onto the drugs, stay on the drug successfully. Many patients don't even have access to doctors.

And while some believe that 12 classes might be enough and that more are not needed, others do think that more innovation is needed and we'd love FDA to consider collecting more opinions about this as well.

So then we -- so we come to -- and this important because this came up in one recent FDA meeting where Tresiba was not approved even though the actual FDA committee said that it should be approved. And it was interesting for us to think about because, of course, we're lucky at my company, at diaTribe, you know, a free online newsletter for patients, we do our homework, we knew that that Tresiba was an input into IDegLira, right, and so IDegLira, you might not think Tresiba itself. You can have your own opinion about whether or not you think how much different that is from the other basal insulins. But we would like FDA also to think a little further down the road at what the inputs create; right? So if you think about

IDegLira, that actually is very different, and this has been according to many researchers that we've heard all over the world.

So even if you might want to argue for safety's sake, you know, because you want zero safety risks so you think that patients can wait for it, but we want to get to the point where patients stay healthy. We want them to go on therapy early. We want them to stay on it, adhere to it, and they will be less likely if they adhere to it to costly hospital visits that are absolutely preventable if people get diabetes management programs at the very start of their diagnosis that are geared toward keeping their glucose levels and cardiovascular health safe and optimal. Those are just a couple of those quotes that I wanted to show you.

Another negative is just that companies are leaving diabetes. This goes back to innovation and we would never say that this is only because of things that are happening at FDA, but we do think that it has something to do with it. You can add Genentech to this. You can add Novartis not for leaving diabetes

but for deciding recently not to make it one of its five areas of major focus; right?

So on that note, I will say that we'll just say a couple of other quick things. We, as patients, do worry about who's paying for all of this. We worry about how ethical it is. We worry about if we're benefitting as a patient community. I can even tell you that as much as we worry in the diabetes community about having shortages of PCPs, having shortages of endocrinologists, this is actually also keeping people from going into research.

And this is only an isolated example but I have to say to you I saw this young resident recently and he said he loved research; he had an article in *Diabetes* recently called "Repurposing Diabetes Drugs for Brain Insulin Resistance in Alzheimer's disease." His group just presented this at the ADA. He said he wasn’t going into diabetes not because he didn't find it intellectually fascinating and incredibly rewarding but from a public health perspective, it was too uncertain in terms of research potential. Obviously, only one person but these are the things that patients

out there worry about. I don't know when my doctor retires in San Francisco who is going to take care of me next.

So we come back and just say patients are advocating for FDA to find ways to better characterize risk and asking to have their opinions counted on how much risk they would like to take on. Clearly, benefit-risk calculations need to be designed in a way that don't unduly shortchange either safety or efficacy. So it would be positive to have to reduce ambiguity. It would be positive to have to -- to reduce ambiguity about the complexities of data.

We are very happy to hear in 2011 that CDER was working to set up a standardized framework for the benefit-risk equation with the aim of encouraging attention on matters that are important and avoiding errors.

Thank you to FDA for seeking to improve the clarity of the review process. Thank you for considering with the interim data confidentiality issue as well as the broader CVOT question how we might move even closer to positive risk-benefit given

that expecting completely 100 percent safe drugs is so daunting and probably ultimately untenable.

The important thing for many patients with whom I have spoken is not eliminating risk but ensuring that it is well understood during and after development so that new therapies can benefit doctors, nurses, patients, payers, families, and society who pays for everything related to diabetes. Thank you.

DR. LaVANGE: Thank you very much. We -- are there any questions now for Ms. Close?

(Whereupon, no response; no questions posed.)

DR. LaVANGE: I think then we'll move on and take a break, and we will possibly call back the four speakers we've heard from already before lunch for additional questions. But to keep us on track, we'll take a 15-minute break which would put us back here at 10 til 11. Okay. Thank you.

(Whereupon, off the record for a brief recess.)

DR. LaVANGE: So our next speaker is Dr. Charles Hennekens from Florida Atlantic University,

and I believe he's representing the American Association of Clinical Endocrinologists.

DR. HENNEKENS: Well, thank you very much. I walked in this morning and met Steve Nissen whom I've known for over 20 years. I've chaired a number of data monitoring boards for him and he always stimulates me to focus my thoughts, and today was no exception when he pointed out that I'd been involved in these issues for over 40 years. So I best begin with a statement that once I accepted the reality that it's far better to be over the hill than under the hill, my life has been the best ever.

And on that score, I did seek input from three of my colleagues and friends, Tom Fleming whom I've known for 35 years; Dave DeMets whom I've known and worked with for 42 years, and Richard Peto whom I've known and worked with for 44 years. I've also been on and off a special government employee here at the FDA and I'm inspired by the growth and development of the many young people like Doug Throckmorton and Norman Stockbridge. They had the great advantage to learn from the masters, Temple, Lopicky (ph), Jenkins

and others whom, in my view, their clarity and judgments are equaled only by their unfailing commitments to the health of the general public over decades of dedicated service to the American public.

I'm here at the invitation of the American Association of Clinical Endocrinologists for whom I serve as an unpaid advisor to their FDA issues committees. They are paying my travel expenses. I've also served on the writing committees for their consensus statements on diabetes and cancer published in *Endocrine Practice* as well as *Obesity*, which is in press in *Endocrine Practice*. Now I've collaborated in several areas with George Grunberger, the current President; Alan Garber, the past President. I also work with Alan on his annual symposium on diabetes for endocrine fellows.

Obesity, of course, is a major risk factor for type 2 diabetes. We found in the nurse's health study a 40-fold risk. In NHANES, 40 percent of Americans over age 40 have metabolic syndrome, a constellation of obesity leading to dyslipidemia, hypertension and insulin resistance leading to

diabetes. Their a 10-year risk of a first event is 16 to 18 percent and, of course, the management of their conditions includes therapeutic lifestyle changes, evidence-based doses of statins, aspirin, ACE inhibitors or ARBs. The drugs for diabetes are less likely to reduce the macro vascular complications but surely will decrease the micro vascular complications of eyes and kidneys and their chief hazard has been hypoglycemia, in my view.

So the AACE is the world's largest organization of endocrinologists and they specialize in endocrinology, diabetes, and metabolism committed to enhancing the ability of its members to provide the highest quality of patient care.

I don't know what's going on with these slides, but they're not cooperating here. They seem to be -- I would just like the slide to come up. I don't need it to come in one thing at a time here.

So these are my financial disclosures. As a life-long academic, I think that sometimes our intellectual disclosures are far more important, although you can see the vast majority of mine relate

to being a chair or a member of data monitoring committees. The information I will present today derives from really three peer-reviewed manuscripts working with Dave DeMets, Tom Fleming, also Peter O'Brien, Jeff Bora (ph).

The first point is that meta analyses of small trials not designed a priority to do so and subgroups analyses are useful to formulate hypotheses but should not be taken as serious evidence of hypothesis testing. In fact, Peto has made a nice comment about this. If you torture the data enough, they'll confess. The problem is what exactly are they confessing to.

So with regard to the academic perspectives on the FDA guidance for industry, we believe that phase two trials should be mainly for proof of concept and dose ranging but to test reliably the most plausible small to moderate effects of drugs. The totality of evidence must include large-scale phase three trials of sufficient size, dose, and duration to achieve a clear answer and high adherence and follow-up and enough endpoints to distinguish reliably

between small benefit or harm and no effect.

And the paper that Tom presented at an national meeting is about to be published, points out that the FDA has taken the lead in mandating data monitoring committees as an integral component of monitoring plans for properly designed, conducted, analyzed trials and the primary role is to safeguard the interest of the subjects randomized and to enhance the credibility and integrity of the trial. So their proper monitoring by independent boards can provide a degree of assurance to study subjects, clinicians, IRBs and regulatory authorities which will give us the necessary integrity to do the most good for the most people.

And the FDA really astutely stated that knowledge of unblended interim comparisons from a clinical trial is not necessary for those conducting or those sponsoring the trials. Therefore, the interim data and the results of interim analyses should generally not be accessible by anyone other than the DMC members, and sponsors should establish procedures to ensure the confidentiality of interim

data.

Now with regard to the guidance for industry, as I understand the state of play, the drug can be approved conditionally if it can rule out a risk of 1.8; the upper bound of the confidence interval is less than 1.8, which requires about 200 events and then can be approved unconditionally if it can rule out a risk of 1.3. And here the upper bound is less than 1.3, which requires about 600 subjects.

Now it's been suggested to use a meta-analysis of phase two and three a trials to rule out a risk of 1.8. It may provide the best estimate of effect that should be tested in a large-scale trial designed to test the question but the utility of this strategy is dependent on the quality and comparability of the data from its component trials and this strategy will reduce the role of chance but may introduce bias and confounding. And one of my mentors when I was in Oxford, Sir Austin Bradford Hill, himself, pointed out "don't let the glitter of the T-table detract from the quality of the fair."

Now the common implementation of the FDA

guidance has been to conduct one large trial and when the interim results rule out 1.8, the sponsors may submit to FDA and request conditional approval. But as has been stated, to obtain unconditional approval to address the 1.3 criterion, it's necessary to continue the trial but this, as others have stated eloquently, may lead to unintended consequence if the FDA requires complete disclosure of interim data.

So we've heard about the principle of equipoise provides the ethical basis for medical research that involves assigning patients to different treatment arms of a trial. My textbook, Epidemiology in Medicine, we pointed out in 1987 as well as Freedman (ph) did, the principle of equipoise implies sufficient belief in the potential of an agent to justify exposing half the subjects and sufficient doubt to justify withholding the other half.

If there is a loss of equipoise and patients don't remain in the remainder of the trial to rule out a cardiovascular relative risk less than 1.3, then bias is an unintended consequence. And in the most extreme cases, all patients in the placebo arm would

start taking the active drug and the trial cannot continue. But even in less extreme cases, the assessment of an association between the drug and CV risk will be bias to the extent that any placebo patients start on the active drug and/or active drug patients drop out of the trial.

So either the release of interim data with relative risk and confidence intervals ruling out a risk of 1.8 to achieve conditional approval, or if a drug is approved conditionally because the relative risk has been ruled out and becomes marketed may lead the clinician and each of his or her randomized patients to conclude that it's neither necessary nor desirable to continue participation in the trial but to take the diabetes drug that appears favorable to them.

So we believe that when the totality of evidence is incomplete, it's appropriate to remain uncertain. Thus, I believe that the answer to questions posed at the beginning are yes, the disclosure of the point estimate and 95 percent confidence interval for ongoing trial will compromise

the trial integrity; and yes, in this case, less is more. And frankly, I do favor Dr. Jenkins' view of the situation, a statement that a hazard of 80 percent is likely to be excluded but a clear benefit has not been found is far less harmful to both the integrity of the trial as well as to the protection of the patients in my view.

So, I thank you very much for your attention.

DR. LaVANGE: Thank you, Dr. Hennekens. Questions from the panel?

(Whereupon, no response; no questions posed.)

DR. LaVANGE: No questions at this time. Okay. We'll move on to the next speaker. Dr. Steve Nissen is Chairman of the Department of Cardiovascular Medicine at the Cleveland Clinic Foundation and Professor of Medicine at Cleveland Clinic Lerner School of Medicine at Case Western Reserve. Slides are up.

DR. NISSEN: Thank you very much and let me express my sincere appreciations to the Agency for

conducting these hearings. Obviously, we're all here because this is a terribly important issue that affects decision-making for an important class of drugs and probably for others as this paradigm is potentially extended.

This is my disclosure. I do work on clinical trials with the companies listed here. However, companies are directed to pay any honorary, speaking, or consulting fees directly to charities so neither income nor a tax deduction is received, and I am paying my own way to this meeting rather than being paid for by a company.

So I want to talk about four things. Does a two-step process for approval of diabetes drugs with uncertain cardiovascular risk scrubs any valuable and viable regulatory approach? What are the most important hazards to scientific integrity if interim results are prematurely disclosed? Is it feasible to maintain confidentiality of interim results to enable completion of the definitive trial? And if interim results are inappropriately disclosed, what are the implications for conducting a new large outcomes

trial?

I want to take everybody back to 2008 when we faced this decision that led to the FDA guidance. And we all came together around this -- I don't think it was in this building but it was somewhere else -- to discuss how do we go forward. And the principle dilemma we were trying to address was how do we balance the need to bring new diabetes agents to patients in a timely fashion versus the need for a more robust outcomes data that inform physicians of how to use these drugs safely and effectively. And we realized that merely showing that a surrogate endpoint, blood glucose lowering, would be reduced by the drugs was not a sufficient regulatory standard, and I think everybody agreed, Agency, academics, that this was the right way to go.

Ultimately, we came together with the following principle: that requiring a large outcome trial prior to approval was undesirable because this approach would delay new diabetes therapies for five to seven years. And I appreciated the comments of Ms. Close who points out, of course, the interest of

patients and also, of course, the interest of people who want to develop drugs that you have to have some approach that would be a compromise.

And the compromise that we all came together around was that it would have two components: initial ruling out of an upper confidence interval of 1.8 and then to continue marketing the drug, a large randomized outcomes trial to rule out 1.3. This was a compromise. This was not -- I mean optimally, you would like to know everything you could about a drug before it came to market but we recognized that there were competing interests. And as one of the people who proposed this paradigm, I fully understood that there were societal benefits to a two-stage process. That's why we did what we did.

Now you've seen this in many different forms and I'm not going to belabor it but just to point out that, you know, what we're talking about here is 122-event pre-approval trial and approximately 620 or 611 if you prefer post-approval. For initial approval, the critical values are with 122-event trial is less than 1.26. I want to make a point it is a prediction

and only the Agency will ever know the answer to this, but I don't think you will see any applications with 1.26. I think if a sponsor's blinded team sees a 1.25 point estimate, they're going to not submit that trial. I think -- this was what we came up with but, in fact, my guess is that those programs will not go forward.

Above that level would be non-approvable. And importantly, even if 1.3 is ruled out as shown in the third example there, it would be approvable but a 620-event trial is still going to be required because what we're looking is their interim analysis at only 20 percent of the data, and so the kind of O'Brien-Fleming analysis would be necessary there. So in the end of the day, once this two-stage process is undertaken, we're going to want to go to the 620-event trial.

The critical point for the post-approval trial is a point estimate of 1.11 which will rule out 1.3, a terribly important decision will need to be made by the Agency sometime in the near future. What happens when you get a study at the end of 620 events

has an upper confidence interval of 1.3? Do you or do you not withdraw the drug from the market? And I won't go -- that's not the purpose of today's meeting but I do think it is important. But in making this proposal, our hope was always that somebody would actually reach superiority, that -- you know, the argument was that merely having a drug that's neutral for treating a morbid mortal disease like diabetes was not a goal. The goal was to stimulate the research that would lead to the development of therapies that could reduce morbidity and mortality. And so by requiring these trials, you have a much greater chance that somebody will actually be able to ultimately demonstrate superiority which would be a tremendous triumph for patients and for society in general.

Now the 122-patient trial to rule out 1.8 represents a reasonable accommodation to allow sponsors earlier access to market and patients earlier access to potentially useful drugs. But in my view, it does not provide sufficiently robust safety and efficacy data to inform physicians adequately about the risks and benefits of diabetes therapies. And if

I make no other point today, is that the goal of these development programs must be the completion of an adequately powered, high-quality outcomes trial to rule out 1.3.

One point eight is not the goal; 1.8 is a convenience and so anything that we do that compromises the ultimate goal of these development programs which is to have a robust outcomes trial is not in the best interest of society.

The societal benefits of this regulatory policy, in my view, are that the insights provided by the new regulatory approach -- and I believe that the Agency acted wisely in issuing the December 2008 guidance -- that these -- these are profound and they're likely to grow substantially in coming years. Preserving this approach is of great societal value because it is ultimately the bridge that may get us to therapies that actually will improve outcomes for patients with this disease that as everybody in this audience knows is growing at incredible rates in the United States. And if you want to see how many diabetics there are, just go to the Third World. I

mean it's just unbelievable. And so by leading the way here, FDA is providing a global advantage for patients, to give us the data we need as clinicians to pick the right drugs to help these patients improve their outcomes.

Now, as a result of the FDA policy change, as has been mentioned by several speakers this morning, there has been an explosion of new studies, and I guaranty this is an underestimation. The Agency probably has much better data than I do, but there are over 100,000 patients in studies. Unlike some of the earlier speakers this morning, I see not one shred of disadvantage in this. Having 100,000 diabetic patients in clinical trials, thank goodness. It's a tremendous to society to be able to have clarity about what these drugs do and what they don't do, and that clarity will extend far beyond cardiovascular outcomes because these large trials are collecting a lot of information, and that information will be informative about how to use the drugs, about unrecognized potential adverse effects. We're going to learn more about diabetes drugs over the next 5 to 10 years than

in the previous 40 years, and I think that the Agency should feel very proud of the fact that you led the way in doing this.

The first of these trials are coming in and as anticipated, are providing insights. It's been discussed, the SAVOR trial which was a well-designed and well-executed cardiovascular outcome trial of saxagliptin, a DPP4 inhibitor and as I think everybody is aware, although it was predicted by many people that the DPP4 inhibitors would reduce cardiovascular adverse outcomes, they did not. They were neutral, 1.00. But I want to look a little further at this trial because I think it does provide some insights about where -- why this guidance makes a lot of sense.

First of all, on the primary endpoint, I would like to point out that this was not a 611 or 620-event trial. This was a 1200-event trial so it was considerably over-powered for demonstration of the 1.3 upper confidence interval. And that wasn't a problem because the drug was neutral. But what would have happened, and I want to make sure everybody thinks about this, had there been an elevated point

estimate for this trial? Let's imagine that the point estimate had been above 1.11. It could have been above 1.11 and still ruled out 1.3 but would it have met the spirit of the guidance? And just -- it's a rhetorical question.

But more importantly, a previously unrecognized hazard of the DPP4 inhibitors was identified, namely in a component of the primary endpoint, hospitalization prior to failure, there was a 1.27 hazard ratio with a p value of 007. Now we always consider components of endpoints to be hypothesis-generating but there is a point I'm trying to make here. And the point is that once the Agency made the decision that they were going to require these outcome trials, we all, in the clinical community, learned important things and are going to learn important things about these drugs that we need to know. And that is why we have to fight to preserve this paradigm, because this paradigm gives us information on the use of these drugs. And I can tell you this information is informative. It's not definitive because it's a component of the primary

endpoint, but it's informative and it is being used today by clinicians to make decisions.

A previously unknown hazard was identified and although the findings for endpoint components should be viewed cautiously, this observation provides vital clinical information for physicians, patients, and regulators, enabling better clinical decision-making and enhancing patient safety.

What are the hazards to scientific integrity if interim results are prematurely disclosed? Well, you've heard from multiple speakers and I don't want to belabor it, but I want to give at least a couple of thoughts about it. In my view, the principle here is always that less is more. If investigators, practicing physicians, or patients are aware of interim results, an ongoing trial would potentially suffer unacceptable loss of viability. We live in a contemporary culture with 24-hour media coverage of medicine and research. Within minutes of a clinical trial announcement, journalists begin reporting on the event. The investment community closely tracks clinical trials. Patients and business interests have

continuous to information via the internet. I mean, literally, this happens in the speed of light, the speed of electrons traveling over the internet. So once there is information out there, everybody knows, patients know, everybody knows.

Let's take an example, and I chose one that's sort of in the, you know, intermediate category. But here's an interim result, 122 events. You have 67 events in the active treatment group and 55 in the control group. That's only in excess of 12 events, not very much. As we have said, this kind of 20 percent information fraction isn't very precise but you get a point estimate of 1.22 with an upper confidence interval of around 1.74 and they meet the guidance.

If that information is in the public domain, the effects on any ongoing trial would almost certainly be catastrophic and would make getting the answer that we really care about, which is the 1.3, impossible to achieve. Many physicians would over-interpret the hazard ratio of 1.22 and they may discourage patients from enrolling. I think it's

almost a certainty.

Lacking statistical sophistication, some patients would read about the interim results and stop study medications or drop out reducing ultimate interpretability of the final result which is that 620-event trial. Sponsors could modify the trial in subtle or not so subtle fashion to mitigate the risk, just behavior changes. And such actions by physicians, patients and sponsors threaten the ability of the trial to reach the needed 620-event milestone which was the actual goal of the guidance in the first place.

Let's take the opposite example: 122-events, 58 in the active group, 64 in the control group, a point estimate of approximately .91 meets the guidance the effects, again, on the ongoing trial could be catastrophic. The drug is subsequently approved and some physicians over-interpret the hazard ratio of .91 encouraging to patients to cross over. They know the drug is trending in a favorable direction. Why not? Patients read about it and they ask their physicians or even another physician to

prescribe open-label treatment and there's cross-over. Sponsors could modify the trial to increase the probability of achieving a final hazard ratio with an upper confidence interval of less than 1.0 because they would say, ah, we have a chance to show superiority and so in subtle or not so subtle ways, the trial is modified. So these actions, again, threaten the viability of the final trial.

So whether the estimate is in the direction of hazard or the direction of benefit, any knowledge of these results would have adverse consequences for the ultimate goal which is clarity about the risks and benefits of the drugs.

Is it feasible to maintain confidentiality of interim results to enable completion of the definitive trial? That is the most important question in front of the agency today at this hearing. Well, the process of trial monitoring by DMCs is a mature science and confidentiality has been routinely maintained for thousands of trials, so DMCs have handled this very, very well thanks to a lot of work over a lot of years by some of the people in the

audience here today. Sponsors operate in a more challenging environment where scientific and business interests may conflict and that's the crux of the problem, business and science have trouble missing.

Smaller companies have more difficulty maintaining confidentiality because they have fewer employees and there's greater materiality of the results. Now if you're a giant drug company, whether one new diabetes drug goes up or down isn't going to mean the life of the company. But if you're a small company, it's everything, and so the temptations are obviously much greater and the difficulty (inaudible). So you have to have carefully designed governance to ensure scientific integrity and interpretability.

This is a problem of oversight in governance and I believe the Agency can lead the way in telling sponsors how to do this correctly. We've had a recent experience with this in a related development with developing a construct for provision of interim data by the DMC to a company for a regulatory filing. In this example, I serve as the principle investigator and Dr. Tom Fleming chairs the data monitoring

committee. The specific company and product is not relevant but the approach may assist the FDA and other companies in developing appropriate processes and procedures.

We developed a data access plan and prior to release, prior to release of interim data by the DMC to the company, an explicit document was jointly developed by the company, myself as principle investigator and Dr. Fleming representing the DMC. It provides rules governing who within the company will gain access to data and for what purposes. We insisted on completion of the agreement before data was released by the data monitoring committee and it governs access at two levels. Knowledge that the study met the regulatory threshold for initial approval, that's one level of access. And the second level is knowledge about the exact distribution of events, hazard ratio, and confidence intervals. It limited access to those person who are absolutely necessary to facilitate global regulatory filings. And who are those people? People who supervise regulatory or scientific-based communication with

global regulatory authorities, so people involved in that filing, biostatistical and/or statistical programming activities, clinical safety oversight and interpretation of the interim data, medical writing activities related to regulatory submissions -- to regulatory submissions, not general medical writing but the people who have to write something that they're going to give to the Agency, document quality control for regulatory submissions and then certain legal counsel for verification of knowledge of threshold and/or patent claims related to interim data supporting regulatory submissions land compliance with federal laws.

Specifically, this document lays out who doesn't get access and it does not -- access is not permitted by the data use agreement. No provision for access by individuals for any marketing activities, partnering discussions, drug licensing, relationships with investors, or any other business interests. This has to be restricted to people that have an appropriate scientific role to play in the regulatory process.

And there are recordkeeping requirements in our data access plan. There is a list of -- unblended personnel must be documented. It must include the level of unblinding. It must show the affiliation or role in the regulatory filing and it must indicate the timing of initial access to data. This is a paper trail that is available and should be available to the agency for confirmation that the integrity of the trial has been protected.

The document specifies that the unblended team in support of the NDA submission must undergo training with information specific to their unblended status, a refresher on their requirement to maintain confidential information, compliance with insider trading policies, and expectations for conduct by the unblended team. There are instructions for handling of unblended data, a very detailed, secure electronic storage, use of printers that are not accessible by other people and communications containing unblended data, how email communication would take place. This is a very specific document about the kind of controls that have to be put in place to make sure that this

information does not get into the wrong hands, and a reminder about unblinded team communications and interactions with the blinded team.

There is truly described a firewall between the blinded and the unblinded people so that the people involved in the ongoing trial are not allowed to communicate with any -- about any information that might undermine the integrity of the trial between those two teams. This firewall provides for a transition. So in clinical science, there is a transition to blinded personnel. For biostatistics, there is a transition to blinded personnel. For safety, there is a transition to blinded personnel. And for regulatory, there is a transition to blinded personnel. And it says explicitly "no further operational or strategic engagement with the potential to influence the conduct of the ongoing trial," laid out and specified in the data access plan.

These types of documents that we executed, a template could be provided by FDA to sponsors. You know, we had approached for doing this. The Agency might want to do it a little bit differently, but the

point is a guidance here could be enormously valuable to everybody involved because it would lay out the principles and it would lay out the areas of concern so that everybody knows what is being expected.

We put in there facilities and technology requirements. There have to be separate work areas, clearly marked restricted conference and printer rooms for the people that are working on the -- who have knowledge of the blinded data. Security is actually specified; you know, secured doors with key cards; unblinded data cannot be distributed over the company's email system nor stored on the company's servers because, obviously, those things cannot be guaranteed to be secure. Team members' access to unblinded data only via a secure internet-based document storage service, so it's independent of the company's internal servers and other areas where there's generalized access; and regulatory submission documents are stored in a location that only unblinded staff can view and access.

Now the document -- and I hope the Agency will provide a template in the future so that other

companies can benefit from the kinds of controls that some of us have thought about and put in place for other trials, and I think, again, tremendous opportunity, but there is a huge issue and several people this morning mentioned it.

Confidentiality of interim results requires global cooperation. If any regulatory agency anywhere in the world releases interim data, the ongoing trial no longer remains viable, and that's really a big and tough issue. I think that's maybe one of the biggest issues faced by the Agency in dealing with this. I, therefore, believe it is critical for the FDA which I think has the global leadership and respect to lead the way here, to lead international efforts to achieve global understanding of the importance of confidentiality for interim data for ongoing trials. If we want to preserve this valuable paradigm, this valuable paradigm -- if, you know, in a tiny country, if somebody puts the interim data in a summary basis of approval, I can guarantee you every competitor, everybody, it's going to get out there, it's going to get into the media, it's going to get into the medical

press, and it's over. And so this has to be a global approach and I think that's probably the toughest issue faced by the Agency right now is how do you keep a lid on this. There is a saying from World War II that applies here, "loose lips sink ships" and this is an example.

Now what about doing two trials. You could ask sponsors to undertake two separate trials to rule out 1.8 and 1.3 as an alternative, but the problems don't go away. Release of the trial data ruling out an upper confidence interval of 1.8 can strongly the larger definitive trial. If you do that and if everything is out in the open and you do two separate trials, well, the problem is what if it is 1.25? What if it is .9 or .88 for the confidence interval -- for the hazard ratio? What's that going to do to the behavior of physicians and the behavior of patients in the trial? If the smaller screening trial shows benefit or harm, the rush to judgment may preclude ever answering the critical scientific question which is ruling out an upper confidence interval of 1.3. That has got to be the ultimate goal.

If the interim results are inappropriately disclosed, what are the implications for conducting a new large outcomes trial? Well, in my view, that if there is release of interim data, if you somehow -- the firewalls fail or the containment of the information fails, the need for a definitive trial remains. The extent to which such a trial is feasible and likely to succeed partially depends on the interim results.

If on the interim, the point estimate is nearer 1.0, the viability of a new trial might be reasonable. And if you got a .99 for a hazard ratio, you know, from the 1.8 screening trial, you know, it's unlikely that anybody's going to act on that information although, obviously, one can't always interpret human behavior. But if the point estimate trends, and the more strongly it trends toward benefit or harm, and although equipoise remains intact, we all agree there is still equipoise, the viability and the ability to enroll could be severely compromised. And I think the follow-up trial could go on for a long time, be tough to enroll, and ultimately we might not

get the answer that we want. And so in the end of the day, it's always going to be preferable to handle this in the way that it's now being handled, which is to do a single trial with an interim result but with very, very strong firewalls.

Let me then summarize. The two-stage approach to approval of diabetes agents represents, I believe, thoughtful regulatory policy and provides really important societal benefits.

And I will disagree with an earlier speaker. This does not -- should not be applied solely to drugs for which there is, quote, "biological plausibility of benefit or harm." One of my favorite sayings is that the road to hell is paved with biological plausibility. When we get a result that we don't expect and anybody goes back and figures out why it's biologically plausible, if -- I mean I can't tell you how many times in medicine something we -- nobody expected there would be more heart failure from DPP4 inhibitors but we found out when somebody did the trial, and so we cannot use this litmus test of biological plausibility to apply this regulatory

policy.

The provision of interim data by the DMC to sponsors has inherent but manageable hazards and those hazards can be managed with a data access plan that is rigorous and that is documented, that is reviewed by the Agency, and I believe the Agency can lead in the development of such approaches.

If interim data are inappropriately released, considerable harm to trial integrity is almost inevitable. These risks can be minimized through careful planning and robust governance procedures.

And I once again thank you very sincerely for leading the way and I hope you will be successful in getting this policy to work on a global basis. Thank you very much for your attention.

DR. LaVANGE: Thank you. We have -- I want to start with a question and I know there's at least one other question. So early on, you had two different slides. One, the situation where an interim trend showed hazard and one where it showed benefit, and in both of these slides you talk about what

physicians might do to mess up the study, what patients might do, and what sponsors might do, and I think in one case, sponsors could modify the trial in a subtle or not so subtle fashion and so forth.

In the recommendations, you go on to talk about keep the patients and the physicians masked to the results but some part of the sponsor's team actually sees the results, and you've done a good job of laying out ways to document who sees what and the agreements that are in place and the paper trial. But have you thought at all about what the sponsor does with the knowledge? I mean it's one thing to control who knows what. It's a little harder, I think, to know what happens because somebody knows something.

DR. NISSEN: So here's the problem and, you know, you put your finger right on the problem, Dr. LaVange. You know, we have to rely upon the integrity of sponsors which means that when they say we have a firewalled team and that team is not allowed to interact with the people making decisions in the ongoing trial, then we have to -- at some level, there has to be some level of trust. And, you know, it's

like everything else in life. I mean if you really want to break the rules, you can break the rules. I mean somebody with a wink and a nod can say between the blinded and the unblinded team, there can be communication. And I think we should and the Agency should require a statement, signed, committing that no such communication has taken place or will take place and we should hold sponsor's feet to the fire about keeping that firewall in place.

At the end of the day, you can't legislate integrity. I wish we could but you can't do that with academic investigators. You know, bad things have happened in medicine when there's been lack of scientific integrity. But we can at least set the standard and lay out the principles so that everybody understands what the Agency expects and then if somebody breaks those rules, the Agency would be quite correct in holding their feet to the fire over that.

DR. LaVANGE: Patrick Archdeacon has a question.

DR. ARCHDEACON: Yeah. So I had similar thoughts and first of all, thanks for the really

thoughtful data access plan that you outlined for us. I agree with you that blinding is difficult for smaller companies maybe but that trusting in people's integrity is sort of a basic step forward.

I guess there's also though some sort of possibility of unforeseen consequence of all the transitioning of personnel so if you had people who are running the clinical program or running the safety program and suddenly switch them out, and so that's a second concern.

I guess it occurs to me that the most difficult part about evaluating an NDA package may not be looking at what happened in this 122-event trial. Maybe that's a very small thing and maybe oftentimes it's fairly straightforward interpreting that. What about the alternate that Dr. Jenkins proposed where only the FDA really sees any of this granular data and the company remains entirely blinded? You don't have to worry about all this transitioning at all?

DR. NISSEN: Well, it's a really interesting idea and I got to tell you, Dr. Jenkins) (sic), I hadn't thought about it in that way but, you know,

there is some history of private communications between DMCs and the Agency. I know about a -- I only know about a few of them because most of the time you don't actually know, but I think it's worth thinking about that.

The difficulty that I have is that a decision by a company to file is made in the context of the totality of information of which the cardiovascular outcome study would only be part of that decision. And again, I made the prediction here that companies would not have the audacity to file if they really had a 1.258, you know, hazard ratio. They would look at it and they would say, you know, I think we're going to wait until the end of the full 600. They could always make a decision not to file and so by having that access, it allows companies to integrate what they know about other benefits, what they know about the cardiovascular outcome trial, and that unblinded team would then be able to say we're not going to file or we are going to file. And so, you know, it does respect the rights of sponsors here to make decisions about what's in the best interest of

their companies. And when you take them out of that, you know, it's -- there's some -- I have some discomfort with that. But I have to think about that some more. It's a really interesting idea.

DR. LaVANGE: Bob Temple has a question. John.

DR. TEMPLE: The consequences to further enrollment and continuing the trial and all that, of disclosure of interim data is clear enough. You also referred to things that people running the trial might do if they knew the interim results to manipulate the results. And I just wondered if you could elaborate on that a little more?

DR. NISSEN: Sure.

DR. TEMPLE: But also, I have one comment. I once heard Richard Peto describe intelligence as how quickly you can explain why the results came out opposite of what you expected.

DR. NISSEN: Yeah. I think you and I have the same view about the road to hell being paved with biological plausibility. And, you know, that is a term that's used in the pharmaceutical industry that I

just absolutely hate because everybody comes up with a biologically plausible reason for whatever happened happened and you only know about it afterwards.

So let me give you an example. IF a company knew that at their -- so I showed you the saxagliptin trial was 1200 patients. Let's imagine that if early on during that development program, the sponsor was seeing some evidence of trends going in a favorable direction and they would have the tantalizing possibility of actually doing a trial that was big enough to show superiority, and so something that was originally intended to be a more modest 620-event safety trial would get expanded to be a much larger, you know, superiority trial so that the sample, since we're changing the sample size, if you think you're pretty close to getting superiority, you know, would be the kind of alteration that might occur if there benefits. And similarly, and this is much more nefarious, but if there were a trend toward h arm, you know, the best way to make a harm go away is to have poor quality in the trial, you know, have lots of people drop out and maybe you got lots of things to

converge on a hazard ratio of 1.0. Now I'm not saying anybody would ever do that, but the problem is you're never going to know. And if somebody knows that they're trending in the wrong direction, then it might just influence how hard they work at keeping people in the trial and, you know, making certain that we have the kind of high quality standards.

And I -- you know, I recently had the opportunity to talk with you guys about we've done this for an NSAID trial where we've rigorously tried to hold our own feet to the fire about the quality of the data that we're collecting. And so I just -- there are too many temptations here if you know what direction things are going in to ultimately change what you do in such a way as to get the outcome that you most desire. And I just don't want to take that risk.

DR. LaVANGE: So we can call him back up unless it's very quick. All right. John Jenkins has a question.

DR. JENKINS: You mentioned, you know, the consequences would need to be present if the data

access plan were not followed and maybe you can tell more what those consequences might be including, say, the results were shared more broadly within the company than was planned in the access plan; can integrity be tested back into that trial through monitoring various parameters of the trial to provide assurance that that disclosure didn't adversely impact on the conduct of the trial, or is that just not feasible?

DR. NISSEN: It's very, very hard, John. I think that -- I can only speak as an investigator and sometimes the chair of steering committees and, you know, fundamentally, if I were inadvertently unblinded, you know, then I would recuse myself from any further involvement. I mean I think people have to just believe that the purpose of medical research is providing high integrity, high quality outcome results. And I think companies have to believe it and individuals have to believe it. The most important thing here is to have standards about who gets to know and who doesn't know and for what reasons they get to know. You know, it's one thing if you have to have

more people. And frankly, the list is pretty long if you think about it. You know, all the people that got to write the NDA and the statisticians and the safety people. I mean it can be a fair number of people but it is the internal controls that are critical and then I think the agency has to look the sponsors in the eye and say we want you to commit -- you know, that we want you to tell us exactly who knew, when they knew, and that you have to assure us that nobody involved in this ongoing trial is aware of the interim results. And I think if sponsors are willing to do that, then I think all we can hope for is that people will act with great integrity.

And I know this, that as academic investigators, it is also our responsibility, not just the data monitoring committee, but it's our responsibility on a steering committee to make certain that the sponsor with whom we are working is operating with the highest level of integrity. And if we sense that they're not, we shouldn't be involved in the ongoing trial.

DR. LaVANGE: Thank you. If there are any

more questions, we'll call you back up.

And we'll move to our next speaker, Mr. Charles Keyserling, and Mr. Keyserling is a retired electronic engineer and his slides are up.

MR. KEYSERLING: Good morning. I want to thank you for allowing me to speak and talk on behalf of my experience with diabetes. Dr. Nissen was absolutely correct. The goal is to stop or to reduce the terrific carnage of cardiovascular disease.

We'll start off with the slid that shows a couple of statements from the AD ACE 214 heart disease and stroke statistics. At least 68 percent of people 65 and older years of age with diabetes will die of some form of heart disease, 16 percent die of stroke. Heart disease death rates among adults with diabetes are two to four times higher than the rate for adults without diabetes.

Now, I want to go to a second chart. This second chart is really important. It's a chart that was put out by the CDC and it shows the percentage of diabetics with coronary heart disease and stroke, the two that I'm most interested in. Now what this chart

shows is from 1997 to 2011 -- and this is actually the period of -- well, 1997 was when TZDs became available and they became more and more used up to the year 2007. 2007, some bad -- some information came out that was very negative. People started moving away from TZDs and heart attack rates started to rise. In 2011, they took a fairly stark jump and this was because of the Avandia REMS program and the link of Actos to bladder cancer.

This chart suggests that the good of TZDs outweighs the bad and the deal is that something went wrong in the testing this -- the things that you're talking about today. I want to go over this and discuss it because it's extremely important. This statement came from one of the FDA officials. I think it was Dr. David Graham but I'm not positive. It was published by the Senate Finance Committee, only stayed on the internet a very short time. But what the statement says is that all TZ drugs, Actos, Avandia and Resulin, cause an increase in blood flow which can cause a piece of plaque to break loose and cause a heart attack or stroke.

The focus has been on the fact that there's a risk here, there's a risk. It's a real risk. It can be mitigated but it's a real risk, and the part of it that says "increased blood flow", an examination of all the diabetic complications will show that all complications list poor blood flow as a cause and treatments or provision stratagems include increasing blood flow.

Preventing blood clots are the most important example. Cardio level, aerobic exercise is considered the best prevention of cardiovascular disease. The short period of high blood flow exercises the heart, opens up the arteries and veins during the exercise period, and after the exercise period, the heart is allowed time to recover. Strokes are prevented by blood thinners that achieve better blood flow and stent re-stenosis is prevented with Plavix which makes blood flow easier.

So what this is saying is this cardiovascular stuff is tied to blood flow and since TZDs only treat insulin resistance, the statement above implies the lower insulin resistance increases

blood flow, prevents cardiovascular disease. And conversely, higher insulin resistance decreases blood flow. Thus, insulin resistance causes diabetic complications. It causes it by decreasing blood flow. And because when you look at drugs, many of them don't treat insulin resistance, they don't affect cardiovascular risks.

The problem of plaque breaking loose and causing a heart attack or stroke has become the focus of cardiovascular disease and type 2 diabetes. And the effective medications -- and if you focus on this risk, you can drive effective medications from the market. The focus should be on how to make effective medications safe. When you increase blood flow, you delay or prevent all diabetic complications except for the plaque risk which we have identified.

We know that a quick rise in blood flow can cause a heart attack or stroke. I call that the snow shoveling effect. As blood flow slowly increases, plaque buildup is reduced or stopped and some plaque may be washed away. Thus, there is a short-term risk of plaque breaking loose and a long-term benefit of

delaying or preventing diabetic complications. This affects the studies that you're talking about. You may see really bad results in the first year, and the next year they might be better, and you need to look on a yearly basis how many myocardial -- MIs, myocardial infarctions, occurred the first year, how many occurred the second year and the third year. And the number is switching, you're looking at a drug that increases blood flow and has the potential to long-term prevent cardiovascular disease.

If one looks at short-term results, then the initial risk of breaking loose a piece of plaque will be emphasized and long term benefits of increased blood flow will be missed. In Dr. Nissen's article, 28 of the 42 studies used in his meta data study were 6 months or less, and only 5 were longer than 1 year. The shortness of Nissen's meta data study show why the wrong conclusion was reached. Examples of studies that show the benefits of higher blood flow caused by Avandia are ADOPT, DREAM, RECORD, (inaudible).

Rules for the safe use of blood flow increasing drugs in type diabetics -- the risk of

using drugs that increase blood flow is actually the same risk faced by those starting an exercise program, and exercise is considered a cornerstone of type 2 diabetic treatment. In exercise programs, this plaque break off risk is lowered by some of the rules that I'm going to state. Use drugs at the earliest possible time in the progression of type 2 diabetes before plaque builds up. As type 2 diabetes progresses, plaque builds up. Two-thirds of the people die from cardiovascular disease so we know that's true and that's in most patients. The less plaque buildup, the less danger it is to increase blood flow. If you don't have plaque, you can't break loose a piece of place. It's that simple. So you want to treat and use things that improve blood flow as early as possible in the treatment of diabetes.

From the old Avandia REMS program, they had a requirement that said that you have to use every other medication before you try Avandia. This, of course, was a killer of a rule because what happens is the longer you go, the more plaque you build up so the only -- new patients could only get it when they were

at a high risk for heart attack or stroke. Fortunately, that's gone.

The recommendation not to use Avandia and insulin is not their incompatibility but that insulin users probably have more plaque buildup and increasing blood flow must be done more carefully if you plaque buildup, just another example. Ramp up dosage like one ramps up exercise. Actos has on its label to start at the lowest dose and increase in steps until glucose is achieved. To my knowledge, Avandia never had such a direction but the new label does state this need to ramp up.

Because TZDs allow muscles to get the glucose they need, the ability to exercise is enhanced by TZD use. You're stronger, you have more endurance, and you recover quicker with reduced insulin resistance. This implies that one can be -- one has to be careful when ramping up exercise and taking TZDs because both enhance blood flow. The new ramp up requirement for Avandia may cause the MI rate to be very close to that of Actos. And in that case, bladder considerations might be the decision factor.

Comparison of ADOPT and DREAM -- these are two of the studies in Dr. Nissen's report, the two long three-year and four-year studies -- results show the expected, that the newly diabetic in ADOPT had more myocardial infarctions than the pre-diabetics in DREAM. But the death rate from cardiac events was higher in the pre-diabetics, three times as much in Avandia and twice as much in the control group. And the question is why. And the answer is simple.

When you exercise as a pre-diabetic, you're encouraged to exercise a lot higher. If you're a diabetic, you're encouraged to do moderately intense exercise. So when the pre-diabetic exercised at a high rate, they broke off a bigger piece of plaque.

And the other thing is to determine plaque buildup and adjust dosage limits just the way you would adjust exercise limits. Some of the 12 cardiac deaths in DREAM, 12 deaths in about 8,000 patient years, which is a small rate, could have been avoided by determining plaque buildup before developing a blood flow increasing program. Sheri Colberg's book, *Exercise and Diabetes* tells doctors how to prescribe

exercise, and the same ideas could be used with any drug that increases blood flow.

Another topic: The statement that a drug has not been proven to reduce cardiovascular risks I don't believe is acceptable for type 2 diabetic medications. The two statements at the original start of this presentation show that that's what you got to do. You have to reduce cardiovascular risks.

An example of a different type of test than the ones you're doing I came across many years. In this test, there were 95 patients that had stents inserted and 47 of the patients were given Avandia, replaced part of their diabetic medications, and 48 patients were in a control group. It was a double-blind study done very carefully and six months later, they went back and did blood tests and they looked to see how much re-stenosis had occurred. Six months later, there was higher HDL, big marker for reduction of cardiovascular disease; lower C-reactive protein, another big marker of the prevention of cardiovascular disease; and fewer needs for -- less re-stenosis. Re-stenosis is a rebuilding of plaque around a stent. So

they went in and did angiograms and they showed that there was much less re-stenosis in the Avandia patients. And the last thing was -- and this was, they said, was not statistically significant but there were nine patients that needed additional stents in the control group and only four in the Avandia group.

I think that there are many tests like these that could be performed that can go a long ways toward establishing the ability of a diabetic medication to prevent cardiovascular disease. You can measure the HDL; you can measure C-reactive protein; you can do an MRA of the carotid arteries to measure plaque buildup; you can do a calcium scan. Most cardiologists can look at an individual and evaluate their risk for cardiovascular events. So if you have two groups, one with Avandia, one with something else, have the cardiologist look at them before, look at them six months, a year, two years, three years later; see which one at the later time has a higher risk. There is great potential for doing this.

This is a thing for the patients, that any patient, when he starts a new diabetic medication,

should look at his lipids, six months, a year afterwards and see if the drug is actually helping them to prevent cardiovascular disease.

I hope some of these things you will think about. I greatly appreciate you taking the time to listen. Thank you.

DR. LaVANGE: Thank you. Are there any questions from the panel for Mr. Keyserling?

(No response; no questions posed.)

DR. LaVANGE: No questions, so --

MR. KEYSERLING: Oh, okay.

DR. LaVANGE: -- thank you very much.

MR. KEYSERLING: All right. Thank you.

DR. LaVANGE: Our next speaker is Andrew Emmett, Managing Director, Science and Regulatory Affairs of the Biotechnology Industry Organization, or BIO.

MR. EMMETT: Good morning, everyone, and on behalf of the Biotechnology Industry Organization, thank you very much for the opportunity to provide our perspectives on the confidentiality of interim results in cardiovascular outcome safety trials.

BIO represents more than 1,000 biotechnology companies, academic institutions, and state biotechnology centers and related organizations across the United States and in 30 other nations. And BIO and our members companies support regulatory processes that speed access to innovative new medicines and improve patient medical outcomes to address our nation's most pressing public health needs.

The opportunity to utilize interim analyses from ongoing trials can be time, cost and patient exposure efficient and, therefore, BIO supports FDA's willingness to use these interim analyses to answer key safety and efficacy questions when additional data is deemed necessary. We're pleased to provide the following feedback on FDA's questions in the *Federal Register* which was developed by a working group, BIO member company experts and biostatisticians with extensive experience in this field.

First, with respect to question one around the "would disclosure undermine the integrity of an ongoing trial," yes, BIO member companies agree and abide by the ICH and FDA guidances on the principles

for high-quality conduct of randomized control trials and specifically agree that when interim analyses are deployed, that provisions should be in place to preserve trial integrity in order to retain the reliability of the results of the ongoing trials.

We recognize that there are special challenges that arise from the use of interim data for regulatory purposes: first, the potential for introducing study bias. By gaining access to the data from interim analyses for purposes of a regulatory submission, investigators, regulators, and patients become exposed to the data. This problem is compounded by multiple, global regulatory submissions as the number of individuals with access to data increases.

Second, implications for global drug development: As was raised this morning, international regulatory authorities around have mandates for transparency of the information used to assess benefit risk, and some regulatory agencies may not maintain the confidentiality of interim data once it has been submitted. If the interim results of an

ongoing trial are disclosed prematurely and without adequate safeguards, these results may become subject to full unblinding and unacceptable levels of data disclosure compromising the trial integrity and, therefore, resulting in uninterpretable results at trial conclusion.

And third, corporate disclosure requirements: Corporate sponsors, once exposed to the interim data, may have special disclosure requirements in risk manage as it relates to Securities and Exchange Commission disclosure requirements, fiduciary duty and product liability, all of which are dependent on the level of materiality of the product, and the data from the interim analysis, the risk of tolerance from the sponsor.

Question 1(a) with respect to the greatest risk to interim findings: Any quantitative information, if publicly released, will create risk to trial integrity and jeopardize trial continuation. Information at this stage will likely not be mature enough to draw meaningful statistical inferences. The greatest risk would be publicly releasing overall

estimates of cardiovascular benefit risks such as MACE, the point estimate and confidence intervals along with the subcomponents of MACE.

Question 1(b) with respect to partial disclosure of the interim analysis: Publicly disclosing that the standard for approval has been met offers some protection against compromises to trial integrity. Sponsors are likely to provide MACE events analyses from their meta analyses of phase two and three trials publicly, and extrapolation of this information to the cardiovascular trial is inevitable. A signal for continuing the CVOT trial could be perceived as validation of the findings from the meta analysis. However, the risk of extrapolation and drawing unscientific conclusions cannot be eliminated and, therefore, partial disclosure serves as a method to reduce potential data integrity issues. Practitioners want to assume equipoise and extrapolate from the existing data while the CVOT matures and provides the more rigorous scientific evidence necessary to support or refute the hypothesis of the trial.

First, with respect to safeguarding premature disclosure, independent data monitoring committees could supply regulators and sponsors with pre-specified (inaudible) information for the risk exclusion trials without the need to expose either part to the actual data in the interim analysis. And this would minimize the risk to trial integrity and legal and policy risks from disclosure and non-disclosure.

Second, we could seek globally harmonized procedures through ICH for retaining confidentiality of interim results that are used for regulatory purposes. Current ICH guidelines do not contemplate this use of interim analysis and data transparency and policies that prefer approved products are inherently at odds with the principles for data confidentiality outlined in the ICH E9 guidance. It should be noted, however, that sponsors need access to this information in order to determine whether to submit the NDA or BLA.

Second, with respect to mitigating the impact of the interim public disclosure, we could

develop best practices for appropriately firewalling any individuals unblinded from individuals that are conducting the trial as discussed at length this morning; develop best practices for development and management of confidentiality obligations to further circumscribe the potential impact of any data disclosure; prospectively development and communicate methods and criteria to identify the sources of trial integrity and potential bias. And should the interim results from an ongoing trial become the subject of a full unblinding and should, therefore, concern the bias due to the data disclosure, we could prospectively determine methodologies to be used to ascertain whether bias was actually introduced in the trial.

Question 1(c) with respect to "would it be feasible to conduct a new large trial": Significant time, energy, and resources go into the planning, initiation, enrollment, and conduct of CVOTs. Great care should be taken to protect the integrity of the initial clinical trial to ensure it can produce high-quality data to answer key safety issues about a drug

or devices efficiently as possible. If it's determined that bias has been introduced in the trial, then new trials may be considered but there is also a high likelihood that the information disclosed would also potentially bias the new trial as well. While regulatory flexibility is appropriate on a case-by-case basis, a new trial conducted in the same population with the same hypothesis as the pre-approval study may be difficult to justify and conduct.

If the ongoing study for which the interim analysis results are publicly released or continued, it may be subject to potential operational bias, missing data due to withdrawal of consent, and many other compromises to data integrity leading potentially to uninterpretable results. Feasibility of completion of the trial itself may be in jeopardy due to the availability of the drug. This set of circumstances biasing the original trial may also apply to a study that is a close replication in terms of design and population of the first study.

However, a post-approval study in a slightly

different population with a different hypothesis and possibly including different comparators that supports an indication while collecting CV outcomes data could generate interest in patients and investigators to obtain the needed information and be done with integrity.

And finally, question number 2 with respect to alternative trial designs: While there are instances where it's appropriate to require a large-scale randomized clinical trial to assess long-term cardiovascular outcomes, it's important that these decisions be made on a case-by-case basis and be scientifically justified. Given the limited resources of our nation's research enterprise and the challenges associated with enrolling patients and conducting clinical trials, we must be mindful that we're employing clinical studies in an efficient and effective manner to answer key questions about the safety and effectiveness of new drugs in biologics. For that reason, we suggest that any potential pre-submission CVOT trials should be justified on a case-by-case basis based upon the biological rationale of

the suspected adverse event and the totality of evidence collected earlier in the stages of pre-clinical and clinical development.

Additionally, in lieu of randomized large-scale clinical trials to assess cardiovascular outcomes, we recommend that the Agency explore how other real-world data sources may be harnessed to answer these important safety questions in a timely manner. In order to assess extraordinarily rare events and an increase in baseline commonly experienced cardiovascular events, a CVOT study must be significantly powered to enroll thousands of patients. This can represent a significant portion of development programs, research allocation, and can be both costly and time consuming.

In 2007, FDA launched its Sentinel network, a national research capacity that leverages real-world data such as electronic health records and health insurance claims data to actively assess key drug safety questions in the post-market setting. And the current Mini-Sentinel database encompasses more than 140 million covered lives thereby providing the

statistical power to more expeditiously assess these same types of adverse events commonly studied in CVOTs.

FDA continues to implement the Sentinel network and further refine these study methodologies, we encourage both the FDA and the sponsors to discuss when and where it might be appropriate to utilize the Sentinel network to assess these research questions in a post-market environment.

So in conclusion, BIO supports FDA's willingness to use cardiovascular outcome trial interim analysis to answer key safety or efficacy questions when additional data is deemed necessary, but great care must be taken to prevent the introduction of potential study bias from public disclosure and to mitigate unintended consequences.

Thank you for the opportunity to present at today's hearing and I'd be pleased to answer any questions from the panel.

DR. LaVANGE: Thank you. I have one quick question. When you talk about under the -- answered the question 1(b), mitigating the impact of interim

public disclosure, which would hopefully be accidental, you mentioned criteria to identify sources of trial integrity and bias and also methodologies to ascertain whether bias was actually introduced. And, of course, the devil's in the details with these sorts of things, but I was just curious if the BIO working group had pursued either of these ideas and you had anything else to say about either one.

MR. EMMETT: It is something that we've discussed and I think the critical aspect is developing prospective criteria for introducing bias. When this question came up earlier, it was noted that that's a very challenging thing to do. So we'd love the opportunity to discuss it further within our working group and provide more detailed feedback in our written comments.

DR. LaVANGE: Any other questions? John Jenkins.

DR. JENKINS: Yeah. Thanks, Andrew, for that presentation. In Dr. Nissen's presentation earlier when he was describing his ideal data access plan, he talked about two levels of access and said

that people within the company who should have no access were those involved in marketing, partnering relationships, investor relations, business interests, and there was a longer list than I jotted down. But I'm curious, can you comment from a BIO perspective of the feasibility of that level of restricting access to small companies with regard to their need to conduct business, raise money for the completion of the ongoing trial, maybe have partnerships, maybe SEC filings? How feasible is it for a small company to actually have the people involved in those relationships not know the actual data?

MR. EMMETT: Thank you for that question. And yes, 90 percent of BIO's membership is represented by small emerging companies, typically those without a product yet on the market, still involved in pre-clinical and in clinical testing and oftentimes relying on investment and venture capital to support clinical investment. And, you know, given that and the limited amount of staff, many members of those companies do have to wear quite a number of hats, as you mentioned earlier, that typically a chief

scientific officer, a chief medical officer could be involved in the R&D side of the operation and also regulatory filings and also be a member of the management team.

That being said, despite those challenges, we believe that this is something that can be managed. It was noted earlier that this is really more of a management and governance challenge, and by appropriately restricting those individuals who are involved in the regulatory filing from those who are involved in key business decisions and from ongoing conduct of the trial, we believe appropriate firewalls can be established as long as it's written prospectively and there are key guidelines in determining exactly which of those staff will be assuming the blind versus unblinded role and the justification for which staff would assume that role. But we believe that it is something that can be managed appropriately regardless of the size of the company.

DR. LaVANGE: Other questions? Patrick.

DR. ARCHDEACON: Just to piggyback onto

that. Is it clearly that that would preferable to having an asymmetry of information where FDA would have access to this information and the BIO companies would not?

MR. EMMETT: So I think it was an interesting point that was raised earlier about the asymmetry of information, and we had really assessed, you know, whether the risk ratios could be communicated by the data monitoring committee or whether it would be more appropriate to monitor staff. We hadn't really discussed in dept the asymmetry of releasing the detailed data to FDA and not the sponsor. So I would have to discuss that further with our members and discuss where they are in that question. I do have some concerns about how the asymmetry of information might impact the ability of BIO member companies to make informed decisions about their positions and how that might influence discussions with FDA and other regulators. But I'll touch in with the working group and provide more written feedback in our comments.

DR. LaVANGE: Thank you very much.

MR. EMMETT: Thank you very much.

DR. LaVANGE: Okay. Our next speaker is John Adler. Mr. Adler is Therapeutic Head of Cardiovascular and Metabolic Disease Biometrics and Information Sciences at AstraZeneca.

MR. ADLER: Okay. Hi, my name is John Adler and I'm the lead statistician for cardiovascular and metabolics at AstraZeneca, and during my tenure at AstraZeneca, I've been involved in over half a dozen of outcome trials in the cardiovascular metabolic area. It's a pleasure for me to be here today on behalf of AstraZeneca to participate in this public hearing. I am Swedish so please excuse any Swedish next to my English as we go through the couple of slides coming up.

So, this is an overview of the agenda. First, some general comments or remarks to frame the questions. Secondly, I want to share with you a proposal and we heard some different proposals this morning but this is reflecting on one of them. Lastly, I'll outline some potential next steps.

So, the background and questions in the

supporting documents that we're providing for this hearing sets the scene in a good way, and we've had very good and interesting discussions this morning, And it also poses a lot of important questions.

I'd like to start by saying that any interim analyses that would be used for regulatory purposes carries a level of risk for disclosure of the results, and as a result of that, it can have an impact on the conduct and interpretability of the trial as we have heard earlier today. Depending on what is disclosed, it may be difficult to continue the ongoing trial or to initiate a new trial to meet regional study objectives. Any new study would, of course, have to be designed using the knowledge and understanding of the impact of the disclosed results. And all this is a very delicate and sensitive area.

Some have argued that not allowing for interim analysis for regulatory purposes could have a marked negative impact on the delivery of new drugs to patients in a timely manner. AstraZeneca recognizes that to allow timely availability of new therapies, there are several complex matters that need to be

considered. The question is how can we navigate the opposing forces here in a scientifically sound way.

So, we just briefly reviewed some of the risks to the trial and others were clearly described this morning as well. It may be possible to contain these risks while keeping good standards for regulatory decision-making in the interest of public health. The risk for negative impact on the conduct and integrity of the trial increases with more information about the trial being known to individuals in the trial. And as others did, when I talk about the individuals in the trial, I mean this very broadly. It's anyone pretty much. It's patients in the studies, physicians treating the patients, it's sponsors, it's patients that could be in the study and so it's very broad.

So, I was going to bring up a proposal here but it's also been brought up earlier today by Professor Fleming, and it's really a proposal for a place to start the conversation. And that proposal is that following the interim analysis, a letter from the DMC stating that the interim data for MACE within the

trial is consistent with the FDA guidance and the pre-specified criteria and that this is the only information shared. This approach goes back to the basics and takes advantage of the already existing apparatus around outcome trials.

On the following slides, I will refer to this as the pragmatic approach, simply for the name for it. I believe it would be hard to argue at this stage that we are essentially Pandora's Box with consequences we can't predict. In essence, to begin the debate, we propose to consider staying at the lower end of the gradient of information shared. Our proposal is to keep things as simple as possible. In the diabetes area, we have an FDA guidance for the MACE endpoint based on the upper limit of the confidence interval. We have DMCs that are used to applying criteria during ongoing trials. We are combining these two. Similar to other levels of information in the data monitoring committee letter, no data will be shared. One can argue this is simply a boundary in the trial and the DMC is reporting whether or not it has been crossed using sound

statistical principles. I will come back to this in a short while.

This approach will then protect against compromising the future conduct and integrity of the trial. Given that regulatory decisions will be made, a number of elements are needed to ensure that the DMC letter will be accompanied by a full system of control mechanics. First, we need to be sure that the data upon which the DMC judges the criteria is of the highest quality. This means we need to have complete or very close to complete follow-up or retention of patients in the study. We need to have agreed statistical method for inference. There needs to be consistent definitions of MACE use. There are many things that can be added to this list so this is just a couple of examples.

In this proposal, we must recognize that the assessment of benefit-risk comes from two distinct sources. The main source which can be interrogated in the usual manner is the completed set of studies. The second source is the ongoing trial which is not then -- which, for the data, is not directly

accessible. So we must be comfortable with the mechanics I described previously to make this a tenable source of evidence.

I should add here that we -- and this is the DMC charter and all the correspondence be made available to regulators.

Lastly, I'll point out that if our concern is to protect against selection bias based on inferred knowledge in the public arena, one could consider having completed enrollment prior to the interim analysis.

So I'd like to spend just a minute or so on one of the design elements of the interim analysis. We've talked a little bit about it this morning, but this is a somewhat different aspect of it. The plans for interim analysis should, of course, be detailing the DMC charter and the impact of doing -- also, the impact of doing repeated formal interim analyses should be considered. And this is for repeated formal interim analyses for meeting the first 1.8 criteria I'm talking about now, so it's not exactly what we heard about earlier today.

As important as it is to have pre-specified criteria to meet that interim analyses, the way these criteria are evaluated is important. One of the memos, and we have seen it earlier this morning as well for this meeting, included power calculations for meeting different criteria. We've seen the numbers before. With 122 events, there is a 90 percent power to rule out an increased risk of 1.8, and to meet this criteria a point estimate of around 1.25 or 1.26 is needed for the hazard ratio, of course.

Of course, if you do an interim analysis after 122 events, if the criteria was met, this does not tell you what the observed hazard ratio neither does it tell you the upper limit of the confidence interval was, just that it was below 1.8. However, if you would do frequent evaluation of the 1.8 criteria as events accumulate in the trial, this is a different situation. The observed hazard ratio can actually, in this case, sometimes be derived mathematically from knowing when the criteria was met. As an example, if the criteria was not met after 122 events but it was met after 150 events, this tells you that the observed

hazard ratio would be close to 1.3. So in practice, you can derive what the observed hazard ratio if you do not set this up in a good way. And I think one can argue that disclosing this kind of information is actually similar to disclosing the results of the trial.

So, what about other endpoints? I'll discuss just a few considerations when we start to move down the gradient of information and in this instance, just a word about additional endpoints. For other pre-specified variables of interest with carefully pre-specified criteria, the letters on the DMC regarding MACE can also state whether these additional criteria were met. However, since the cardiovascular safety trial is generally powered based on cardiovascular events, this study can, of course, be over or under powered for these other safety variables.

So regardless, it's important to define the criteria up front based on what is known about the clinical relevance. When it is possible on an priority approach, could be used if there is

sufficient data. I think rare events is one example where it might not be feasible to do that. One can also, from here, consider other ways of moving down the gradient towards additional information being shared.

So, in summary and next steps, interim analyses used for regulatory purposes carries a level of risk for disclosure outside the agencies and as a result of that on the conduct and interpretability of the trial. To contain the risk to the trial and maintain sound decision-making, a pragmatic approach to data sharing is a reasonable starting position to start from. This will require common methodological, statistical, and quality standards for cardiovascular outcome trials.

Finally, concrete proposals to working groups to attack (inaudible) statistical, methodological and other issues will be welcome and AstraZeneca is willing to engage with the Agency on this topic.

Thank you for listening and giving me the time to present.

DR. LaVANGE: Thank you. Questions from the panel? John Jenkins.

DR. JENKINS: So in this proposed approach, the regulatory agency doesn't even know the point estimate or the confidence intervals of the analysis, only that the boundary was met. Maybe if you could switch places and put on a regulatory hat, how much comfort would you have a s a regulator approving a drug in this disease setting where that point estimate could have been as high as 1.26?

MR. ADLER: Yes. I don't want to put on a regulator hat but --

(Laughter.)

MR. ADLER: -- the -- I think we're bringing this up here as a starting position. I think it's good to start in one of the sort of extreme positions. This would be one position where you share as little data as possible and you can evaluate that method versus other methods and see what you actually -- what's needed, so what are the additional information. If we're saying -- and we heard this a couple of times -- if we do see the 1.26, we don't want to file.

We've heard that several times. So is that then the right criteria to have? I mean these are the kind -- or I think that's a broader discussion but I think it's a reasonable starting position to start from there. But yes, I can understand that.

DR. JENKINS: I think it goes to the question of how much attention should the regulators be paying to the point estimate. We heard examples in some of the earlier talks about early point estimates that were proven later to be far off the mark, so it goes to the question of is this a "yes" "no" criteria, you're less than 1.8 so we don't need to know more; or should we, as regulators, know more knowing that sometimes that point estimate is going to be far from what the actual point estimate is. You can imagine being a regulator and approving something if an interim analysis point estimate was a 1.26 and the final analysis is the same and being questioned why did you do that.

MR. ADLER: Yes. I can see that but it's also, as you brought up, the point estimates are very uncertain and that's really one of the good reasons

for having pre-specified criteria so that we are not being mislead by the actual results when we do see them. But yes, I think this is a -- there are other -- there are benefits of not having shared data broadly, and that's sort of -- so we are talking here about the balance because we have the balance of getting drugs to patients as early as possible and we don't want to jeopardize the integrity and the conduct of the trial. And the more data that is being shared, the larger the risk is, so the key thing here, I think, is to find that balance, where we want to be on that balance.

DR. LaVANGE: Dr. Temple.

DR. TEMPLE: Is your worry about sharing that more people at the company would have to know in order to share properly? Or suppose the data monitoring committee just shared with the FDA; that's not a problem, is it?

MR. ADLER: Well, it can be. I mean I first want to say we haven't had a complete internal discussion on this yet, so it's in the early stages for that. I do see that there -- I can in this

stage -- that there are situations which become complicated, and I'm not sure at this point on how to handle those. I mean when -- in my experience, when we do a submission, let's say it's shared with FDA. You say it's final, however that's handled to do the submission. We submit it and we then have discussions about benefit risk. We have discussions on the ongoing cardiovascular outcome trial. How would FDA be handling those discussions with the sponsor? Who will be having those discussions with the sponsor? So there are complications there that are not clear to me at this point on how those would be handled.

DR. TEMPLE: Yeah. I think the ability to have those discussions is the very thing John was asking about, he sort of wants to.

DR. LaVANGE: Other questions? Karim.

MR. CALIS: I guess from your proposal, I was assuming that you were say also that the sponsor would not know the -- the DMC, in other words, would just sort of basically have a letter.

MR. ADLER: Completely confined to the DMC, yes.

MR. CALIS: Okay. So just sort of a new approach, so neither side would know.

DR. LaVANGE: Are there any other questions? Do we want -- we have eight minutes before our -- sorry, thank you, Mr. Adler.

MR. ADLER: Thank you.

DR. LaVANGE: We have eight minutes that we could bring people up for unanswered questions earlier. I think you said your question for Dr. Fleming was already answered?

MR. CALIS: It was the same as Dr. Jenkins'.

DR. LaVANGE: All right. Dr. Jenkins.

DR. JENKINS: I'd like to maybe ask Dr. Fleming the same question I asked Dr. Nissen about if the disclosure within the company is broader than the data access plan would have been suggested, Dr. Nissen said there should be consequences, and I asked, "Is it possible to test back into the trial for the integrity of the trial, or is it impossible to test the integrity of that broader disclosure than was intended?"

DR. FLEMING: Well, it's a very relevant

point because, obviously, if the data are released to the unblinded team within the sponsor for the sole purpose of facilitating a regulatory filing, there is a risk that broader dissemination could occur. And as Dr. Nissen has said, there always is a reliance on commitment to maintaining integrity and we do rely on that; obviously, only when it's necessary. And if we do wish to pursue the concept of being able to use the 122-event trial to facilitate an earlier regulatory decision, that creates the necessity for taking some level of risk but absolutely minimizing it as best possible.

I want to reiterate we will all in the academic community and in industry benefit greatly from a guidance coming from FDA that clearly lays out what expectations are and guidances for how to proceed. I do think we have some ability to monitor this. I know as a member of a data monitoring committee working closely with sponsors in DMC meetings, we get some definite insight about how interactions are occurring within a company. We don't see everything but we do develop a sense of whether or

not the procedures that are laid out in a data access plan are being followed.

We also are carefully following the performance standards document which is looking at what's the rate of enrollment; what's the level of adherence to the experimental intervention; is it achieving best real-world achievable standards; what's the level of cross-in. We're looking at those very carefully and we would continue to look at those in a post-marketing setting after a regulatory approval decision was made. And ultimately, if those standards are met and we have direct evidence about that, that does provide a certain important level of reassurance about trial integrity. It's not proof and it's not absolute, but there are definitely insights that we would gain from that.

DR. JENKINS: As a follow-up while you're still at the microphone, can you address the proposal that the DMC alone be responsible for communicating to the regulatory agency that the boundary has been met about communicating any additional information such as the point estimate, the confidence interval, the

subcomponents of the MACE? How do you feel about that proposal as someone who is frequently a DMC chair?

DR. FLEMING: Well, it certainly provides an enhanced confidence about maintaining confidentiality f the data monitoring committee were simply asked to convey to regulatory authorities that the standards that had been set up by the agency and by the sponsor had been met. Obviously, though, it puts regulatory authorities at a compromised position of knowing or understanding the best insights that they could possibly have. There is some precedent for this but it's not an ideal precedent.

So if we go back to 1992-93 when accelerated approval came into place, the concept in accelerated approval was we're going to use, in most cases, definitive evidence about an effect on a biomarker reasonably likely to predict clinical benefit for an ultimate clinical endpoint for a conditional approval or for accelerated approval where then the validation trial needed to be completed successfully and many of us believe to get the ultimate important answer.

So in oncology, for example, there were

instances where this was carried out using progression-free survival. Now at least in that setting, regulatory authorities received the data on progression-free survival. But some of us on the data monitoring committee argued that the clinical endpoint, in this case survival, shouldn't be released at all to maintain and protect the confidentiality of survival.

In working with you, there are instances where you agreed that we would simply convey to you, data monitoring committee to the FDA, that the survival data went in the wrong direction. That was essentially the level of communication that occurred. There wasn't release to the sponsor. There wasn't more detailed release to the FDA. It's not by any means an exact model for what we're talking about here, but there is precedent to the FDA being willing to accept somewhat less than complete insight in order to help protect the integrity of, in that case, the ultimate validation trial assessment of the clinical endpoint.

This is, though, much -- this is a

significantly bigger step and so in my presentation, I said, I know you've had some discussion about this. Clearly, there would have to be a lot more discussion.

Your concept of saying is it possible to have the data monitoring committee, with the acceptance of the sponsor, submit the essence of the information directly to the Agency addresses that concern from the perspective of the Agency. Now we would have to find out. And in fact, it would relieve sponsors of considerable concerns abound challenges they have in maintaining confidentiality when there is an unblinded team within the sponsor. So it provides that benefit to them, but there have been legitimate uncertainties raised today about whether sponsors would find that acceptable. If they did, from my perspective on a data monitoring committee, it's a very constructive way of empowering the FDA to have access to what they would need to know and in a way that would still allow us to have considerable enhanced ability to ensure trial integrity by maintaining confidentiality.

DR. LaVANGE: I think Dr. Nissen had a

comment and then we'll break.

DR. NISSEN: I just wanted to also add one comment, John, and that is that executive steering committees also gain certain insights. A sponsor comes to a steering committee and says we want to modify the trial, it's appropriate and important that that steering committee, when we're in that period between the ruling out of 1.8 and the final end of the trial to say on what basis is this recommendation being made and, you know, I think we have to be able to ask questions as well and the Agency should as well. Any time the trial is modified after that 1.8 has been ruled out, there has to be serious discussion about why, who makes that recommendation, and what their knowledge was.

And so, you know, in fact, I would even argue that modification becomes very, very risky, you know, in that period of time between the interim and the final analysis, and I think that's a potential source of insight.

DR. LaVANGE: So we'll stop now and break for lunch. We'll have one hour and there is lunch.

It's on your own but there is a facility right outside that will offer you lunch. And so we will reconvene at 1:45 to hear the remaining speakers and then ask additional questions. Thank you.

(Whereupon, off the record at 12:33 p.m., and back on the record at 1:46.)

DR. LaVANGE: We'll go ahead and get started and our other panelists will join soon.

So our next speaker is Dr. Matthew Roe representing the American Heath Association.

DR. ROE: Thank you for the opportunity to present today. I'm a cardiologist from Duke University and on behalf of the American Heart Association, I'm here to represent the viewpoint of a number of scientific experts who were polled regarding the questions for this meeting and the presentation will reflect the consensus viewpoint.

The American Heart Association represents patients with cardiovascular disease from the perspective of the scientific community and the professional members of the AHA. And as a professional member of the organization, I hope to

show that perspective during this presentation today and offer some further insight into the topics at hand.

So the traditional model of drug development in that you do your pivotal clinic trials, obtain a license and approval and then do post-market surveillance is shown the top here. Considerations such as those discussed at the meeting today include an adaptive licensing model whereby you'll receive conditional approval but patients will still be followed in controlled studies rather than in routine practice to gain more insight and understanding into the therapy at hand and accumulate additional safety data that would help to then potentially augment the final approval as we've discussed.

And this is the model that is really under consideration today and is most well-suited for this topic in this area. However, when we do a traditional clinical trial where we randomize patients, assign them to treatment, follow them throughout the expected duration, accumulate the records with number of events and then do final ascertainment of the primary

endpoint, there's no interruption of the trial, there's no interim analysis in terms of other than those that would be conducted for normal safety review.

So in the adaptive trial design, you'd actually plan an interim analysis as we've discussed. That interim analysis would then dictate whether the trial would continue, whether there may be conditional approval offered and then potentially could lead to adaptations of the trials we've discussed. But then is the final ascertainment of the primary endpoint and the mean stated results unbiased in this regard? And I think you've heard fairly routine consensus from the academic experts that there would -- there is great concern that such an approach, if those data were released publicly, would irreversibly bias the conduct of the rest of the study.

So I think representing the AHA, there is agreement that detailed data released at interim analysis from these types of studies would substantially alter the conduct of the trial. It's been discussed repeatedly during the morning session,

and we feel it would also bias the study results. The participating sites and the investigators would have likely some changes in the type of patients they would enroll, some would be subtle, some would be overt. The management of concurrent medical conditions that these patients are likely to experience during their time in the trial would likely potentially change if these data were released and then the reporting, and ascertainment of suspected endpoints would also change. How much they would change and how much influence that would have on the final study results is unclear but clearly, this would lead to irreversible changes in the trial.

And the issue of equipoise has been discussed repeatedly, and we feel that this would irreversibly alter the equipoise for all stakeholders in the trial, not only the physicians the patients, for that matter, who are participating but the leadership of the trial both at the academic and sponsor level as well as potentially even the independent adjudication committee who's ascertaining endpoints and classifying them per original

designations.

So is it possible to start a new trial in one of those scenarios that was originally discussed this morning, meaning you stop the first trial and then start a second trial to go for your requisite number of safety events? I think, you know, clinical trial experts all agree that it's very difficult to dismantle and then reassemble a trial in this regard. The operational components take some time. It's very complicated and those would change quite a bit. So logistically, that would be a very big challenge. There would be no difference here in terms of the biases that the investigators and the patients who are in the second phase of the trial would be subject to as well as the equipoise issue underlying such a trial would not change. And so this doesn't really seem like a very feasible option.

Now this issue of partial disclosure of data for interim analyses has considerations both from the scientific experts and the public. And certainly the public has the right and the desire to be informed about interim analyses, but those rights also need to

be counterbalanced with the realities of clinical trial data. As has been shown repeatedly, there is uncertainty regarding the impact of new treatment cardiovascular outcomes early and midway through a trial, and that uncertainty would be very hard to distinguish and communicate to the broader public. And in that regard, the incomplete release of interim trial data could lead to erroneous actions by the public and patient advocacy groups that may actually harm public safety. And I think we should keep that in mind and I think there have been some examples of that this morning.

And it's very complicated to maintain confidentiality and determine what type of data are actually released, and there have been a number of provocative suggestions this morning that we have discussed very well. But in that regard, we still, I don't think, have the clear answer and just another example of the different levels of uncertainty that occur during a trial early on versus later once more endpoints are ascertained, and this is the issue that's very difficult to communicate publicly.

So are there alternative trial designs or approaches that could be considered? There has been a lot of interest recently around large sample cardiovascular outcomes trials. There is a whole initiative now funded through the PCORI network to conduct such trials. The NIH has clearly changed their position in term of their funding priorities for clinical trials to focus on this.

And one option to consider would be to do a single large sample cardiovascular outcomes trial with initial more intensive data collection for the areas of interest for the efficacy in points such as glucose lowering for diabetes therapies and other non CV safety risk. And based upon interim analyses, some of the more intensive data collection modules that would lead to this conditional approval could be dropped and then the trial could continue on unaltered in terms of its major objectives of cardiovascular outcomes through its entirety. And you could do a unique operational design to scale up such a trial. No changes in the countries and the sites but in this regard, you could have one trial mechanism. You could

consider using electronic health record data to support high enrollment rates, data collection and CV endpoint ascertainment, and there's much work underway right now to determine how to actually do this. You could simplify study drug dispensation and accountability to limit the burden on the sites and limit the costs to some extent but still maintain accountability in the necessary procedures, and simplify the study visit schedule per standard of care which is actually how these patients would receive a therapy if they were treated in routine practice anyways.

And as has been shown from recent publications, both the FDA and the NIH are supportive of this concept of large sample trials, and this seems to me to be the ideal opportunity to conduct such type of trials in the future and modify them in a way to meet the needs that in the space of these large cardiovascular outcomes trials would need.

There has been a lot of discussion about the role and the scope of the DSMB regardless of what trial design is utilized. I think, you know, this has

been well-discussed already but certainly it is the opinion of the AHA that discussions between the DSMB and the FDA for interim analysis results are helpful and could really add quite a bit to this dynamic. The DSMB members have quite a bit of experience for the most part and can provide recommendations regarding conditional approval. All that, obviously, would be confidential and the role of the sponsor in those discussions has been well-described in the morning session so I won't reiterate that. But clearly, this is a potential path forward and the exact mechanisms and details of who could see data and who would be unblinded have -- there have been very good proposals regarding that, but that seems also to be a path forward on these discussions.

And so to reflect, the interpretation of interim results of trials is complicated and needs to be handled rigorously. I think all would agree upon that. We feel that we do not want the process for developing new promising therapies to be hampered by revealing non-definitive data from interim analyses and potentially stopping trials that really should be

borne forward to conclusion.

And it's important that patient and patient advocacy groups are involved and engaged in the development of these therapies and with a number of federally-funded initiatives right now, that exact thing is happening in new programs being developed. That is patients are involved from the beginning in research that relates to their disease conditions, and we think that's a good thing and should be integrated into the approach moving forward.

And so with creative approaches, solutions can be determined. I think this pubic meeting is a great step forward in that regard, but the integrity and conduct of CV outcomes trials and subjects' rights and their commitment to participate all need to be held in the highest regard and honored as much as possible. And any options that are likely to compromise the equipoise that underlies a trial that could irreversibly bias investigators and subject and that could limit the likelihood of colleting the required number of CV events are really not tenable and are not recommended.

So, I know that many of the principles that I've spoken about have been reiterated from the morning session, but hopefully you can see there's unanimity of opinion on many of these issues, and I hope that's valuable for the FDA in their considerations. Thank you

DR. LaVANGE: Thank you very much. Are there questions from the panel for Dr. Roe? Dr. Temple.

DR. TEMPLE: You probably know, and maybe other people at the table do, the sorts of trials that have been done better than I do. Have any of them tried to take a more aggressive simplification model?

DR. ROE: Not that I'm aware of. I think -- as you know, we've had recent meetings on this and despite your endorsement of that approach and the NIH's endorsement about that, there just hasn't been anyone that's really jumped in at full force. But I think, you know, the PCORnet group is about to launch their first trial of looking at aspirin dosing in the HR-based platform. Other groups are starting to do this, so I think it could be a very unique path

forward. IT's just as you've said over and over again, there has to be upfront discussions to have some commitments in place in the program, I think, in order for drug sponsors to be at least amenable to that option.

DR. LaVANGE: Other questions?

(Whereupon, no response; no questions posed.)

DR. LaVANGE: Okay. Thank you.

DR. ROE: Thank you

DR. LaVANGE: The next speaker is Dr. Jonathan Seltzer, President, ACI Clinical and Director, Clinical Research at the Lankenau Heart Institute.

DR. SELTZER: Thanks very much for having me here. It's an honor to be on a platform with people who have been sort of mentors to me through writing and some in person. I'm here on my own but my perspective is colored by my activities, most prominently with respect to this meeting and some of the writing group for the CSRC cardiovascular outcome trial paper.

I've been involved with the clinical trials transformation initiative and working with a couple people and up here today for the group leaders of DSMB workgroup; again, the DSMB workgroup of the multiregional clinical trials network. I'm in the writing subgroup also. Been on a lot of DSMBs and my group outside of Philadelphia works in that area.

Additionally, I'm on staff at Lankenau Hospital which is an academic affiliate and have represented the Academy of Physicians in Clinical Research. So my perspective is that of a DSMB member and as somebody working with clinical investigators and really practicing physicians.

So one of the things -- I first say I agree with almost everything that everybody said here today, but my perspective is a little different and it may be because I have three teenagers at home. I know some of you probably feel my pain but essentially, they have information way before I have it and they expect the right to have information. And one of the -- in sort of looking at the material prior to this meeting, there is -- you know, it's in the law. There's a sort

of a duty to disclose information on approved products that people feel they have a right to. I think we have representatives, some of the, glad to see, patient representatives in the audience who want to see that information.

That's balanced -- needs to be balanced with issues in interpretation. We've heard a lot of people say that generalized public release may do more harm than good, and I'd like to suggest that maybe perhaps a modified DMC-like process might be a useful solution for this; okay? So if you're a -- from a -- I think this is a physician's role as well as society's role -- is we don't want to do any harm; okay? But a drug gets approved and there are two questions that we want to know and this is what I think needs to be released: What is the data that lets you know is a post-marketed drug or device any worse or better than alternative treatments. And second, you're wondering for your patient are there particular patient or subgroup factors that may encourage you or discourage you from using this already approved product. And I think it's fair to say that the public would want to

have a right to know that, and I think they would probably get it under the way I understand the law is written right now.

The question is how and how do they maintain faith? And without this balance of disclosure, there is not faith in sort of the clinical enterprise. And I think it's really important that we keep that in mind.

So, you know, we've talked a lot about problems with interpretation of interim data, and I'll skip through. You know, there are questions about the trial. I think Dr. Fleming was pretty eloquent on performance standards, etcetera. Those are really important things. This is sort of an interim of an antihypertensive that, again, shows -- something worked on that shows that side effects also move with time, that have confidence intervals so you may -- you know, this also shows placebo is bad for you by the end of the trial, too, and caused some hypertension and stuff. But, you know, docs want to know because this may -- these types of side effects, they're not primary endpoints but they're secondary sort of

endpoints that may influence who you use these approved drugs for in the cardiovascular world.

So to me, this is not just about the diabetes problem, 1.3 or 1.8. I mean who knows -- many people said we've done 150,000 patients is enough. But, you know, there's a lot of other drugs with cardiovascular outcomes. We're going to be using registry data. We're going to be using big data. We're going to be using large-scale safety data. And what is our mechanism of figuring out whether it's safe for people.

So the question is, that I see it, is how likely it is the consumer of these analyses will have the skill to protect patients. So I agree with everybody that when you release this data that it can be misinterpreted, but there are a lot of other audiences for this other than physicians or research investigators. We have the public is interested. And when I look up one of the pages for this meeting, half of the hits were from attorneys, interestingly enough, so they have an interest in this; you know, "mysideeffects.com" and payers, of course -- I see you

shaking your head but it's true. It's two pages; half of them are hits. And payers have a real interest in this information.

So how do we get across the information? How do we get trust in the system? Docs aren't really good at statistics. As we know, if we just release it to doctors, we've seen examples of them misinterpreting it. Probably, you know, my favorite headline is this one down here, "Statistical literacy among doctors is lower than chance." Okay?

(Laughter.)

DR. SELTZER: And this article right here was very interesting. These guys did a great study. They sent out four simple statistical questions like, you know, what's a hazard ratio, what's relative risk. They sent four out to corresponding authors and research journals and they got about 42 percent correct.

So, you know, this doesn't enhance the public's confidence in us but there are -- I think that I'd like to suggest is a methodology so where when we get into the details and we say we let out

data it's a 1.26 versus a 1.3, etcetera, that's very technical. It's very hard to communicate that. I was glad to see Dr. Roe talk about large sample studies because I think it's kind of a communication problem.

So we have an example. I think the DMCs we've been talking about is a really good tool. We use it in clinical trials. Clinical researchers, IRBs, all sorts of people believe it. And some work at our place that we've done in conjunction with Rob Califf down at Duke is we've looked at ct.gov seeing there's -- this will be -- is part I presented to you guys last week -- that there's a lot of DMCs out there.

It's about 30 to 40 percent of trials check off in clinicatrials.gov that they have a data monitoring committee. But then we looked both through literature review as well as ct.gov of what exactly do these DMCs do. And guess what? Surprise, nobody knows. It's very, very hard to find out. It's not detailed. You know, I see a lot of different examples and they're very different and I'm sure that many of members who have sat on them have seen different DMCs

and how they act.

But the process of a DMC, there's a lot of confidence that if the trial has a DMC, people looking, and people feel a degree of comfort. Investigators feel comfort and I know as -- you know, my (inaudible) IRB I sat on, the IRB had a lot of confidence when -- and I think patients have confidence when they know there's a DMC overlooking.

So what -- how can we use this in the duty to disclose? Again, I think, real quickly, why do they believe a DMC does a good job in protecting patients as well as the integrity of the trial even when nobody says what does the DMC actually do? I mean I've been doing *Journal* club at my place for like 10 years and nobody's ever said what do they do. They ask did they have a DMC on that trial. And you go yeah and that's enough. They know that members are independent; the charter's often available as is the SAP; the people, the consumers of this information are research-oriented people; and the other consumers are kind of research-aware if they're not researchers themselves. So you have sort of a captive audience

waiting for this information and it has the proper peers to hold up the enterprise.

So I'd like us to consider something a DMC plus process for approved products. It's a little different, has some of the same characteristics. Okay, number one, it has a simple publicly digestible description of the surveillance strategy as well as the rationale. So for instance, we're going to look at this point estimate. If it's a 1.26, that's good and in plain English why that's good. It's very simple and that's as good as a .9 for the purposes of when we look at it and just a simple explanation. I think people demand these days and deserve more about how we think.

Secondly, what are the clear descriptors which we should have now, the really perspective descriptors for allowing trials to continue; and what are those things like performance standards, like data access standards that might affect those perspective decisions?

Third, I think for approved products, we have to figure out a model and this is good because it

will gives statisticians career -- you know, new things to do. What are some models to begin to entertain subgroup analysis as things go on to help the medical community deal with approved drugs, payers deal with these things also?

I also think -- and this is a little out there maybe -- but I think that we need to have people who are not just expert physicians and statisticians looking at this. I think we need to start to include other people who have a stake in the enterprise for approved products. I think there should be, if not voting members, at least, you know, representatives who are observers of the DMC process. It can be a statistician, it can -- if a statistician can explain a confidence interval to a physician, they certainly can explain it to a patient representative or a payer or somebody like that.

So there is sort of a unified opinion of, you know, we have people rowing in the same direction; yes, we let this trial go on; yes, we're -- you know, we think it's okay, and we've heard all these various constituencies at least listen and agree with our

rationale.

And then I think, you know, we need communication, communication, communication.

So I lost my last slide there but -- or maybe it's on here. I wanted to just end up saying that I liken this to sort of the "black box" process for the airlines. Nobody knows even that black boxes are actually orange but they believe in the black box. They believe when something happens, there's a bunch of -- they know it measures altitude and speed and wind flap and stuff, but nobody actually knows what they do but they have faith in the process, that that's the way we go through.

And I think for approved drugs that are unleashed upon the public, you know, we need to take that responsibility seriously and I would like to, again, argue for a process that's a little more inclusive and more open. And I guess that's my difference in perspective as opposed to restricting the number of people who know about it, etcetera. I'd like to sort of open it up a little but with the same caveats that we heard before. Thank you

DR. LaVANGE: Thank you. Are there questions for the panel for Dr. Seltzer? Sir, either side. Yes, sorry. Dr. Seltzer, we have a question. Dr. Chakravarty.

DR. CHAKARAVARTY: In your new DMC-plus process, how do you see the regulators role to be? Is there any change that you foresee a regulator to --

DR. SELTZER: No. I think it's reasonable to say a regulator could sit in on the meetings and process, too. I mean I think that that type of thinking -- I mean I will tell you that the regulatory thinking is an important part of the DMC process. And sometimes -- I can just tell you from my experience, it's nice -- you know, a really good DMC with folks like this here, they understand how regulators think and those are really good DMCs. But there are a lot of little companies out there. There are lots of people on DMCs with very little experience. So I don't -- I think maybe having somebody with regulatory experience; if not, maybe a regulator who is not directly involved in the approval or the process might be a good idea; actually, a good idea.

DR. LaVANGE: Other questions from the panel?

(Whereupon, no response; no questions posed.)

DR. LaVANGE: Okay. Thank you. Our next speaker is Dr. Lee Kaplan, Director, Obesity and Metabolism and Nutrition Institute at Massachusetts General Hospital, and he is speaking on behalf of the Obesity Society.

DR. KAPLAN: Thank you very much and thank you for allowing me to speak on behalf of the Obesity Society which is the organization I'm representing today.

So my disclosures are that I'm a basic and clinical investigator and a clinician working in the area of obesity and its complications, and I serve as a scientific consultant to several companies across the spectrum of new agents for the treatment of these diseases. As I mentioned, I'm here representing the Obesity Society in the role as Chair of their Clinical Committee and the Obesity Society has underwritten the costs of my being here. No for-profit organization

has participated.

So the Obesity Society, for those of you who are less focused on that aspect of pre-disposers to diabetes, is a professional organization founded on the basis of being a research organization and now including health care providers. There are 2400 members from across North America. We advocate for improved prevention and treatment of obesity and its complications and develop and publish clinical guidelines like so many of the other organizations represented here today.

We publish *Obesity* which is the leading subspecialty research journal, and we are a founding member with the Surgical Society, the American Society of Metabolic and Bariatric Surgery of *Obesity Week*.

So I'm going to focus on what we're calling bridge CVOTs or cardiovascular outcome trials begun pre-market and extended post-market. We're specifically not addressing those that are designed to be completed before FDA evaluation or those begun after initial FDA approval that does not rely -- or the approval does not rely on interim cardiovascular

outcomes data.

So with respect to type 2 diabetes and obesity which is really where our focus comes, obesity, which is defined as excess body fat having an adverse effect on health -- I'm not defining it by BMI specifically -- is the major factor predisposing to type 2 diabetes across the world. And although the 2008 FDA guidance on evaluating cardiovascular risk was focused on the development of agents to treat type 2 diabetes, it has also been applied to agents that treat obesity itself. It specifically required them to do so if the indication that's sought is for the treatment of diabetes even if it's a weight loss drug but has been applied more broadly than that.

So in terms of the issues that have already been discussed several times today, I'm just going to, in two slides, review what we think is the most important. Obviously, this is a summary of all of the discussions that were had earlier. They're designed to provide power and to extend actionable information. Actionable information in this case is the approval of the drug or biological product obtained from the

interim analysis. The specific outcomes are overall cardiovascular risk rather than specific subcategories of risk which I'll talk about.

The design anticipates the need for substantial additional subject recruitment and all of the things that we've already talked about several times today. But it also anticipates that there may be more detailed information such as the rate of specific types of cardiovascular risks, subgroup analyses, and other less common potential risks, even if they're not in the area of cardiovascular outcomes. And obviously, we, like all of the other speakers today with few exceptions, believe that the early release of such information could be highly misleading land have adverse effects.

From an operational perspective, this first statement re-emphasizes what we've already heard several times today in terms of the subsequent identification and reporting of adverse events. But in so doing, it could lead to errors in both directions including an over-estimation of specific risks suggested in the interim analysis, but it also

could lead to selective under-reporting of risks not identified in the interim analysis.

But the flip side of this is that it could have the opposite effect, because if you bias either continuation of the trial or further recruitment to the trial or in other ways bias the conduct of the trial, you might see subjects at highest risk for a particular outcome be less well represented or those risks be less well recorded leading to a decrease or so-called regression to the mean with respect to the perception of those risks.

In addition, we've talked a little about public disclosure but public disclosure of these incomplete results could establish an incorrect impression of the safety profile to another group of critical stakeholders including patients and providers because they’re going to be using these approved agents in the public domain, in the commercial domain, and they'll be doing it perhaps with incomplete understanding of the released interim data. That's above and beyond the effect of those released data on the subsequent conduct of the cardiovascular outcomes

trial.

So having said all that and having agreed with most of the previous speakers, I want to add a couple of caveats. First, in the reporting of any approval decision that relies upon the interim analysis, the FDA needs to provide a clear description of the manner in which that analysis was conducted, the specific interim outcomes criteria used for approval consideration, and whether those criteria were met. I say these things because just in follow-up to Dr. Seltzer's comments, the public is even less knowledgeable about the implications of some of the bases for these decisions than the medical establishment, and we've already just heard that the medical establishment is not so well informed about statistical principles. So as a result, it's incumbent that even though there may be printed documents, in every individual case, this information needs to be emphasized.

Second, while we believe the overall benefit is enhanced by preservation of the integrity of the trials, there may be specific outcomes beyond the

relative cardiovascular risk that could contribute in certain circumstances to the overall decision about approval and the manner in which they contribute if those are used, if there are unanticipated risks that might be used to influence the approval or other subgroup analyses. Again, that has to be transparently clear to the public if they're going to be used to make an approval decision. And we would hope that most of those criteria, meaning not necessarily the specific risks that might be discovered but the manner in which those additional risks might be evaluated, that the criteria for such evaluation be determined before the onset of the trial. So although the trial is a cardiovascular risk trial in its design, if it's going to be used or if specific unanticipated effects might be used for the approval decision, that should be determined in advance.

Now what kinds of examples am I talked about? I'm talking about the interim results that where specific adverse event signals might pose a risk to selected patients. And in that case, the

indications for the drug might be used -- might be changed rather even though the drug is approved for commercial use.

Another example is although the rate of adverse events overall may be within the criteria for approval, elevated rates of such events within specific subpopulations of patients might reasonable influence indications.

In the first case, I'm talking about subsets of complications. In the second case, I'm talking about subgroups of patients with either specific or broad cardiovascular risks.

Now, several people have discussed the role of the data monitoring committee and although my suggestions based -- or the Obesity Society's suggestions are not as broad ranging as Dr. Seltzer's were a minute ago, we do recommend that the DMC for such bridge CVOTs be charged with certain responsibilities to advise the sponsor and the FDA -- I forgot to put the FDA in this slide -- as to whether selected information from the analyses should be included in the publicly available regulatory

documents, whether the DMC concerns about specific information generated by the trial meet a threshold that mandates either deferral of the FDA approval, and that deferral could be based on a later interim analysis or until the full completion of the trial.

So these proposed new DMC responsibilities would be consistent, we believe, with the 2006 FDA guidance on establishment and operation of clinical trial data monitoring committees which emphasizes the importance of safeguarding the confidentiality of data but recognizes the need for exceptions. And we would argue that exceptions could also be -- new exceptions could be placed on release of these data given the new use of these data for approval decisions.

So in response to the questions then, with response to question one, which I won't repeat, dissemination of the details of an interim analysis would undermine the integrity of an ongoing CVOT and jeopardize its continuation. We agree with the other speakers in this regard. The loss of perceived equipoise generated by this dissemination and misunderstanding of the meaning of the data would

adversely affect the overall trial.

We're also concerned that disclosure of such analyses could mislead the public, prescribing clinicians and other stakeholders that prematurely influences the appropriate use of the therapy in the clinical arena.

Question 1(a) about interim findings, which ones: Point estimates of risk and identification of outcomes not used for the regulatory approval decision could be misinterpreted and, therefore, we would recommend that they would provide a great risk. But we also recognize a selected interim analyses, even those beyond the primary intended outcome may be used for in determining whether to continue a trial if they're based on preordained stopping rules.

In response to the question about partial disclosure, limited disclosure of interim results can generally offer protection of trial integrity and provide clinicians with essential scientific information. However, they will undoubtedly be situations as I described earlier in which disclosure and dissemination of more detailed information will be

required to guide providers and protect the public. We believe that the DMC can and should play a major role in adjudicating when and how additional information from interim analyses are to be disclosed.

And if I could add, we didn't make any recommendations about whether the DMC ought to be communicating through the normal channels to the executive committee, to the sponsor, to the FDA directly. I will leave that to some of the other comments that were raised earlier today.

With respect to if they were disclosed, would it be feasible to conduct a new large trial, yes, it's feasible but burdened by all of the effects of dissemination of the interim results that we've heard talked about several times today, such a new large trial would incur substantial otherwise avoidable costs as well as delays in the approval of potentially valuable new agents. This could generate a chilling effect on the development of and operations for these disorders given that the time delay in particular and the costs could be enormous. Given the large unmet need for new safe and effective therapies

as is particular true for obesity, perhaps even more so than diabetes, minimizing such avoidable barriers to their development would be strongly beneficial, and this is a point that the Obesity Society wants to emphasize. We're in a different situation with obesity versus diabetes with respect to the currently available therapies.

Are there other alternate trial designs? Well, we don't have too much to comment about that except to say employment of an adaptive design, particularly a basing design could potential enhance the predictive value of the interim analysis for the final results. I'll leave that further discussion to the statisticians, but I want to emphasize that even with such an approach, we believe that routine disclosure of detailed results at the time of product approval would significantly and adversely affect the utility and accuracy of the data derived from the final analysis of the trial. Therefore, the Obesity Society strongly recommends, as do our colleagues, that these data not be disclosed except as I've described above.

And final considerations, obesity, while providing the major predisposition to type 2 diabetes, is a disorder with more than 70 described medical complications that generate heightened morbidity and mortality. They include many serious metabolic, non-diabetes disorders such as fatty liver disease, sleep apnea and the like, inflammatory and neuropsychiatric disorders and several cancers.

Diabetes itself and the cardiovascular outcomes specifically are not the only or necessarily the most important considerations in evaluating the efficacy, safety, and clinical utility of various treatments for obesity. Other types of adverse outcomes may be of greater relevance in assessing the safety of such agents and improvements in or prevention of such other company-morbidities may offset the limited adverse cardiovascular outcomes in terms of mortality and other clinically meaningful outcomes. So while there is a common application of these cardiovascular concerns appropriately to obesity, which has so many if not direct, certainly indirect potential cardiovascular outcomes, we can't

lose sight of the fact that obesity is much broader than diabetes. Its adverse effects are much broader than the adverse effects of diabetes alone, and the unmet needs are much greater than the unmet needs in diabetes and those considerations should also be taken to heart when looking at the application of these approaches to obesity or weight loss drugs specifically.

I want to thank you on behalf of the Obesity Society. We all appreciate the leadership of the FDA in this area and, of course, the opportunity to present to the panel. Thank you very much.

DR. LaVANGE: Thank you, Dr. Kaplan. I'll start with a question. You talked about having more flexibility around what is disclosed at interim as opposed to just trying to disclose everything but the fact that the boundary was met, and I wondered if you could -- did your group talk at all about any examples? Are you referring to other safety data, non-cardiovascular or adverse event rates, for example?

DR. KAPLAN: So we were talking

specifically -- in the slides, I had two examples. One would be a subgroup of individuals easily identified that met a predetermined criterion, the criterion predetermined but the specific outcome not predetermined. And the other would be a specific subset of cardiovascular outcomes that in the whole group might be predetermined that it was a very high signal. And again, this would have to be predetermined. A third group that I didn't mention would be another non-cardiovascular outcome that could be detected, as was described by Dr. Nissen earlier today.

DR. LaVANGE: Other questions? Dr. Jenkins.

DR. JENKINS: Yeah. In some of the presentations this morning, we saw various pathways that sponsors have chosen to meet the diabetes guidance including a meta analysis of the phase three trials to try to meet the 1.8 boundary. There has been a proposal that you do a study one to meet the 1.8 and then study two to meet the 1.3 and then the single study with the interim analysis. And I think we've had discussions about how does it differ if all

of those approaches have point estimates and confidence intervals that either lean favorable or lean adverse to the drug. Are they all the same in the ability to do another trial or are they different in some way? So if the meta analysis has the 1.22 adverse lean or the .92 favorable lien that I think was in one of the presentations earlier, does that have an impact on enrolling and conducting the large definitive trial, or are they somehow different from that finding in the meta analysis that gets disclosed publicly?

DR. KAPLAN: So I would argue that the -- that unless you're straight down the middle that you have the same risks in terms of biasing the behavior of the participants, all the participants, whether they be recruited subjects or they be trial designers -- or I'm sorry -- trial executors. The -- so I mean there are practical considerations if the other data are released. Doing the meta analysis is an open process so you can't really block that effect. But we would recommend -- we like the, as Dr. Nissen described, the compromise of the continuation of a

predetermined or pre-organized bridge cardiovascular outcomes trial as compared to any of the other alternatives. So if there are going to be requirements for cardiovascular outcome trials and there is, in addition, going to be the opportunity for a more relaxed outcome, the 1.8 outcome as opposed to the 1.3 outcome, then we would recommend that that all be set up in advance just as according to good trial practice.

DR. LaVANGE: Other questions?

(Whereupon, no response; no questions posed.)

DR. LaVANGE: All right. Thank you very much. Our next speaker is Dr. Steven Marso, Director of Interventional Cardiology and Professor of Medicine at University of Texas Southwestern Medical Center.

DR. MARSO: Good afternoon and thank you very much for allowing me to be here today. It's a privilege and honor. I see a lot of friends and former colleagues in the audience today.

By the way of disclosure -- are on this slide -- I've been a clinician and a researcher now

for almost 20 years. I've been involved with the clinical care of people with diabetes and advanced heart disease in a cath lab and involved in clinical trials now for the last many years. And all of my conflicts relate to these activities, the research activities. Relative to these hearings, I received personal payment from Baldman (ph) Clinical Trials. I'm personally the study chair in two, the co-chair in one, and steering committee member in other diabetes and cardiovascular clinical trials.

Like so many before me, I will advocate for the use of interim analysis in clinical trials that evaluate the cardiovascular safety of emerging therapies to treat diabetes. I absolutely think it's imperative that clinical trials be conducted both scientifically and statistically rigorous. I think it's equally imperative and important that clinical trials be conducted as efficiently as possible.

The IOM projected that by 2020, 90 percent of clinical decisions will be supported by accurately, timely, and current clinical evidence. In 2014, I would argue we are far from realizing this goal.

There are many reasons for this failure. There remain gaps in care. There remain disparities in care, lack of provider accountability in care and, in fact, system failures to coordinate care. But there for sure is a limited capacity for the timely generation of data on the effectiveness and safety of care which truly form the foundation of evidence-based care. In short, we need more evidence from trials if we are to ever realize the IOM goal.

Trials are costly, time-consuming, resource intensive and we've heard many times today we live in a resource-constrained environment. We must develop model strategies to minimize trial inefficiencies. And I think if done properly, incorporating interim analysis is a viable option to improve these inefficiencies. The benefit has been articulated many times.

There have been many, many paradigms that have been demonstrated today but I would submit to you a common paradigm in the current regulatory environment is to conduct a trial to rule out 1.8 followed by a second trial to rule out 1.3.

Incorporating an interim in a single, well-designed clinical trial to rule out first 1.8, then 1.3 would have a number of expected benefits. It will reduce the number of patients needed to evaluate the experimental treatment. Dr. Ratner mentioned today there are a lot of patients in clinical trials. There are. The question is is it the right number. Is it too many or is too less? We must manage trial inefficiencies so that we only enroll the right number of people to answer the specific question. An interim analysis will also decrease costs, one trial being functionally cheaper than two and may streamline new therapies for patients.

Like everyone before me, I think performing interim without consideration of confidentiality of data has the real potential to jeopardize the integrity of the trial. The principle of confidentiality of interim data is now widely upheld and central to good clinical practices. Maintaining confidentiality safeguards the interests of study participants and absolutely ensures the integrity and credibility of the clinical trials. This core

principle is especially important in phase two and phase three trials when these trials are conducted in settings where interventions may impact mortality and morbidity. This practice is recognized globally in published literature and guidelines. Tom Fleming has summarized it.

I think it's proper to just briefly summarize what he eloquently stated earlier. It's not a theoretical threat. There are practical implications for clinical trials. Prejudgment of unreliable early results, diminished enthusiasm for enrolling patients, increased duration of enrollment, unjustified early termination of trials and discordance between the final trial result and other ongoing clinical trials.

So in response to the FDA question, I would submit that a detailed disclosure of the trial findings at the interim would absolutely jeopardize the trial. I do not believe it's possible to determine which of these data, whether it be the point estimates, the confidence limits, would be more or less likely to place the trial at risk. It really is

an all or none phenomenon. Therefore, I would advocate for a general statement from the Agency that the interim trial met or did not meet the established criteria for CV safety.

Lastly, and I'll expand on this more than the others perhaps, I think it's unwise to disclose secondary measures in a dedicated cardiovascular outcome trial. And in the case of diabetes, glycemic efficacy standards and outcomes probably should be left to other clinical trials to answer that question. Keep it simple. Less is more here.

When designing the trial, I think the design matters. Tom mentioned it quite a bit, Steve a little bit. Performance standards matter. And I think in interim trials, performance standards matter more than in any other trial, and we'll come to that shortly. I think I can quickly move through this. We all agree at 90 percent power, we need 122 to rule out 1.8, 611 -- Steven put 620. I think functionally, 611 or 620 is the same to rule out that.

But I want to talk about really this trial scenario. If the power to rule out 1.8, then 1.3 set

to 90 percent, then the interim analysis should be conducted like we've heard today at 122 and the 1.3 at 611. In the scenario 122 events define the pre-interim and it's shaded in light blue, so 122 events define the pre-interim; 489 events will define the post-interim, shaded in dark blue.

And I want to talk about the post-interim phase because I think there are practical implications to the study design. The post-interim phase, by definition, can be separated into two further segments. The post-interim pre-agency phase and the post-interim post-agency phase or rather the post-interim post public disclosure. So here I mean when the FDA disclosed the results to the public, not when the FDA, you know, had access to the data.

In the post-interim pre-agency phase, attribution for limiting unblinding of the interim results rests solely with the steering committee and the sponsor. Now while I agree that no steering committee member or other individual participating at trial for that matter will be unblinded, it is critical, in fact, foundational that methods be

implemented by these individuals to ensure that the interim is executed using best practices. It's a shared responsibility between academia and the sponsor. The sponsor has a very large burden of non-disclosure. I will discuss this later but if I just digress a moment, I absolutely thing that the sponsor will be involved or think it should be involved in this process and we can discuss that perhaps on the question period.

There is a shared responsibility to minimize unblinding between not only trial leaders, sponsors, but also the Agency. Again, this is an all or none phenomena. All three entities must manage the interim. The Agency has an additional responsibility to not only publicly disclose the interim or limit disclosure of the interim but also to coordinate with regulatory authorities in various regions of the world. We talked it about a little bit today, but I think it's an unanswered question how one would roll out this process to the rest of the world. And I might disagree subtly with the prior speaker that relying on sponsors to make that decision might be

somewhat risky. I think that's a risk that I might be uncomfortable with.

The duration of the three interim segments will vary substantially based on the design of the trials. Drivers of this range include sample size, duration of recruitment, annual event rate, and timing of public disclosure. These have important practical implications for the time in each interim, and I think it should be thought about a little bit when you design the trial. In the following scenarios, it assumed that public disclosure occurs 12 months following the interim analysis, sort of an arbitrary time but about the time it takes to analyze the data, submit the data to the FDA, FDA goes over the data, just make it 12 months for the sake of argument. We'll also assume that the loss to follow-up rate is about one percent and so I illustrate two scenarios: Trial a is a 10,000-patient trial with uniform rapid enrollment of one year. Trial scenario b, 5,000 patients with a two-year uniform enrollment.

So this is trial scenario a, 10,000 patients. The annualized event rate is two, three,

and four percent on the blue, the red, and the green lines respectively. And this example will model the two percent annual event rate. And what you see here is number of events accrued on the y and the duration trial is on the x. The final interim events would accrue around month 13. The post-interim pre-agency phase is about 12 months. It's predefined and the post-interim post-agency phase would last about 18 months with a total trial duration of 44 months. In this example, you know, the 10-5-2 trial design, there are many favorable design features. For example, the interim and final enrollment occur at approximately the same time thus limiting the potential for selection bias. The median exposure in the pre-interim, I think, is reasonably acceptable, just under a year and in the post-agency phase is limited to about 18 to 24 months; thus the time to rule out 1.3 after 1.8 is about 18 to 24 months.

If one looks at the same trial with a four percent annualized event rates, you see that the interims are shifted leftward and the trial is shorter. The final events would accrue around month

nine. The post-interim post-agency phase would be reduced to three months, the trial duration to 24 months. While it is true this trial is shorter and the post-interim is shorter, pre-interim exposure is dangerously short and the interim completes well before the enrollment. This type of trial would actually be seen in high-risk ACS patients, and I would actually caution against this type of trial design with an interim. We can talk about caveats to this design in the future, but I think there are many adverse events to this trial design.

If the trial is to be cut from 10,000 to 5,000 and the planned enrollment duration doubled from one to two years, the segments are lengthened and right-shifted. In this example, the pre-interim phase is 27 months; the post-interim phase is 54 months with a total trial duration of 94 months. The duration of interim trial segments are shown in this table. While there are countless permutations to these scenarios, I would propose that a 10,000-patient trial annual event rate of two percent may be a preferred interim design. A smaller 5,000-patient trial with a higher estimated

annual event rate would also seem acceptable if enrollment was postponed out to one to two years.

These scenarios notwithstanding, there will be an absolute predictable relationship between trial design and duration of the interim trial segments and this relationship should be considered when designing the interim.

So here I've added the number of events that will accrue in each segment of the slide, and the take-home point here is that in the preferred trial design at the top row and the third row, half of the trials accrue in the post-interim. A lot of events will accrue once the potential for bias has occurred. There are too many events to ignore.

So how do we manage the risk? I would like to transition from the trial design features to operational details. If the interim analysis is generally a good thing, how can we assure that the trial design, the operational elements, the regulatory view, and the communication of data will assure that the ongoing trial will not be compromised? Is it possible? Actually, I firmly believe that it is if

the right systems are in place for the sponsor and if the agency doing the regulatory review does not reveal specific data to the public.

I think Steve talked about a very detailed data plan and I advocate for a lot of that. I'm going to walk through some elements that I think are key to that concept. Firstly, I think it's imperative that there be a transparent standard operating procedure that's developed, from the FDA would be great, from academia would also be acceptable, so we know who to unblind, how to unblind, and what will be unblinded. I think these are core principles about how to move forward.

It's incredibly important to develop an institutional firewall between blinded and unblinded members, to unblind and analyze only a parsimonious data set -- we haven't talked a lot about that but I think there's real value for unblinding less rather than more; the comfort level falls on the Agency of that, of course -- to create a no larger than absolutely necessary unblinded team, whether at the agency or the sponsor or at the DMC and recognize the

shared responsibility between sponsor and agency to ensure minimal unblinding, set very high expectations and establish personal accountability for each unblinded team member.

I actually believe it's important that the sponsor develop an inward and outward facing strategy of planning to submit the interim results to the Agency. This sets the expectation for both internal and external stakeholders that the company is actually planning on submitting and taking the requisite steps to plan to submit to the Agency. This strategy is seemingly simply yet essential in order to internally prepare for the submission. If this message of planned to submit can be held constant through vital early phases of the clinical trial, it's conceivable that this strategy may be effective in reducing the potential for bias, from prejudgment from employees of the sponsor, investigators, and the investor community.

Similarly, it's important that both trial leadership and sponsor adopt a proactive pre-interim decision-making stance. It would be preferable that

both the sponsor and the academic leaders anticipate matters arising in the post-interim. For example, given trial amendments are commonplace in clinical trials, it would absolutely be ideal if major amendments could be made prior to the interim. I think this is a shared responsibility between sponsors and academics.

Conversely, in the post-interim, I would actually encourage a sponsor and the investigators to restrain from making major changes to trial design other than for obvious safety reasons or other external data arising to the matter to make the change. The temporal association of these changes in the post-interim could have unpredictable and unmeasurable consequences. It may also be useful to have unblinded individuals acknowledge the importance of maintaining confidentiality and a pledge to maintain secrecy. Other speakers have talked about that. I actually think that's vitally important to get personal accountability.

Lastly, one may need to establish consequences for failing to maintain principles set

forth in the SOP of managing an interim trial. I might phrase this -- it's been said before -- I might phrase it this way. Breaking new ground requires new ground rules. I think it's absolutely essential and that the FDA take a leadership on this position. Ground rules will provide a frame of reference for what is expected and what is acceptable. Ground rules will provide a path forward to assure concordance of trial methodology when utilizing an interim analysis. They will also result in established cross-trial methodologies which will minimize trial-to-trial variation when executing interims.

I would encourage the FDA to convene a multidisciplinary team to weighing in on best practices for interim analysis to be used in RCTs and based upon these learnings consider updating the 2008 guidance or issue a new guidance on interims that might be translatable or generalizable to other trials.

Lastly and in summary, incorporating interim analysis is absolutely a viable option to improve RCT efficiencies. Disclosure of detailed interim analysis

will likely undermine the integrity of the trial. I think nearly every academic has articulated that today. There is an absolute need to recognize the shared responsibility between a sponsor and the Agency. And like Tom Fleming, like Steve Nissen, I think the active involvement of the academic community is critical.

The time under the curve of the post-interim will vary substantially as a function to trial design, and the Agency could think of ways to minimize the post-interim time period so you're at less time at risk, if you will. I think there are many design features to a 10-2-1 design, a 10,000-patient trial, two percent event rate, and a rapid one-year enrollment.

I would encourage the FDA to establish new ground rules and after deliberating today and in the upcoming weeks, I would actually hope the FDA would be comfortable and, in fact, advocate for trial designs using interims. And with that, I'd like to conclude and thank you very much for allowing me to be here today.

DR. LaVANGE: Thank you. Questions from the panel? Dr. Jenkins.

So would you advocate that one of the criteria for when the interim analysis occur would be that enrollment has completed? Right now the interim is slated to occur based on the number of events, but would you advocate that that be delayed until enrollment is competed to avoid some of the impact of inadvertent disclosure on enrollment?

DR. MARSO: So I think that's -- I think it would be ideal if the interim and enrollment could complete around the same time. It could be a concept to discuss further. What I would advocate for in lieu of that mandate would be a clinical trial design whereby the interim would likely accrue at the time of planned enrollment. The challenge with that is you're talking about trial efficiencies and enrollment efficiencies. And as a person not on a DMC, I spend a lot of my time talking about enrollment rates, and I think that becomes a critical issue when you're doing an interim analysis. And I would absolutely favor that the interim and enrollment kind of happen about

the same time. It basically negates the need or the concern for selection bias if there is some concern in the trial. Now you can have dropouts. I mean there are a million other ways you can become biased, of course, but I think that is one way to mitigate the selection of patients in that trial.

DR. LaVANGE: Are there -- yes. Lee Kaplan.

DR. KAPLAN: So I heard that -- you said a couple of times that we have to recognize a shared responsibility between the sponsor and the Agency. I also heard you say that it was critical that the sponsor have the minimal number of individuals be unblinded.

What's your opinion on the number of sponsor employees being unblinded being zero? Is that still sharing the responsibility?

DR. MARSO: So you mean -- is the question my point of view if the interim results are bypassed from the sponsor and go directly from the DMC to the Agency --

DR. KAPLAN: Right.

DR. MARSO: -- what would my position that

be?

DR. KAPLAN: The DMC certainly has the role of making sure that sufficient equipoise remains so that it's ethical that the trial continue. The Agency has a responsibility to make sure that the overall risk-benefit of all the data that's available is favorable for it to be approved. It's unclear to me what the absolute role for the sponsor is in terms of having any of this unblinded data.

DR. MARSO: Sure. So, you know, maybe there are some -- several downsides to going last in the day, right, but the benefit is I've got to mull over this question. I'm a little bit longer this most and I think a couple of things. I think that -- I agree with Steve Nissen on this point that I think the decision for sponsors to submit the data is larger than just the, you know, cardiovascular outcome data but yet that's a vital piece of information to submit or not to submit. So I would, you know, I guess, ask sponsors their opinion on that but I actually -- if I put my sponsor hat on as you asked another person to put the regulatory hat on -- I would be uncomfortable

making a strategic decision on a compound and submitting it to the Agency without knowing what the point estimate is and confidence limit is.

The other answer to that question, I guess, is a practical -- I'm a very practical guy -- because I hear people like Tom Fleming talk and I have to translate this great theoretical knowledge in the operations of clinical trials. But for me, the DMC role and responsibility would have to be expanded if this were to be the case; or the FDA would have to be comfortable with summary-level data. In my experience of this is 10 years, not 20 years, but when I look at the NDA or the material that is prepared for the Agency, I imagine it to be much bigger in scope than a DMC is used to submitting a report to move forward or not. So if that was to move forward, I would actually have to ask the Agency if they would be willing to have an abbreviated data set to review, because it's hard for me to imagine that the DMC is going to put together a complete response for you. And if they have to hire that workout to a third-party writer or the CRO, that essentially becomes an extension of the

sponsor. And to me, that's, you know, semantics in some ways.

So I mean if I had to answer that question today, and I guess I do, I would opt for involvement of the sponsor because of the decision to submit or not submit and the scope of the work from the DMC, I think, would have to be greatly increased. Others in the academic community may disagree with that, but if that's the case, then I would think that the Agency would then have to give on the quantitative data that they receive from the DMC.

DR. LaVANGE: Other questions from the panel? Dr. Jenkins.

DR. JENKINS: Yeah. One of the conundra I think we face from all parties is that we heard a lot about the unreliability of the point estimate for interim analysis but we all seem to want to look at the point estimate of the interim analysis if we're making business decisions to submit the application or even regulatory decisions on whether to approve the applications. And I guess there's an underlying question of is that valid. We're saying on the one

hand the point estimate is highly unreliable. I think Tom Fleming showed an example where the initial point estimate was s two-fold adverse finding which later turned out to be neutral. But I suspect that sponsors would be more favorably inclined to submit if it's .9 than 1.25 and regulators are going to be more inclined to approve if it's .9 versus 1.25. So knowing the interim point estimate unavoidably, I think, influences behavior and decisions.

So are we kind of talking out of both sides of our mouths in regard to the point estimate?

DR. MARSO: We are and when I was listening to Tom earlier today, I couldn't help but think that. You know, I was a fellow at the Cleveland Clinic and Steve Nissen was my mentor, and I rounded at Cleveland Clinic, and he would always say, listen, you have to have the courage of your convictions to act on it. For the courage of the conviction in this group today would be to that the DMC and the sponsor not know the point estimate -- I mean not the DMC but the sponsor and the Agency not know the point estimate confidence limits and approve the drug for use in the United

States and submit the package to the FDA based upon a DMC general commitment. That is an absolute pure strategy. I love it. I don't think it's going to fly because I think we all don't have the courage of our convictions and we're not incredibly convinced that Tom Fleming is right all the time. He's right most of the time, right?

(Laughter.)

DR. MARSO: But listening today, that's the solution of the courage of your conviction is that you don't -- that the sponsor doesn't know, the Agency doesn't know, that you approve it for use in the United States, and they submit it from that standpoint. But it goes hand-in-hand to me.

DR. ARCHDEACON: So I've had that thought as well a couple of times today, but I think maybe it's still slightly different, right, because the charge to the DMC is this ethical question about equipoise which is a little bit different than what the regulatory agency is being asked to do with this overall risk benefit.

DR. MARSO: Yeah.

DR. ARCHDEACON: So you'd have to ask the DMC to take on a charge that's a little bit different than their traditional role because they would have to also say, well, what if in this small subgroup, there's this other safety -- so --

DR. MARSO: Yeah.

DR. ARCHDEACON: -- I think we do stuff with that data that DMCs aren't traditionally doing.

DR. MARSO: You for sure do that, yeah.

DR. ARCHDEACON: So that's why I think it's somewhat valid and not entirely talking out of both sides of our mouths to say that perhaps there is a role for somebody to evaluate this data.

DR. MARSO: But as long as I think the Agency and the sponsors and academia recognizes that when we look at a subset of a subset of a first interim look, it's a highly unstable environment and to sort of predicate major business decisions or societal decisions on that is challenging. But yet, I think it's human nature to want to know it so we can throw in the totality of the risk-benefit equation.

DR. ARCHDEACON: Sure. Now there'd be

nothing stopping a company, though, from putting in their DMC charter that we'd only like this to go forward to FDA if the point estimate is 1.1 or less, right? So they could choose to be more conservative in the instructions they gave to the DMC?

DR. MARSO: Yeah. I think that's a discussion that we would have to have with statisticians and other because one of the things I wanted to avoid was to adapt the design of the trial based upon the interim. And I guess you're advocating just submitting that so it really doesn't adapt the trial design, so I guess it's possible that you could do that if the companies were comfortable with it.

DR. JENKINS: Dr. Temple and I actually discussed that paradigm on our way back to our office from lunch, but when you do that, you've effectively changed the boundary.

DR. MARSO: You do.

DR. JENKINS: So instead of it being a 1.8 boundary, the boundary is smaller than 1.8 to make people comfortable that the point estimate is 1.1. And I think that boundary is actually the 1.3 boundary

--

DR. MARSO: It is.

DR. JENKINS: -- what we're trying to get to eventually, so --

DR. MARSO: That's right.

DR. JENKINS: -- that's kind of a false construct to tell the DMC do the 1.8 analysis but don't refer it to the Agency unless the point estimate is less than 1.1. You've effectively changed the boundary.

DR. LaVANGE: Do you have another question, Dr. Temple?

DR. TEMPLE: Yeah. All of those are interesting considerations but what I hear you saying is you don't think, as a practical matter, companies really want to let somebody else do this without knowing at least some of the crucial data. So that's at least a little bit at odds of what a lot of people have said. I mean there was some enthusiasm for the idea that the data monitoring committee would do it and nobody in the company would know. But you're, if I understand you, somewhat skeptical about the company

allowing itself to be entirely blinded or blindsided, whatever we're talking about.

So do you have particular thoughts about how many people in the company would be allowed to know, because you were talking about a business decision? That means not just the people running the trial but, I don't know, the people in charge of deciding whether to continue and all that? So what's your view about how much exposure within the company there could be without getting into trouble?

DR. MARSO: So -- well, I mean, so this is, you know, my opinion and so I'm here solely articulating my vision on this, but I think Steve's slide -- you know, when I looked at my notes coming here, there's high overlap in the -- in my thinking about who needs to know. The thing that I probably -- and it's a practical solution because it's my opinion that companies will want to know the data as much as the regulator authorities will want to know about submission or approvability. So I think that the list is bigger than academician would be comfortable with and I think Tom summarized it nicely that there's

inherent risk. The more people know, the more risk that is. But if you look at Steve's list, it's a long list and there are a lot of activities that need to happen and that list is bigger than I would love.

The thing I struggle with is whether or not, you know, the chief executives need to know or a single chief executive needs to know. I mean if I was running a global pharmaceutical company and if I was the CEO for this trial, would I want to know the answer for submitting or not submitting that. And I can't answer it. I'm not the right person. I'm not a CEO of a pharma company. I just don't have the insight or the intelligence or the experience to know what drives those issues. From a pragmatic clinical trialist, I could be convinced one way or the other. What's more important to me is that we define it, they take a pledge of silence, they don't talk about it, and we have firewalls in place. If that number is 72 people or 26 people, I'd like it to be small but I'd rather have operations in place that would decrease the likelihood of it. So it's not an answer to your question but I can see the list being longer than I

would like.

DR. LaVANGE: Thank you very much. We've got one more speaker to get to and this is Manu Venkat from diaTribe.

MR. VENKAT: Hello. My name is Manu Venkat. I'm happy to be here today to speak on the behalf of *diaTribe*, a non-profit diabetes online patient newsletter where I'm an editor and a writer. Before I begin, I'd like to mention by way of disclosures that I'm also an employee at Close Concerns which is a for-profit diabetes-focused healthcare information company.

I'd like to thank the FDA for granting me the time to speak today and for providing a venue today for public comments on the question of interim data analyses from cardiovascular outcomes trials. This is a very important issue that both directly and indirectly affects millions of diabetes patients in the U.S.

For patients, diabetes management is rarely exciting. In fact, most of the time it's quite the opposite but we at *diaTribe* aim to give patients a

reason to really be excited about the new therapies and technologies that are available to them now or that are on the horizon. Through our free, online patient newsletter, we help patients better manage their diabetes and pursue the very attainable goal of living longer healthier lives.

Simply stated, the need for new therapies for type 2 diabetes is as urgent as ever. That need is grounded in the fact that type 2 diabetes is a progressive disease along with the fact that many current therapies that are available today have safety or tolerability issues that make adherence difficult for many patients. Patients also desire to have a voice before the FDA. We must remember that ultimately, changes in policies that lead to increases in development costs for diabetes therapies are passed on to consumers which can impact patient access.

This hearing is one of many instances in which the FDA has demonstrated real receptiveness to input from the public. Another example would be the FDA's upcoming virtual town hall meeting in November on diabetes.

Moving onto the topic of this hearing, it's very important to keep in mind the way that we in this room learn about clinical data is very different from the way that most patients experience that data. Many of us draw upon extensive science or clinical backgrounds and have the time to pour over the FDA advisory committee documents in advance of the advisory committee or even to be at the committee meetings in person. What patients see is often more along the lines of what you see here on the screen, news headlines and blog posts. Here I included just a selection from a quick online search, and these are not from very obscure news sources. These are from sources as big as *CNN*, *Bloomberg*, and the *Huffington Post* which are all widely read.

As we heard during the FDA presentations that introduced this meeting today, findings from stage one of the two-stage process should be considered very unstable and caution should be advised in interpreting such findings. Interpreting interim data requires full acknowledgment of these limitations. But just because the FDA is sometimes

the group to release these findings in this interim data does not mean that it gets to control the conversation. And very unfortunately, patients are sometimes presented findings from clinical trials in a counterproductive manner that can be unsettling and frightening and lead to behavior that is not in patients' best interests.

Current scientific standards such as the ICH E9 guidance make it very clear that fully public interim data disclosure from ongoing trials is to be avoided whenever possible. But we at *diaTribe* wanted to dig a little deeper into how and why interim data in the setting of a CVOT, when disclosed, can threaten trial integrity. Ultimately, when we were putting this presentation together, we knew we'd be speaking before a room of clinician, scientists, and the FDA, and what better to bring to a room like that than some new data.

We worked with our close friends at DQ&A, which is a market research company that runs a panel of over 5,300 type 1 and type 2 diabetes patients to build a survey to answer that question. To begin the

survey, we provided respondents with some background on CVOTs both in terms of their purpose and duration. Because of the limited amount of time I have here today, I'm not going to read through exactly this but we're more than glad to provide the full text of the survey as well as the findings to those who are interested.

We next asked all respondents two questions in a randomized order. These questions presented two cases in which there was either a slight increase or reduction in 10:32:34**/1:21:xx**(verse/gross/risk) cardiovascular events that was disclosed from our simulated CVOT. Although this presentation format might seem simplistic at first glance, as I mentioned earlier, we're not always in control of the way that patients see the data or learn of the data when it is disclosed from an ongoing trial. For each of the questions, we presented respondents with four choices: would the patient stay in the trial; would they consider withdrawing from the trial; or would they definitely withdraw from the trial either to pursue to the newly approved therapy or to revert to their

original diabetes therapy.

As you can see from these results drawn from the entire survey population, the disclosure of either positive or negative cardiovascular safety data has the potential to cause substantial changes in patient behavior in the trial. Nearly half of patients would at least consider withdrawing from the trial if there was a reduction in risk and three of four respondents would at least consider withdrawing if there was an increased risk, even if the drug was improved.

When we analyzed different patient subgroups including patients at high cardiovascular risk, as is shown here, the results we found were strikingly similar to the results of the entire patient population.

Though not shown here, we also looked at the results specifically for type 2 diabetes patients at high self-reported cardiovascular risk and we found very similar results. We would be glad to show this dataset to those interested.

So what are the key takeaways from both this survey and from what we've heard in the room today?

Clearly, our findings and points being made have suggested that interim data disclosure from ongoing CV outcomes trials do indeed have the potential to significantly alter patient enrollment dynamics for that trial. If the drug demonstrates a benefit, patients who are at that point randomized to either drug or placebo might drop out of the trial to directly pursue that therapy.

If there is a slight increase in risk seen in this interim data, patients might still drop out of the trial due to security concerns, safety concerns.

Although there is room for substantial deviation between patients responses on a survey like this and their action in the real world, withdrawal rates even far below the ones that we saw in this survey could still easily compromise a trial. Clinical trials require investment of valuable resources and increasingly rare resources such as provider time and research funding. And CVOT requires more investment than most other clinical trials.

We also cannot forget that patients themselves invest an immense amount of time and energy

in their participation in clinical trials and have a stake in that trial's mission.

CVOTs have the power to answer some very compelling questions and if and when these trials are compromised, it is a loss and a disappointment to everyone involved.

Given that the day is winding down and that we in the audience will soon be leaving for home and the FDA will have its work cut out for it to really sit down and consider what is to be done with all the information that has been presented today, I wanted to spend a minute to consider what is at stake here both with regards to the question of interim data disclosure but ultimately broadly about the way we currently evaluate the safety and the regulatory process for diabetes drugs. Clearly, these issues impact the over 29 million estimated diabetes patients living today in the U.S. These are the people that we at *diaTribe* and that all of us in this room work so hard to serve.

However, when considering how drugs are evaluated and approved, my concern is not only for the

patients of today but for my friends, my coworkers and my peers who could potentially be diabetes patients 20 to 30 years from now. We at *diaTribe* have noted with worry, as have some others in this room today, that some potentially transformational drugs that have been approved in other countries have had their timelines pushed back in the U.S., sometimes by years. And this is something that is disappointing and frustrating for many patients here in the U.S. The patients of today and tomorrow need scientists and companies to want to develop new therapies for diabetes.

Now so not to steal the thunder from Dr. LaVange who will be soon talking about where to go from here, but we wanted to present some thoughts from our perspective on the steps for the future.

Regarding the core topic of this hearing, the unblinding of ongoing trials, as it is practiced, appears to be problematic for patients, for providers, and for perhaps even the FDA when trying to make a regulatory decision. Based on the ideas expressed at this hearing and the FDA's immense expertise, we really have confidence that a better compromise

between evaluating safety and expediting approval in a way that does not compromise ongoing trials can be reached.

We heartily applaud the FDA for convening this hearing today and demonstrating its receptiveness to multiple stakeholder viewpoints. However, quite frankly, we will be somewhat disappointed if the conversation we began this morning ends with this issue. Our hopes are higher than that. Building on today's momentum, we hope that the FDA and other stakeholders can begin discussing broader questions about the policies that have now been in place for a few years to evaluate cardiovascular safety for diabetes drugs. We recognize that it's certainly harder to address big picture issues than to work on fine-tuning existing policies, but if the members of the panel were satisfied with working on issues that were simple and easy, we imagine you wouldn't be working at the FDA. We appreciate it's a very difficult job and you deal with some very challenging issues.

The Agency demonstrated real initiative last

year when it held its advisory committee on rosiglitazone and the re-adjudication of the RECORD trial largely exonerating a drug that had started a cardiovascular safety scar and thus alleviating the worry that many, many patients felt, patients who had been on that drug for many years. We wonder should that decision impact the way that we think about the policies that were borne from that controversy.

Another key question is whether the current emphasis of cardiovascular safety and such a heightened emphasis on cardiovascular safety is in patients' best interests. The default for drug evaluation historically has been a whole body assessment of both benefit and risk and emphasizing one area potentially draws focus away from others that are also of importance to patients. We must also consider the ethics of enrolling over 100,000 very vulnerable at high cardiovascular risk in these trials as Dr. Ratner of the ADA mentioned earlier today.

And finally, we must ensure that our diabetes drug approval paradigm will ensure that the therapies will be available for future generations of

diabetes patients and we must also ensure that the policies that are enacted to evaluate diabetes drugs are responsible in terms of the cost that the healthcare system and ultimately consumers will to bear.

To conclude, I'd like to read some open-ended responses regarding diabetes drug approval that we received from our DQ&A survey and from the Glu online type 1 diabetes community. We received thousands of comments last week alone and picked a few that represented the spirit of what we heard. These comments are directed towards the panel and towards the FDA. Quote, I realize that safety and efficacy must both be considered but I fear that the process may be delaying the release of potentially life-saving medications and/or technology. Quote, Thank you for working more closely with the diabetes patient community recently and for listening to what we have to say. It's so great to see change and feel able to be a part of it. And finally, quote, Please hurry, the need is tremendous.

For the sake of patients like these, let's

keep the conversation going. Thank you.

DR. LaVANGE: Thank you. Any questions from the panel?

(Whereupon, no response; no questions posed.)

DR. LaVANGE: Okay. Thank you very much. So that concludes our planned presentations and we have time allotted for other questions from the panel or other general comments from the audience and then a sum-up. And I wonder if we -- I'd like to possibly break for 10 minutes so that we can just do a quick canvas about questions for specific speakers, and so if that's all right, we'll just take a very quick break, 10 minutes and we'll be right back.

(Whereupon, a brief recess was taken.)

DR. LaVANGE: So before we ask for any other comments from the audience, we wanted to ask a couple of questions. Of the many things we've heard today, we have had various viewpoints given to us about who should know what when, and the only general agreement is that the DMC can always know everything but beyond that, there's no agreement. So you have some people

proposing that the DMC and FDA only exchange information and the sponsor's left out in the cold. You've got others suggesting that parts of the sponsor, possibly just the minimal number of people who are needed to put the submission together know but nobody in management. And then you have other folks suggesting that management, the management team and the sponsor absolutely needs to know because they have to make a decision about whether to file.

So we've seen, I think, all three -- or we've heard all three of those different scenarios and we were just curious if we could put a question to anyone, the presenters or anyone in the audience today, if they have any thoughts about any of those three scenarios. So in particular, what would it -- would it be palatable if the FDA and the DMC were the only ones who knew the details of the interim analyses and decisions were made. So that would assume nobody in the sponsor. The sponsor outsources the submission and basically the sponsor is kept out in the cold. And so what do you think about that?

And then secondly, what is the risk for the

two models of who in the sponsor knows? So does the management team -- I think Dr. Marso was the one who -- well, first, Dr. Offen, I think, and also the gentleman from AstraZeneca both suggested that possibly a good number of people in the sponsor should be kept blinded. And I think, Walt, you said no management, not necessarily speaking for PhRMA but, you know, for yourself; whereas Dr. Marso later on said, no, he felt that management should know. And not to single you out but these are two very different concepts that we've heard. So we were just interested in helping us understand a little bit more what the risks are for management in the sponsor to know the results and how badly could they harm the continuation of the study with that knowledge? So, John, did I characterize that adequately? And this is --

DR. JENKINS: Well, you actually -- there was actually a fourth scenario which was the DMC communicating to the sponsor and FDA simply that the boundary was or was not met and then decisions made just on the DMC communication. So we've heard, I think, four scenarios.

DR. LaVANGE: Right. I totally left out the one where the FDA only knows that the boundary was met for obvious reasons. Sorry. But yes, that is another. So, okay, Walt, do you want to start?

DR. OFFEN: Yeah, let me start. First of all, regarding the issue of management, whether management at the sponsor, whether any of them should see the interim data, when I answered the question earlier, I was thinking in terms of a management committee, so I mean our companies have CEO and then, you know, their direct reports and so on. I don't think that full group of people need to see the data. I do think, however, that somebody -- and it could very often be the therapeutic medical VP responsible for that are, for diabetes, let's say, diabetes care would see the data and make that decision of whether -- should we file or not or at least be the one accountable. So I'll straighten that out here.

The other thing I want to point out regarding the options. There are a couple of options you point out where the sponsor does not see the data at all. I don't think its tenable from PhRMA's

perspective but let me give two good reasons why. Number one, Beatrice, Tom Fleming or others, I've heard many, including Tom, people like Susan Ellenberg, Dave DeMets speak about DMCs, and the one message that's been very clear to me from them is DMCs do not want the authority to make decisions. They're making recommendations. If a DMC is sending data to the FDA without sponsor involvement, they have *de facto* made the decision to file and later on, some lawyer -- yeah, somebody mentioned half the people that are interested in this are lawyers -- some lawyer is going to find a patient and say "we'll sue that DMC, they made the decision and they shouldn't have done what they did." So I think that's one thing to keep in perspective.

Maybe the most important thing, however, of speaking out of both sides, Dr. Jenkins, of our mouth, it seems like maybe we are. I don't think we are. Talking about public disclosure of those interim data is something where, all due respect to the public, but they don't necessarily -- they'll look at the CV -- or sorry, the -- yeah, the hazard ratio of increased CV

risk and the upper limit confidence interval very much in isolation, not thinking about any of the other data and make what we could argue is irrational decisions on whether to participate in the trial, whether to drop out, cross over, all those sorts of things.

When we're talking about sponsors looking at that data, the sponsor is making a very important decision whether to file or not.

And I'll give you an example of why they may not file. So again, if you get one of these interim datas where you have maybe 1.25 estimate, 1.79 upper limit, it's achieved the requirements so they could file, but suppose that drug had weight gain. Some diabetic drugs have weight loss so now this drug has weight gain. Maybe it has weak efficacy relative-- you know, in phase three, relative to placebo, it doesn't look to be as good as some of the others that are on the market. Sponsor would very likely, actually, not file because they need to think is this going to be something that we can sell; will payers pay for this; you know, all those kinds of things as opposed to if the same scenario, maybe a little bit of

weight gain, maybe the efficacy is average, but that point estimate is now .8 and knowing it's .8, as Dr. Fleming pointed out, those companies now would say, "We want to run this to the end. We may get superiority out of this." And that would be enough to say we're going to file and we're going to let the trial continue. We don't want other -- we're going to keep it confidential and so on.

So I don't think it's speaking out of both sides of our mouths. I think they're different situations.

DR. LaVANGE: And while you're at the mic, just a quick follow-up. Are there specific concerns --just playing the devil's advocate, are there specific concerns with the management team knowing too many details of the interim analysis beyond the obvious which is they would then not be able to make decisions about altering the study for the remainder? But is there anything else that was behind your original statement?

DR. OFFEN: As far as not having the full management community see the data? No. Only -- and

maybe this -- I'll speak for myself. I'm only agreeing with the spirit of many of the speakers today, that is keep the access to that interim data as minimal as you can. And if there is a good reason that somebody has to know it, not just curiosity, not just that, you know, I'm an officer in this company and so, therefore, I need to know. That's not a good enough reason in itself, my opinion. But I don't think nobody from management should -- how am I saying this? Certainly, some management folks will need to see the interim data.

DR. JENKINS: Actually, can I follow-up on that? So hearing your comment but what if people in the company say "I'm in management, I have to know these data to make responsible decisions for the company as far as, you know, to submit, to go forward with the trial. I'm not going to have any role in deciding to make changes to the trial if we go forward," what, if any, concerns would you have in that scenario where senior management in the company says "we have to know these data to make decisions that are relevant to our company and we're not going

to do anything with that information that's going to change the trial design or anything like that"? What would be your concerns in that scenario, if any?

DR. OFFEN: In that scenario, I guess you're saying that the senior management would know the hazard ratio, so the point estimate at least, right?

DR. JENKINS: Yes. Still no public disclosure.

DR. OFFEN: I'm trying to get at -- we heard kind of two different models today, what I call the pure academic model that no one within the company that has anything to do with the business decisions for the company, partnering decisions, investor, fundraising, etcetera, would know about the interim analysis other than we met the boundary. And then we've heard other suggestions along the way that people within the company would need to know that information, so I'm going to the second scenario. What would be the concern, again, no public disclosure, not disclosure to the team that's running the rest of the trial, no disclosure to the investigators but management in the company knew the

data; what would be the concern?

DR. OFFEN: Well, beyond what I said a minute ago, just trying to minimize the number of people that have access to the unblinded data is something that we would always, I think, want to see done. So whether that's a group of management or saying, you know, a large group of statisticians know, I think we just need a couple that are -- have access to the unblinded data.

Maybe the other thing I could say, I think when we're talking about management within R&D of the science and the clinical development, that's different than management of marketing or, you know, sales and marketing and that sort of thing, is I don't want them to be tempted to saying things or trying -- you know, that they shouldn't and don't really understand. So I don't know if that helps but…

DR. JENKINS: Well, maybe taking the scenario you described earlier, if the point estimate is .8 and it looks favorable for submission, as you said, the management may say "we'll go forward because we may get superiority," do we have concerns about

that process occurring as far as maintaining trial integrity? Others may want to comment on that as well. I don't mean to pick on you.

DR. LaVANGE: Yeah, Walt's --

DR. OFFEN: Yeah.

DR. LaVANGE: -- may be tired of being on the spot.

DR. OFFEN: I can turn it over to Tom.

DR. LaVANGE: Tom, you had had your hand up earlier.

DR. OFFEN: We probably make sure that the speakers introduce themselves for the transcript.

DR. LaVANGE: Yes. So that was Walt Offen and this is Tom Fleming.

DR. FLEMING: Tom Fleming. I am worried about management getting access to information if, in fact, that information would lead to influencing subsequent management decisions. If it's known that those people had access and you see what decisions are made based on that access, that could be indirectly informative. If those business people are integral to the regulatory filing process, then that is, in fact,

potentially what would be the justification for this.

My sense about this is -- and Walt was very correct when he predicted my -- data monitoring committees aren't decision-making bodies. We have a very significant role but we're advisory. Ultimate decision-making is made by sponsors, steering committees and regulatory authorities. Hopefully, in the organizational meeting and in the protocol, there is a great deal of clarity about the thinking by sponsors and regulatory authorities and steering committees in setting up guidelines. Ultimately, we'll use our judgment and we'll carry out what we best can to safeguard patient interests and preserve integrity and credibility of a trial.

In any superiority trial, because we're making recommendations, if we arrive at a recommendation to terminate a trial, we don't make that decision. To empower the sponsor, we will ask the sponsor to have a small core group of leadership that might involve steering committee leadership. They may choose to contact regulatory authorities as they make that decision, but we make the

recommendation and they make the decision.

I can't think of an instance where we made a recommendation as something as serious as terminating the trial and the sponsor didn't agree to it and that partly reflects the level of understanding that we have with the sponsor s to what the criteria would have to be. But in essence, the sponsor makes the decision. So as I think about that -- it was fascinating discussions today and thoughts that were raised, and as I thought about the discussions today, I kept coming back to John's proposal of this middle ground approach in between 2(a) and 2(b), not where the DMC makes the recommendation that the boundary has been crossed and regulatory authorities get nothing. I don't think that's what a DMC wishes to do.

I like your idea that the regulatory authorities would get access to the data.

I also understand when a sponsor would say I would like to have some way of understanding the nature of those data to bring our perspectives into context just as we ask you to do when we would recommend terminating a superiority trial. So I'm

wondering whether a hybrid or a version of John Jenkins' proposal would make sense here, and that is the DMC would arrive at a recommendation to say the criteria for release of these data, we believe, has been met. We don't release this to the unblinded team that could have 60 people. We release it to the same size group that we would do in a superiority trial, three or four or five well-chosen people that have the broad context, understanding the scientific issues here from the perspective of the sponsor who could then endorse that DMC recommendation for releasing the information to the regulatory authorities.

Now, you still have some involvement but it's far more contained. It's not quite the Jenkins proposal but it's a close version to it where you'd have a very small number of people recognizing still the DMC is not making this decision. We made a recommendation. It was I think, in all likelihood, endorsed by that small core group and this could -- and there have been some sponsors who have been very clever about this recently where this intervening step was actually done confidentially. It was set up so

that if we recommended termination of the trial, they would, the small core group would meet without it being know that they were meeting, empowering the sponsor in essence to make a decision to continue the trial, if that was the case, without it being known. And that allows for the greatest allocation of responsibility as it should be to the sponsor, the steering committee, and the FDA.

So obviously, this needs to be thought more through but I think what you're proposing or what you raised as a possibility, John, could still be achievable even if there is a perspective that the sponsor needs to be involved by, in essence, having those people who aren't going to handle all of the regulatory filing but they're the core group that needs to endorse that this is a dataset that should, in fact, lead to a regulatory submission.

DR. JENKINS: Just before we go to the next speaker, I want to be very clear. I didn't make a proposal. I raised a possibility.

DR. FLEMING: Okay.

DR. JENKINS: So I'd really like this not to

show up in the pink sheet tomorrow as my proposal.

DR. FLEMING: So I amend this --

DR. JENKINS: I raised it as a scenario.

DR. FLEMING: -- the Jenkins proposed possibility.

DR. LaVANGE: Dr. Nissen.

DR. NISSEN: Yeah. I'd like to address the issue of the minimalist approach where the DMC would inform the FDA that the threshold for the guidance was met but give no further data. And I'd like to argue against doing that and let me see if I can articulate why.

I think the Agency, you know, has to have the ability to look at the point estimate and confidence intervals in the context of everything else that's known about the drug. You know, Bob Temple uses a word sometimes when you have a drug class, your priors, you know, you have maybe other drugs in the class. You have other benefits and risks that have been documented in the development program. The ability for the Agency to tolerate a 1.25 hazard ratio might be different for a drug that had other known

risks -- they may not be morbid mortal risks but they would be potentially important -- or benefits. I would argue that a drug that, you know, barely meets the threshold for lowering your hemoglobin A1C where there are many alternatives in the same class might be viewed very differently from a drug that had very high degrees of efficacy, promoted weight loss, did a bunch of other things that we thought were important.

And so that point estimate and confidence interval, I think the Agency has a right to be able to see that in order to make the decision that regardless of whether it's 1.25 or 1.17 or 1.16 is taken in the context of everything that's known about the drug so that in representing the public interest, you could make a decisions that you think in, you know, your heart of hearts is in the best interests of patients and the public.

DR. MARSO: Steve Marso. I just wanted to echo a couple of comments and maybe expand one or two. You know, there are functionally two things that need to happen after the interim -- getting back to the pragmatic approach here. One is the decision to

submit or not to submit and then doing the legwork to do the submission. And for the reasons that Steve articulated actually on the agency side, I think those same issues apply on the pharma side, and that is you want to see the totality of the data and you want to see the point estimates. You want to decide whether or not you're going to submit or not.

And at break, we were talking about that and I'm wondering, you know, there might be as many solutions for this as there companies or, you know, other sponsors but that -- I think that the compelling thing is that we have the firewall in place, the mechanisms in place and that we strive to have the fewest number of people unblinded as possible whether they're in the company, whether they're in a for-profit CRO doing the submission. So for example, I could envision a DMC doing analysis or a for profit contracting statistical group to do the work going to the company to decide to submit or not to submit, then having a group of individuals do the legwork. I just think that the driving principles here are to drive down that number as much as possible, and I think

there will be a comfort level with the pharmaceutical side. I don't want to speak for them but I could envision a culture of a company being such that they don't want to empower one or two people to make the decision to submit and they bypass the interim.

But I think that driving down the numbers is incredibly important and I think, you know, on the academic side, on the DMC side, and on the pharma side, there's a difference between -- and we need to recognize in a meaningful way that there is a difference between those that need to know and those that have an intense desire to know. And I think when we write the data use plans, we need to be very cognizant of who really needs to know versus who really wants to know whether you're at a CRO doing the work or a pharma company making the decisions.

DR. KAPLAN: Lee Kaplan. I have a little bit of concern about the use of the interim data to make the kinds of judgments that were just being discussed, because what -- if I understand this correctly, and I'll admit that my history in this area is more limited, the final decision is being made

based on the totality of the study and so the approval that we're talking about is in interim or provisional approval -- we haven't talked a lot about what happens if the final analysis doesn't support the interim analysis -- but the approval that we're talking about, I'll assume for the moment, that it is an interim approval and there are very specific criteria.

So I'm a little bit perplexed by the use of an enormous amount of judgment for -- with this interim data. I think that the judgment should be used with respect to the efficacy data at the time of the interim approval and with the cardiovascular safety data at the time of the final approval at the end of the study.

So, Steve, I hear what you're saying but I don't -- I think at the time of the interim approval, the application of the judgment that you're talking about seems a little bit misplaced. I think the company has made a decision to accept an early evaluation based on these interim data. They could, of course, object that possibility and go to the end of the trial, but there's an appropriate -- there's

all the reasons why we stated why we think that this should happen but it is -- that doesn't seem to me to be as amenable to all of this additional judgment. I think it should be more fact-based than the kinds of judgment that are used in totality when examining risk against benefit in the very final analysis.

And so you have to make a compromise and I think that's one of the compromises that has to be made. If you make that compromise, some of the other considerations about who in the company needs to know are a little bit easier to contemplate because at that point, the major decision that the company has to make is do we continue the development of this product. It's about to be approved. If it's not going to be approved, it's not going to be approved, but if it is approved on an interim basis, then the company has to decide, say even though it's approved, we are not going to go ahead with the development of this product. That's really the decision that the company has to make at that particular point, because if the drug is approved and the company says come hell or high water, I want to bring this drug to market, then

there's really not much information that the company needs to know. They can wait. They have an approval. They market their drug and they move it on til the final analysis comes in.

So I think we really have to look at what exactly -- what decision points are exactly being made by the company in order to drive who needs to know and what they need to know. And I think the key decision point, as I said a second ago, is the decision to continue to allow the drug to be approved. That's really the decision that the company has to make and is it -- how many situations will there be where a company has decided to accept the interim analysis and then based on the numbers in that interim analysis is going to say, "no, but never mind, we don't want to bring this drug forward." I don't know the answer to that. I would love to hear from some representatives of industry as to how often that would occur and under what conditions that might occur, because I think that would influence at least how I think about some of these need to know versus want to know issues.

DR. JENKINS: Lisa, can I make a couple of

clarifying comments because I've heard various terms used today, conditional approval, interim approval, etcetera? So let me clarify what we've actually been doing in the diabetes field.

We have two flavors of approval. We have fully approval. We have accelerated approval. We don't have a conditional, we don't have an interim. What we've been in diabetes is full approval. We accept hemoglobin A1C as a validated surrogate for approval of drugs to treat diabetes assuming benefits outweigh the risk, etcetera, etcetera.

So when we approve these based on these interim analyses, we're using the interim analysis to assess the cardiovascular safety as part of that benefit-risk equation and then we issue a post-marketing requirement that the company complete the study to get to that 1.3 boundary. So we have the authority to require post-approval safety studies, and people have raised legitimately the question "well, what happens if the post-approval safety study doesn't rule out 1.3." We haven't crossed that situation yet but it may occur.

You know, options might include asking the company to withdraw the drug from the market; might include limiting the indication to, you know, third-line setting, for example; may require doing another trial if we think that there was a subgroup that might have benefitted. So there are a lot of scenarios.

I just wanted to clarify in the diabetes context, we're talking about full approval with a requirement that they complete the study for safety purposes after the trial. It's not conditional approval. It's not interim approval. The company has the same rights of an approved drug as any other approved drug has in that scenario.

DR. KAPLAN: I appreciate that clarification. The only response that I would have is that makes it even easier, it seems to me, to -- because at the -- the only point where there is a decision to be made is whether you submit the full package to the FDA, not the decision about what to do after the drug is approved. I would think it would be highly unlikely that somebody would decide to -- a company would decide to submit the full package and

then reject the approval of the drug that they just submitted for. So it's at that very single point and since you're going for a full approval, it actually seems to me it would be easier.

But I would still like to hear from representatives of industry about the issue of what would influence your decision at that point to go forward or not go forward with the submission to the FDA, because if there's nothing that would influence that decision, then there's not much need to know.

DR. LaVANGE: So if anybody wants to answer that, that's fine. Otherwise, I have another question.

DR. TEMPLE: Lisa, I think we heard from various people that if it was perilously close to 1.3 and ruled out 1.8 just barely, they might not thing that was a very smart application to go because it was likely to go under later and that could also depend on how big the affect on hemoglobin A1C. I mean all those perfectly sensible considerations would go into it.

(UNIDENTIFIED SPEAKER): (Inaudible) a narrow

group of people. Only that decision-maker would need to know.

DR. TEMPLE: Well, I think most people have agreed that you'd want to keep it as narrow as possible, right.

DR. LaVANGE: Okay. So that's a good segue. I asked a question earlier from Dr. Nissen and I want to bring it up again if anybody else wants to add anything. We've had almost every speaker talk about what can go wrong if the physicians or the patients in the study get too much detail about the interim analysis. We've had people talk about equipoise. We even had Mr. Venkat present new data collected about what patients would do on a sample of over 5,000 patients if they heard the drug was good or the drug was bad, would they take themselves out of the study.

Dr. Nissen had on one of his slides that sponsors can also cause problem with the loss of equipoise but in more subtle ways.

And then Dr. Offen talked about, when we were asked what is it that we're concerned about with sponsors' knowledge, what is the behavior that we're

worried about and the answer seems to be we just know it's good to minimize who knows, but we always stop short of this. And I think one of the reasons -- I'm just going to put words in your mouth -- one of the reasons is that if it's hard -- it's very hard if subtle changes are made on behalf of anybody, then it's very hard to first, figure out what the impact is and second, conclude that damage was done. I mean it sort of goes back to the FDA's policy, the way we were sure that -- you know, trust goes a long way but, in fact, the way we're sure that sponsors pre-specify all of their analyses and not do data mining at the end of a study is we require them to do exactly that, pre-specify and submit to us what their primary analyses are going to be.

This is a little bit harder. So we -- I think -- my question is is there something that we're not thinking about? John referred to it as designing in the quality. Is there anything you can do up front other than a data access plan to be able to show later on during the study perhaps that nothing's been breached, that there has been no damage done? We know

if you wait until the end of the study, you can often see that bad things might -- you know, happened. And Dr. Fleming and others gave us examples where studies, had they been stopped earlier -- Ms. Close gave us an example with the DCCT, had it been stopped early, then it would have been a real shame because the behavior is very different.

But it's harder to look back until you get to the end of the study. And again, Dr. Fleming gave us examples with the SWOG that clearly, too much disclosure hampered those studies. They couldn't enroll, they couldn't finish and so forth, but that's at the end of the study.

If you've got studies ongoing, then what -- is there any hope at all in terms of designing end quality, because I think that's what we're concerned about. We just -- we have this need to minimize who knows what. We can't always say exactly what behavior we're concerned about, but we know that it's so hard to measure if something has gone wrong, therefore, try to prevent it from going wrong is -- so there's a question in there somewhere.

DR. NISSEN: If I may, one of the documents that we all need to look at, and in fact increasingly now, journals are requiring this, is to look carefully at the protocol and all amendments, as you do always, and the SAP and when was the SAP finalized and what changes were made to the statistical analysis plan and when were they made. And, you know, clearly, if you have a change to the SAP that occurs between the interim and the final analysis, particularly if those changes have a significant impact on the way the data are being analyzed, that is a cause for significant concern, and there may be some things the agency can do around the issue of, you know, when does the SAP need to be finalized.

You know, I'm increasingly uncomfortable that in some modern contemporary trials, the statistical analysis plan is held back and it's not really finalized until fairly near the end of the trial. And that means that that document, which is an important statement of how will the data be actually analyzed. If that's an evolution then it can evolve at a time when there would be concerns raised about

whether -- you know, what happened in the interim somehow was influencing how the ultimate data were being analyzed at the end of the trial. So there may be some things the agencies can do around that that would help to protect the integrity of the study.

DR. MARSO: Yeah, so I tried to highlight and maybe expand a little bit, but I do think there are some design features that might mitigate the risk of the post-interim. And I think if you could -- if enrollment could complete around the interim, that's beneficial. I think that if major protocol amendments could be done prior to the interim, that's beneficial. I, like Steve, think that the SAP should be done well before the interim. And I do agree that it's a prevention strategy because you're not going to be able to identify it, likely; and if you are, you're not going to be able to measure it; and if you can measure it, you don't know which way the bias is going to -- it will be an impossible task. So prevention is absolutely the strategy.

I also think that the size of the trial, the rate of enrollment, and the event rate -- I mean I

would just, you know, ask the statistical group to think through scenarios and vary those so that the Agency understands what it does to the duration of the post-interim, the relationship between the final patient enrolled versus when the final interim, because I think you'll find that there is substantial variance in the phases of the interim trial.

DR. FLEMING: Just very quickly reiterate what I was saying before, on monitoring committees of cardiovascular safety trials, we've spent a lot of time carefully reviewing the performance standards. They're established in advance what are targets, what are minimally acceptable, the enrollment rate, the event rate, the adherence rate, the retention rate, the cross-in rate, the currentness of data. We're going to monitor over all time because these are strong indicators of the integrity and reliability and interpretability of conclusions.

So, Lisa, when you mentioned that, and properly, if we have concerns post release of these data for purposes of regulatory filing, that they may be some leakage of that insight beyond the public in

ways that would negatively impact quality of trial conduct. I can't be certain that we would detect it with these measures, but these are real-time assessments that we're going to do, and they are, in fact, principle issues that we worry about that are integral for integrity. So I do think that there is a considerable likelihood that if there was a serious compromising to the integrity of the trial that was a consequence of the leakage, these are issues that could be detected as we continue what we would do anyway, which is a careful monitoring of the performance standards at every DMC meeting.

DR. JENKINS: Tom, to follow-up that up, let's say you're monitoring those and you start seeing patterns of behavior in the trial post interim analysis use for regulatory purposes which raises questions in your mind about the integrity of the trial results, what do we do then? Do we stop the trial and deal with the hazards of trying to start a new one or what do we do?

DR. FLEMING: That's a great question, John, and what we've heard is that stopping the trial and

starting a new one has many negative consequences in terms of the new trial and the context for that new trial and information having been released and having to start over. So our goal is to not be in that position. Our goal is to prospectively plan the trial in an active, not passive way in terms of how it's going to be conducted so that we are maximizing the likelihood that it will be conducted with integrity, and that we're going to monitor in real-time early on. My view is the time to determine that things aren't going well is not near the end of the trial. It's as early as you can, as early as you can detect this.

And part of the performance standards document should be not only an indication of what is the target for each of these standards and minimally acceptable but what are you going to do if, in fact, you are falling close to what is minimally acceptable, what are the creative things that you're going to do. And there are things that we can do.

Ultimately, though, I understand your point. If there a sufficiently serious compromising to the integrity of the trial, none of these other procedures

that we may fall back on to address this will be sufficient which is why we're having this meeting, which is why we need you. We need FDA to come forward. No one is as influential to the integrity of science and research as you are. We can do the best we can but when you lay out standards for what we have to do, and we'll do our best to help you thinking about those, as many have done today, those standards have considerable influence. We will then do our best to proactively ensure as best we can that the studies are being conducted in a way to meet those standards. And that is the best strategy for having a greater likelihood that there will be integrity.

We can monitor. If we see things that aren't going according to what has been set for the standards, there are constructive things that we can suggest, and that will be effective unless there is too sufficiently serious compromising to integrity. And that's what we need to prevent by thinking through what our good clinical practice is here for how we're going to be able to carry out this approach of simultaneously allowing for early marketing approval

on the 122 while maintaining the integrity of the 610 to get a timely answer that is reliable and interpretable.

DR. RATNER: Robert Ratner. Doctors Nissen and Marso have taken the low-hanging fruit and it's absolutely correct. All off those issues are critical and those are easily done. Dr. Fleming and Dr. Jenkins have really gone to the core issue. There are a lot of subtle ways that you can influence the operation of a trial whether it's how hard you try and retain patients, how hard you try and collect endpoint data on patients that have been lost to follow-up, how intensively you try and maintain the adherence rates, and all of that really comes to what are the provisions that the investigators have from the sponsor. That can be manipulated very easily. It's changing in clinical trials all the time in terms of what is available to the investigators to maintain adherence or what's available to the investigators to collect additional data.

Those are the subtle changes that I'm not sure Dr. Fleming's DMC is going to be able to pick up.

I think that he hit the nail on the head as to what the problem is. I'm just not sure what the solution is other than not having the sponsor know what direction things are going. That's why we blind studies.

DR. LaVANGE: I think that just supports what we hear, minimize the number of people that know the information.

So I'm ready to summarize unless the panel has other questions. Worn you out? All right. I'll see what I can do here.

So I think we have heard a lot of good discussion today. As I was joking earlier, we had general agreement that the DMC is about the only group we trust with access and everybody else we're suspicious of including ourselves. But we have several models that have been talked about and the pros and cons.

We did not hear today much concern with FDA's plan to redact information about cardiovascular safety in our summary basis of approval. At interim, we did release the memos for the one case where we've

done this, the alogliptin approval, and they were released with a *Federal Register* notice to illustrate our practice. We did receive at least one comment to the docket arguing that we should follow a policy of full disclosure and not redact this information, but we didn't hear anything today from the audience about that.

However, we heard from one speaker suggestions that we should allow more flexibility in disclosure such as releasing information about subgroups of patients or subsets of endpoints but not other person spoke to that, so we'll take that as general agreement, at least of those present today, with our policy as evidenced by our -- the alogliptin case.

Well, there was general agreement expressed today that this is a balancing act, balance is need to get effective therapies to patients as soon as possible but not jeopardizing our ability to answer the primary questions of interest about cardiovascular safety which does require the completion of the ongoing study if that's the approval pathway the

sponsor has chosen to take. All have acknowledged this balancing problem. Some solutions were offered There was request from several corners that the FDA should give some guidance on this topic. We will certainly take the comments we have heard today under advisement. We'll continue to discuss internally whether and how our current guidances for diabetes drug development, for DMCs should be updated and when they should be updated, and we also acknowledge the request that FDA actually provide templates for data access plans, presumably with input from those of you already using these. So we have heard all of that.

You'll notice I stopped short of saying that we'll do it by such and such a date. Okay.

The answer to, I think it was question 1(c) about starting a second study, is something that we're interested in and we heard from several of you and if we didn't hear from you, we asked you directly and, in particular, Dr. Temple, asked you whether there were issues with starting a second study once interim results were run and whether that was different than continuing the first study. And I think we heard loud

and clear that many of the same problems exist in terms of equipoise but we also heard that that two-study approach was not desirable, which I think we already knew, because of the startup time and the delay in getting the answer. It would be much more preferable to be able to continue the first study. But nonetheless, the second study -- starting a second study when we have concern about interim disclosure is not an easy solution either.

We heard some general concern with small companies and their obligations regarding knowledge of material information being known by some but not all persons in the company, what their fiduciary responsibilities are and so forth.

And we also heard concerns from at least two speakers that our cardiovascular safety requirements may be driving companies, may be driving physicians and, therefore, innovation away from diabetes research and into other areas of drug development.

We have heard from several of you that the concerns -- or the voice of the patients, the patients of today and tomorrow, need better therapies and just

want to make sure you know that we have heard this.

We also heard a concern that I had not thought about previously but possibly others have that by studying the heavily enriched populations which are required to make these cardiovascular safety studies doable in a reasonable amount of time means that diabetes patients are studied late in their disease stage and that that might then mean that the studies are less relevant in terms of informing patient care, and I want to acknowledge that concern as well.

And then the final concern I'll mention is that not all sponsors may be able to convene a DMC that has Tom Fleming or Dave DeMets or one of the other more experienced statisticians on it. We did see some statistics about what proportion of the studies have DMCs but there are DMCs out there that will be operating possibly for diabetes safety studies without the expertise that's represented in the room today and perhaps, as Dr. Fleming suggested, more guidance from the FDA could help in situations such as those.

I think we had a challenge by the next-to-

last speaker to have courage behind our convictions or courage to follow our convictions -- I forgot which it was -- the challenge could FDAs and sponsors get by with less information than they think they could, and we'll certainly talk about that. But we do -- as Dr. Jenkins reiterated, we are talking about full approval here. This is not a conditional approval and we can't take that lightly and we do have to be certain that drugs are safe and effective before they are approved. So only knowing that the boundary was met would probably not suffice. Somebody could argue with me there but I'm going out on a limb.

Okay. All right. So there are many other good points that have been made. I've taken notes. I've been typing them up. We haven't missed anything. We've got your slides. I guess, in conclusion, I think that we all want to -- we all want the same thing. We want to achieve the balance of getting effective drugs to patients while ensuring that the drugs are safe and that the patients are safe, particularly with regard to events that are harder to ascertain during the development stage of that therapy

and require these post-marketing commitments and that this is a difficult problem. There are solutions. There is no easy fix, maybe a little low-hanging fruit, but the harder solutions are going to require more thought, more engagement, and we appreciate your time today helping us think through possible solutions and at least getting the dialogue started.

Do any of my panel members want to add? Yes, Dr. Temple.

DR. TEMPLE: Only one thing. I thought the point about whether the trials done in late-stage diabetics are likely to show a benefit is a perfectly good point, but it's worth remembering that these were cardiovascular outcome trials designed to see if the drugs were toxic, and those trials have to have enough events to see anything or they won't succeed. So whether in diabetes or weight loss, they're always done in people who are relatively sick in the cardiovascular sense in one way or another, either because they're older or because they have risk factors or something like that. So remember these were identified as safety trials. It doesn't mean

that other trials wouldn't be interesting but that's what these were. so that's why they tend to have people -- they tend to be enriched with people who are at high risk.

DR. JENKINS: Lisa, a couple of things I would mention just in the summaries. We heard this is a global issue.

DR. LaVANGE: Right, sorry.

DR. JENKINS: So if FDA protects the data but other regulators don't, it's all for naught, so it's a global issue that we need to work with other regulators on.

DR. LaVANGE: Yes.

DR. JENKINS: And I think we also heard several people suggest that it may be time for us to revisit the basis for the cardiovascular outcome study requirements for diabetes drugs. We hear different proposals of how we might look for alternative ways of identifying drugs that might require that, but I don't think we heard much in the way of detail. But I just wanted to flag for the record that we did hear calls for re-evaluating whether we need to be doing these

large outcome studies for all diabetes agents going forward.

DR. LaVANGE: Yes. Thank you. Certainly, the global point was in my more detailed notes and we understand the challenges with regional approvals.

And then the call for us to re-evaluate the evidence to date and revisit our requirements was mentioned by several speakers as well.

This side of the panel notice anything I missed?

(No response.)

DR. LaVANGE: All right. Any other comments from the audience before we convene?

(No response.)

DR. LaVANGE: Okay. Thank you again for your time.

(Whereupon, at 4:22 p.m., the meeting was adjourned.)

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I, MICHAEL FARKAS, the officer before whom the foregoing hearing was taken, do hereby certify that the testimony appearing in the foregoing hearing was taken by me in audio recording and thereafter reduced to typewriting under my supervision; that said transcription is a true record of the proceedings; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this deposition 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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I, LUCY T. TURNBULL, hereby certify that I am not the Court Reporter who reported the following proceeding and that I have typed the transcript of this proceeding using the Court Reporter's notes and recordings. The foregoing/attached transcript is a true, correct, and complete transcription of said proceeding.

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