Webinar: Final Guidance on Adaptive Designs for Medical Device Clinical Studies
September 22, 2016
12:00 pm ET
Moderator: Irene Aihie

Coordinator: Welcome and thank you for standing. All participants will be in a listen-only mode until the question and answer session of today's call which we will take by phone only. At that time you can press Star 1 to ask a question from the phone lines.

I'd also like to inform parties that the call is now being recorded. If you have any objections you may disconnect at this time.

And I'd now like to turn the call over to Ms. Irene Aihie. Thank you ma'am. You may begin.

Irene Aihie: Thank you. Hello. And welcome to today's FDA webinar. I am Irene Aihie of CDRH's office of communication and education. On July 27, 2016 the US Food and Drug Administration published a final guidance document, Adaptive Designs for Medical Device Clinical Studies which provides clarity on how to plan and implement adaptive designs for clinical studies using medical device development.

The focus of today's webinar is to share information and answer questions about the final guidance document. Today's presenters are Dr. Gerry Gray,

deputy director for CDRH's Division of Biostatistics and Dr. Estelle Russek-Cohen division director in the Office of Biostatistics and Epidemiology in the Center for Biologic Evaluation and Research.

Following the presentation we will open the line for your questions related to topics in the final guidance only. Additionally there are other center subject matter experts available to assist with the Q&A portion of our webinar.

Now I give you Gerry.

Gerry Gray: Okay. Thank you, Irene. I just want to say that in the room today with us we have Anne Costello, Abe Tzou, and Tara Ryan to help us to answer questions at the end. And these folks were instrumental to helping develop this guidance.

So for our agenda for today we're going to go into a little bit on the background of the guidance. And we'll talk about adaptive designs, what they are and what are the benefits and limitations of these kinds of designs.

We'll go a little bit into when to choose an adaptive design and then various considerations and approaches you might take. And then when I'm done Estelle is going to talk about adaptive designs specific to the Center for Biologics.

And then when we close out after that we'll have a question and answer period. So this guidance, the draft was issued on May 18, 2015. And a final guidance came out at the end of July of this year. And I just want to point out that this is a joint guidance between the Center for Devices and Radiological Health and the Center for Biologics.

So what are adaptive designs? They're studies, clinical studies that include some prospectively planned opportunity or set of opportunities to change the study design based on data that you've accumulated during the course of the study without undermining the integrity and validity of the study.

So this can potentially include modifications after a trial is underway but before unmasking or un-blinding occurs. It does - specifically though it does not include retrospective ad hoc changes that are introduced after you know the outcomes or a chance to salvage failed trials after the fact.

So why should someone consider using an adaptive design? So clinical studies are usually - the design of a clinical study is based on your expectation for the outcomes that you're going to see including things like event range for the treatments and control groups, rates of accrual, amount of dropout of the variances in the various things you're measuring.

And if everything in the study actually exactly according to that plan then the fixed trial design's really the optimal thing to do. But these assumptions that we make they're just that, assumptions. And there - sometimes all too often they're further away from reality or what we actually see in the trial.

So an adaptive design can be used to address, I would say, moderate levels of uncertainty of these assumptions then to change trial as necessary to adapt for this - for being a little bit off.

So adaptive designs, they can be frequentist. They can use Bayesian Methodology and in CDRA agencies where we have experience with both of those types.

These designs are usually analyzed in stages with - at each stage you have a potential to do some sort of adaptation that you've pre-specified. And device submissions, and I should say biologics as well, I think the adaptation needs to be planned in pretty great detail before un-blinded data are observed.

This is all outlined pretty well in the guidance in one of the first sections. So what are examples of adaptations that people might make? The primary one that we see most of the time I think is sample size adjustment.

So we include in this group sequential designs. We include sample size re-estimation. We include designs that have adaptive recruitment as well. I'm using this term for Bayesian designs where you decide at some intermediate point that you don't need to recruit anymore.

Adaptations can also include adaptive randomization where the probability of being assigned a treatment or control can change through the course of the trial. It can incur changes to study eligibility criteria like inclusion/exclusion criteria for patients.

You might drop, add or change treatment arm. You might change the statistical analysis plan or the hypotheses you're testing. You might change the endpoint. The duration of the trial might change.

So there's all kinds of opportunities for adaptation as long as they're pre-specified. But again the majority we see are sample size adjustments. Here are some of the differences between the kinds of fixed trial and adaptive trial and the number of patients you would include in the trial.

A fixed trial you pre-specify that up front. In an adaptive trial that can be variable. The patient population in fixed trial is, again, pretty rigidly specified and laid out in the inclusion-exclusion criteria.

Whereas in an adaptive trial you can narrow the patient population during the course of the trial. In a fixed trial the randomization between treatment and control is constant. In an adaptive trial that could be adjusted according to outcomes or patient covariates.

The primary hypothesis in a fixed trial is fixed. Whereas in an adaptive trial that can be changed. And the decision rules in a fixed trial, they're really not that many during the course of the trial. They're pretty much simple.

Whereas an adaptive trial can have a fairly complicated set of decision rules as you go through the stages of the trial. So there's some pros and cons of an adaptive design. And, again, a lot of this - this is all laid out in the guidance if you want to read it in detail.

The “pro” is that they are usually more efficient, fewer patients, shorter duration, less money. A con, the flipside of that coin is complexity. A pro is in terms of duration it may be shorter but the con is that's not a guarantee, you know, the duration is sometimes an unknown and could possibly be longer than a fixed trial.

Adaptive designs are usually - and if you've done the adaptation right more likely to, succeed. But on the other hand sometimes the results are harder to interpret.

Adaptive designs if they're going to fail, - a good point is that you will fail more quickly and spend less resources on that trial. Although it might be harder to conduct the trial because it is more complicated.

Adaptive designs can be better in terms of patient protection and flexibility because of the adaptive randomization or the stopping early or the probability - the chances of changing the randomization probabilities gives you more flexibility.

Whereas in - the con to that is there's potential for operational bias. You might actually - you have to worry a lot about people finding out what's going on in the trial and potentially changing their behavior as a result of that knowledge.

So if we're thinking about should a trial be adaptive the first thing to consider is whether it's even feasible to do so or not. And really one of the prime considerations is whether there's time to make an adaptation.

So if all the patients in the trial are enrolled very rapidly then basically there's no time left. There's no chance to be making any change. So there has to be a sufficient amount of time between the ends of the trial.

And the enrollment of the patients has to be rapid enough so you can actually make changes as necessary. If there are multiple endpoints that are really important it may not be possible. It's usually not possible to simultaneously adapt for all of those endpoints.

You know if the sample size is driven by safety concerns then adapting on effectiveness is not really feasible. So once we've decided that a trial should be adaptive then a question is, is it worth it or not.

Is it advantageous to us? Adaptive designs are usually advantageous if there is some uncertainty in the design parameters that you use to design the trial that can be addressed by the adaptation.

An adaptive design is feasible if the operating characteristics of the design are favorable over a fairly wide range of plausible scenarios. In the guidance we talk about this. We want to especially encourage folks to consider what we call anticipated regret scenarios.

So in other words don't just think about the strictly most positive outcomes but think about what might happen if the trial - if the outcomes aren't quite as favorable as you think or hope they're going to be or if you see a little bit of deviation from what you assumed.

So under those circumstances there can be situations where there are clear advantages in an adaptive design over the fixed design. We would proceed with that.

In an adaptive trial is really not advantageous if there are too many unknowns. So if there's too many unknowns regarding patient outcomes, regarding recrual rates, regarding the variances that you're going to see and the endpoints you're measuring.

Then it's really not optimal to do an adaptive design because there's too many things you're trying to - you're going to be changing at once. What happens when you do that is it turns out the trial is not really very efficient.

So if the designs parameters aren't know with sufficient precision you really can't adapt it efficiently. And under these circumstances the gain over a fixed design is going to be small.

So what phases of the development process would you use an adaptive design? Really at any phase; dose finding studies are commonly at this point adaptive.

There are trials, adaptive trials, that we call seamless phase two and three studies where people go from sort of a midsize feasibility study that's narrowing down some of the design parameters and smoothly moving to a pivotal trial, a phase three study.

And of course if there's a pivotal study that's most often what we see. At CDRH most of our experience in adaptive designs is with pivotal studies. CBER I believe has more experience in early stages.

So from a regulatory point of view of course most of our concern and interest is with studies that are pivotal adaptive designs. The kinds of things we think about when we see an adaptive design in the regulatory world type one error control is often one of the prime consideration and operating characteristics of the design.

We are concerned that the estimation of treatment effect is going to be appropriate, and the confidence intervals. Sometimes you have to worry about statistical biases that can creep in because of the nature of the adaptive design.

Operational bias is always an issue. The question is who knows what and when and how that might affect their behavior in ways that might bias the results of the study. And everyone wants a trial that has a high probability of succeeding. So power is important.

And finally there are often practical considerations related to trial infrastructure, trial conduct, and availability of alternative treatments, etcetera that come into play.

So recently in CDRH some folks went through a survey of out adaptive design experience over the span from 2007 to 2013 and found 250 adaptive studies that we had seen.

Most of these are in the - because adaptive designs are still a little bit new, most of these are in the design stage. But some of them 32 of them were products submissions of either PMAs or 510Ks.

And just to reiterate what I said in one of the earlier slides, the overwhelming majority of these are sample size related adaptations. On the frequentist side156 of 176 studies were sample size adaptations that included group sequential and sample size re-estimation.

And on the Bayesian side, 67 of the 75 were sample size re-estimation or some sort of adaptive recruitment scheme. I just want to point out here, related to issues of operational bias, is there blinding? Sometimes it's very important that blinding scrupulously maintained.

And if that is the case then it's much easier to accomplish adaptation and there are less questions about statistical or operational bias that might have crept in.

And sometimes folks incorporate changes that are based on aggregate results that don't break the blind. We see a fair amount of those as well.

And now just to get into a little bit about adaptive sample size.

The estimates of the parameters that we use to size a study are usually different than what we actually observe. The result of that is the studies are often over or under powered. So we have more patients than we probably needed to show the result, or the study finishes and you wish you had 10% more patients to achieve statistical significance.

Sample size re-estimation can correct this kind of problem to some degree. And what it does is it uses estimates that we obtain at interim looks to revise the sample size for the study.

In the frequentist world we're including group sequential designs here. A group sequential design is one where you have fixed looks at the data at certain intervals of patients and at each point can stop for futility or stop for success.

We have frequentist sample size re-estimation methods. Those include things like conditional power, conditional type one error, p-value combinations, etcetera.

And sometimes again we see internal pilots that are maintaining the blind. In the Bayesian world we see studies that employ more frequent interim analyses where there are decision rules that are based on predictive probability.

We are including here studies that have what we're calling an adaptive recruitment process where recruitment ends when there's a predicted probability of success that's sufficiently large to stop recruiting and just follow the patients to the end.

This also includes the Bayesian versions of group sequential designs.

So like I said earlier, these kinds of designs are usually done in stages. And in the adaptive sample size world the general approach is usually something like this.

You start by fixing a sample size for the first stage. And at the end of that, at that point you calculate some appropriate summary of the results, like test statistics, conditional power, what the predictive distribution is, things like that.

And then based on the outcome at that stage you have a decision rule. You can say you're going to stop for futility. You can stop for success if the result is sufficiently impressive. Or you can decide to go back and recruit more patients or re-estimate the sample size.

So at that point you continue to the next stage, stage two, and you repeat the process until you get to the maximum number of (looks). And at that point you - at the end of the study you compute your overall - then you do your overall analysis configure test statistic using some method that we have agreed - that reaches an agreed upon type one error.

Another kind of study that we see sometimes are adaptive enrichment studies. For these kinds of studies at the interim analysis point you evaluate the results from the study overall. And at the same time you do an analysis within some set of prespecified subgroups.

And again you have decisional options you can make. The study could be stopped for futility or for overall success. You could continue with the entire population. Or you could continue by restricting the enrollment from that point onward to some subset of these pre-specified subgroups.

And again we have to use appropriate design and decision rules that control the type one error regardless of whether the methodology is frequentist or Bayesian.

So in general the sample size adaptations protect again poor estimates of the important parameters at the design stage and the adaptive enrichment studies protect against poor choices of the appropriate patient population.

There are cases where you might have seen false positives in preliminary studies or perhaps there are covariates that have an influence on the outcome that you're not quite sure of.

We have a section in the guidance that talks about simulations because for some of these complicated designs you really - there's not analytical methods that we have to understand the operating characteristics. So we need extensive simulations to figure out what those are.

Another advantage of the simulations is they can help inform the operational plans. They can be used to evaluate probabilities or different kinds of outcomes occurring during the course of the trial which can help to plan for example where you might need supplies of particular drugs or whatever to do the study.

The details of the simulation obviously matter. You need to think about designing it like an experiment and whatever the parameter space we're talking about for the particular design has to be appropriately covered by the simulations.

And of course there's always good programing practice because programing mistakes do occur and we like to see independent coding, etcetera for those simulations.

Just a little bit on bias. Operational bias is something that can occur if the information regarding the progress of the trial leaks out and if the participants in the trial - and that can include patients, investigators or analysts - change their behavior based on what those emerging results are.

Then you can get biases in the study. And as we outlined in the guidance, the best solution that we know about is to maintain appropriate firewalls so that only those who need to know have access to the data about randomization and outcomes.

There are always operational challenges in any trial. And in these kinds of trials that are somewhat complicated it's a bit more difficult sometimes. There needs to be a group, an adaptation or steering committee who decides when to adapt a trial.

And if the blind is being maintained then that group needs to be firewalled off from the folks who actually are conducting the trial. Many trials that have much risk to patients have a data monitoring committee.

Their primary role is to protect the patients in that trial. But sometimes those folks are also charged with determining the adaptations. And that requires a little bit extra knowledge that the DMC statistician knows about what's going on in the adaptive side as well as the DMC process.

Operational bias, I've mentioned that several times. It's a concern in all trials but especially in these adaptive trials. We want to try to reduce information leakage as far as possible.

And finally operational challenges in terms of IRBs. The IRBs at the individual institutions are primarily concerned with safety. But sometimes if they don't know exactly what's - if they aren't clear what's going on in a trial and then it adapts, there might be delays in getting IRB approval of these adaptations.

So there needs to be some advanced planning to make sure all the IRBs know what's going on and are able to do or redo approvals when necessary. And finally logistics is always something that you all need to consider.

We need to have a smooth flow in data checking so we can actually do the adaptation in a timely way. We need some common understanding of how the trial will be conducting and what the options - the decision options are at each stage.

And then you need to have supplies, etcetera available to accommodate changes to treatment through the course of the trial if they occur.

So finally from the CDRH point of view and I will include CBER on this one, we discuss interactions between us and the sponsors.

Of course earlier is always better. We have a presubmission process that we use here at CDRH and there's a whole guidance about how to do that. And that's the preferred method to interact with us on these kinds of trials.

At the design stage the FDA is always interested in the operating characteristics. Because these kinds of trials are complicated we do encourage folks to get to us on a pre-submission stage before an IDE comes in the door so we understand what's going on.

And if you are using simulations to produce operating characteristics then we can agree that the appropriate range of possible scenarios are covered. The monitoring plan for the trial is always important. And we do care about the other techniques that can help reduce operational bias.

So now I'm going to turn it over to Dr. Russek-Cohen who's going to give a few slides on the CBER perspective.

Estelle Russek-Cohen: Hello. One of things I did want to point out. Dr. Gray talked about pre-submissions. We regulate devices, PMAs, 510Ks and we also have the same type of presubmission process. So it's a good idea that if you're thinking about an adaptive design at CBER that you also make use of that same process.

Our devices are mostly diagnostic. A few are therapeutic. They often include products that process blood cells and tissue. And what we get concerned about is the safety and effectiveness of the resulting products.

So our clinical trials tend to be much more similar even when they're evaluating a device, they're much more similar to trials for biologics. Most of our adaptive and/or Bayesian submissions have been for biologic products only because we review more of them.

But the assessment tends to be similar when we're using an investigational device exception or an IDE and an investigational new drug or IND which is the parallel for drugs and biologics.

Like CDRH we have also conducted our own survey of adaptive designs. The reference is on the slide. It covers 2008 to 2013. We think we're seeing more now. We're definitely seeing Bayesian methods more commonly in phase one and phase two in oncology.

But we are seeing proposals for Bayesian adaptive designs in phase three which is our version of a pivotal study. Proposals for adaptive designs with type one error that's demonstrated - control type one error is demonstrated by a simulation is something that we have also seen.

I think one of the things that we'd point out is the more complex the design is, it may result in more than one round of discussion with the agency. And the other point I would make is that sometimes the acceptance of the particular design is not just totally statistical. It could be clinical.

And it's usually a review team effort. I'd like to say a little bit about diagnostics having worked on diagnostic devices in both centers. Usually we derive sample size which as Dr. Gray pointed out is usually the driving reason for doing adaptive designs.

In a diagnostic setting it's usually a prevalence of rare conditions will often drive sample size in what are called diagnostic performance studies. Those are described as the guidance on pivotal investigations issued by both centers a while ago.

But you're often comparing against another method, either the best available reference method or in the 510K paradigm (repetitive) device. Protocols for prospective studies can define rules to add samples based on observed prevalence as is defined by the comparator or the reference method.

The assumption is that the person running the new test is not aware of the results of the reference method. And when you do this phasing your protocols there's alpha penalty as there would be with a classic randomized design.

Sometimes we wanted to keep the sample size down. Banked specimens are sometimes allowed. But we would suggest the first contact review division, because it does vary with the setting and the kind of device that you're evaluating.

So I'd like to thank you very much on behalf of both centers. Now we're to the question and answers. Right?

Gerry Gray: Yes.

Irene Aihie: We'll now take questions.

Coordinator: Thank you. We will now begin the question and answer session. Questions will be submitted by phone only. To ask a question please press Star 1, unmute your phone and record your name clearly when prompted.

To withdraw your request you can press Star 2. Once again it is Star 1 to ask a question from the phone lines. One moment please for the first question.

I believe our first question comes from (Jin Jong). Your line is now open.

(Jin Jong): Hi. This is (Jin Jong) from AdvaMed. I have a question regarding FDA's expectation on the coming occasions between the sponsor and the FDA, you know, during the course of the trial when there's adaptive design used.

Because as you've mentioned it will be - there could be multiple interim analysis during which, you know, the decision may be just to proceed without any change or to stop early or at sample size.

So what's the expectation in terms of, you know, communicated these, you know, decisions to the agency during the trial? Thank you.

Tara Ryan: Hi. This is Tara Ryan. I'm the medical officer in the Division of Cardiovascular Devices. My opinion is I think more would be better.

I don't think we have at this point any specific template that says you must report at a particular time or you need to tell us the results at certain interims.

But I think you can't go wrong if you, , contact us and we can let you know whether a formal supplement needs to be submitted. Or whether this is something that we need to have a conference call about.

I think it's just to your benefit to just stay in contact with us as much as possible. I don't know if anybody has any thoughts about it.

Gerry Gray: This is Gerry Gray. There is a little - there is one thing that has occasionally come up when - if an IDE is fairly long running in their reports that come into FDA. And sometimes if this - you have to be a little bit careful about doing those annual reports and making sure that blinding is maintained if necessary.

So sometimes there's a little bit of operational worry in terms of annual reports that are due to FDA. We need to make sure that whoever the person doing the analysis for that - to submit that in as firewalled off from the people who are conducting the trial. So those are situations that do come up on occasion.

Estelle Russek-Cohen: This is Estelle Russet-Cohen. Safety is always paramount in these studies. So you'd still continue to deal the safety issues as they emerge in accordance with any other adaptive and non-adaptive design.

Irene Aihie: We'll take our next question.

Coordinator: Our next question comes from Robert Magari. Your line is open.

Robert Magari: Yes. Hi. This is Robert Magari from Beckman Coulter. My question is in general one related to diagnostic device. Do you have any number of any general idea how many submissions are adaptive design related to diagnostics? And what kind of adaptations they are looking for? Thank you.

Estelle Russek-Cohen: Most of the time - this is Estelle Russek-Cohen. And hi Robert. There aren't - there have not been all that many adaptive designs and diagnostics. Now keep in mind I did not mention the fact that contained diagnostics are outside the scope of this guidance.

And one might very well anticipate in the context of evaluating a drug that you might very well see in adaptive design in that setting. But it's not in the scope of this particular guidance document.

In the diagnostic performance studies, companies have come in and asked to add to their sample size. But because they had demonstrated the reference method and the person running the investigational test is too blinded to the

reference method, they're allowed to augment their sample size without penalty.

The real question is, is whether other adaptive designs are there. And I think I have been at CDRH for five years. I think I can remember two of them. I mean it's just not a very large volume of what's there.

And they would not be traditional diagnostic performance. Obviously if it's a randomized trial that's evaluating a diagnostic device you could in fact have adaptive designs. But they're very unusual.

Robert Magari: Thank you.

Gerry Gray: This is Gerry again. If you - I put back up the slide about the CDRH experience. And if you go to the (Yang) Paper there are more details in there about the kinds of designs that we saw.

And Estelle's right. There were only a few that were diagnostics. But I would agree with Estelle that the personalized medicine world is one area where I think some of these enrichment designs might show up in the future. But we haven't seen very many of them yet.

Robert Magari: Thank you.

Irene Aihie: We'll take our next question.

Coordinator: Our next question comes from (Ya Ming Chang). Your line is now open.

(Ya Ming Chang): Okay. Yes. Thanks for the presentation. So I have two questions. Oh first of all my name is (Ya Ming Chang) from Medtronic. So my questions relate to Gerry's presentation. So the first is for the slide number 615.

So regarding CDRH experience insight is that of the 251 adaptive studies in 2007 to 2013. So only 32 have (applied) that submission. So I'm curious would you I mean maybe share a little bit more?

Like so why there's only 32. Because the trials failed or because, you know, they're just a more, you know, could not get, you know, more studies designed between like, you know, like 2013 and 2012? So studies they are ongoing.

So my next question is for the Slide 25, is it a control firewall? So just wondering if you can help me leverage? I mean this is kind of important to eliminate the operation bias. So you mentioned maybe we can maintain appropriate firewalls.

So I'm just wondering, you know, could you leverage what kind of firewalls, you know, you're looking for, for the industries? If the companies are, you know, (unintelligible). And then - so yes. Thanks.

Gerry Gray: Okay. So related to the first question on CDRH experience there was a survey we did from all the submissions that we got, that we had received between 2007 and 2013. I think that most of the reason most of those are designed and there weren't that many submissions is purely the time lag between.

Because some - many of these studies take several years to complete. So a lot of the submissions were I think still ongoing. The other thing to be clear in this - and the paper talks about this is, you know, it's not necessarily a one to

one correspondence between submissions, IDE submissions and what comes back to us as a PMA or a 510K.

And I will - I do have to acknowledge that we don't really know necessarily why someone doesn't come back. So, you know, an IDE can go out and be approved, a sponsor can conduct the trial and then for whatever reason don't come back to FDA because the trial failed, because they ran out of money, because they got bought by another entity who decided that they didn't want the product. We don't know for sure why.

But I think that most of the submissions that we saw earlier on in the period and so most of those studies are still probably ongoing.

Regarding the second question about firewalls the issue really is to try to maintain as much as possible sort of on a need to know basis who knows what's going on in the study.

Because we don't want to have investigators knowing how the trial is proceeding and thinking about or maybe not thinking about it and inadvertently altering randomizations or altering who are they selecting to enroll in the trial, things like that.

So what we try to - like to see are written into the protocol plans that basically insulate the outcome data or the randomization business scheme to - from the investigators. And that's not that much different than what you would do in a normal clinical trial, in a fixed clinical trial.

We don't - we never want the folks conducting the trial to know too much about how it's going during the course of the trial so we can prevent any questions about whether that altered their behavior.

There are some - I believe there are some products out there, some companies that create - have created products that help to maintain this kind of blinding in these trials. And folks use those for example to make sure that the trial - the board who maintains the safety of the patients doesn't leak out that information outside.

So there products I think that will help to make that process easier.

Irene Aihie: We'll take our next question.

Coordinator: Thank you. And again as a reminder it is star 1 to ask a question from the phone lines. Our next question come from Ying Wan. Your line is open.

Ying Wan: Hi. This is Ying Wan from the C.R. Bard. I have a question specifically regarding sample size re-estimation. So during the interim analysis to recalculate the sample, whether it can be communicated to the study team.

So I understand that the new, you know, recalculate the sample size potentially can be better calculated and, you know, the interim analysis results potentially can be compromised.

But on the other hand, you know, it's not very practical to hide the recalculated sample size. So I just want to know what the FDA's take is on this issue.

Gerry Gray: So yes. That is an issue that people could potentially back calculate based on a revised sample size. And knowing what's in the protocol could potentially back calculate to figure out what the interim result is.

So because of that we try to make sure that the actual recalculation is not necessarily given out. But what you can do is, you know, most of these trials that are adaptive sample size trials have some maximum.

And so instead of saying, you know, we changed the sample size to some particular number you can say, well, we're going to - we haven't - there's no reason to stop now. We're going to continue. And our maximum stays where it is.

So I think you can communicate the results in a little more vague terms but we're continuing the trial without - so it doesn't people to actually do a detailed back calculation.

But that being said there always is, you know, any kind of information is information. And so just knowing that the trial is continuing and not stopping for futility or early success is information.

So there's no way really to prevent that amount leakage if you want to call it that.

Irene Aihie: Operator do we have any more questions?

Coordinator: We're showing no further questions at this time.

Irene Aihie: Well thank is. This is Irene Aihie. And we do appreciate your participation and thoughtful questions. Today's presentation and transcript will be made available on the CDRH Learn Web page at www.fda.gov/training/CDRHlearn by Friday, September 30.

If you have additional questions about the final guidance please use the contact information provided at the end of the slide presentation. As always we appreciate you feedback.

Again thank you for participating and this concludes today's webinar.

Coordinator: Thank you. That does conclude today's call. Thank you all for participating. You may disconnect your lines at this time.

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