Transcript- 17 Apr 2020-Innovative Tech WG Adapting Trials for Remote Assessments 2

We appreciate your joining us. This is Mary Bea with the ISCTM. And I'm going to turn it over to Rich Keefe first, and then he'll turn it over to Mike Davis, the chairs of the ISCTM Innovative Technologies Working Group. Thank you, everyone. Great, thanks very much, Mary Bea. This is Rich Keefe. So welcome to the ISCTM Innovative Technologies Working Group, second special seminar on adapting trials in a hurry for remote assessment. I'm Rich Keefe from Duke University Medical Center and VeraSci.

And our co-chair today is Mike Davis from FDA, who will be making introductory comments in just a moment. So I think that the need for remote assessment these days is pretty clear to everyone. It's also pretty clear that this transition can be very challenging and can call into question the validity of any assessment approach that is done remotely. There are many other issues, some of which have data to contribute and some that don't. And so I think that the advice of those who have experience in this area and those who have regulatory authority is particularly important.

We felt that this topic landed squarely into the domain of our working group and given the speed needed for some people to adapt to the current situation. Mike and I felt that we should provide a forum for discussion. If you are not familiar with CTM, although I know most of you are as members, I as ISCTM is really an ideal organization for this activity. It involves a variety of different constituencies, including government, particularly FDA representatives who are attending today and representatives from academia, industry, as well as site investigators.

Those who are on the front lines actually implementing the policies and the strategies that will discuss today. So in sum, this is a very important time for collaboration. And my experience is that nobody collaborates better than the ISC team. So we're delighted to be able to provide this forum for information. For those of you who are in a quandary about what to do. A couple of rules of engagement.

Mary Bea has mentioned them. You will be muted. The panelists there are 12 of them will be unmute. Attendees, though, can make comments in the chat section and we will do our best to pay attention to them. But as Mary Bea said, we can't promise that all comments and all questions will be attended to. Particularly important is the non-commercial nature of this passion. So comments and questions should be those that are directed to the collaborative spirit of this seminar.

And not one that is serving to promote any individual interests, particularly a commercial interest. Also, this session is being recorded. So that's a nice coincidence. So if you do go on a commercial diatribe, it will be recorded. So let some let let's move on. I'm going to turn this over to Mike. But I also wanted to just introduce the two additional panelists that are not with the FDA today. And both of them are pretty well known to team membership.

They are Dave Walling, who is the CEO at a collaborative neuroscience network in California. And he has been the lead investigator on many clinical trials. And Bob Builder, who is the chief of psychology and professor of psychiatry at UCLA. And Bob actually was the chair of a Covid writing committee formed by a

group of seven neuropsychological societies devoted to the idea of what could they do in terms of neuropsychological assessment to make guidelines for how that would be done remotely during the Covid crisis.

So both of them are very well qualified to make comments on the discussions that will begin to have that we're going to have today. So thanks very much. And I look forward to interacting with you throughout the hour and a half that we'll have this. And I'll I'll turn it over to Mike. Thanks, Rich. Yeah, I wanted to thank AC Khyam and my work co-chair. Let's keep having this excellent idea to do these series of calls. And I just want to thank our panelists from FDA Doctors Builder and Walling for taking the time to participate in this important discussion.

And we are all the Covid 19 pandemic is having a heavy impact on clinical trials and all the individuals and organizations that conduct support and oversee the trials. And we've heard a bit about this call a couple weeks ago, and we think doctors ran sand and fallowed, were sharing their experiences. And we've received a number of comments and questions before the last meeting and and prior to this meeting. And I really appreciate in reviewing them the strong emphasis on the safety of clinical trial participants as well as the emphasis on maintaining the integrity of the clinical trials.

And it's also very clear that many in our community are innovating and taking the initiative to incorporate and utilize technology and other creative approaches to facilitate clinical trials during this pandemic period. The FDA has published a number of guidances to address key needs and considerations with stakeholders, but it is keenly aware that there are likely additional areas in need for clarification and further dialogue. And that's why we really appreciate all the input from people. And ISCTM and participants on these calls to help point to point us to such areas and gaps.

And after his staff is working hard on addressing these issues and as one example, the FDA guidance on the conduct of clinical trials of medical products during the Cold War 19 pandemic has already been updated several times since its initial publication. And there's actually an update published yesterday that included questions and answers specifically related to remote assessments. So I'd like to now introduce our special guest panelists from the FDA, from the Office of Medical Policy. Dr. Kent al-Asaad is the deputy director of ARPUs and is also part of the clinical trial conduct work stream for the FDA seeder coordinating response efforts.

And after the rest of the introductions, I'm going to give Dr Khair ElZarrad either a chance to make some initial remarks. And we also have Dr. Leonard Sacks, who's the associate director for clinical methodology in the Policy, as well as both Elizabeth Kunkoski and Isaac Rodriguez. Chavez, who are on science policy analysts working with Dr. Sacks in the Clinical Methodology Group. And they're both very involved in projects related to digital technologies and decentralized trials and other areas. The prudent to this discussion next from the division of psychiatry, like to introduce Dr.

Tiffany Farchione, the division director, and also doctors, volunteer, mentor and let me who are clinical reviewers in the division who work will work closely with us. And on these sorts of issues have been very

integral members part of the discussion. And I'm a I'm a clinical team leader in the division of psychiatry as well from the division of clinical outcome assessments. Dr. Elektra Papadopoulos is the associate director of that group and she purchased in the last call as well as internal discussions prior to this call.

She unfortunately has a conflicting engagement this morning, but is able she may may have a chance to call and meaning. So I want to turn it over to Dr. Khair ElZarrad just to give in the opportunity to say a few words before we get into the discussion. Thank you so much, Mike. And thank you to the ISCTM community as well for having this dialogue. As Mike mentioned them from the Office of Medical Policy, and my office manages the work around the guidance developments for the conduct of the clinical trials of medical products during this Covid 19 pandemic.

We also manage the mail box that you will find listed on the guidance for any kind of relevant questions that are on clinical trial contact. We're trying to bring a multidisciplinary group to do our best in answering the questions and being responsive. So our community. I want to thank also all of you, as Michael so mentioned, would realize that a lot of the innovations and a lot of the bush to utilize technology and innovations coming from our community across the board.

And this is across academia, industry and even our bees. And we're very grateful to that. I do not personally come from the your psychiatry backgrounds or I'm not. I'm also from that I CTM. My training is actually in oncology. However, I feel like this kind of interaction and this kind of dialogue is extremely important for us to identify what areas need to further elaboration and need for further clarity. And that will enable us as an agency to be responsive and to have this kind of level of dialogues.

So, again, I'm extremely appreciative of this dialogue. To the ISCTM community to the division itself and everybody else involved today. Thank you. So now, now, as we get into the discussion, it's up, I want to first make just a couple of disclaimers from from the FDA perspective. So comments from FDA officials on this call represent the current thinking of the commenters and they should not be taken as official FDA guidance. And those official FDA guidance that can be obtained from contacting the clinical trial conduct covered 19 mailbox that Dr.

al-Asaad was discussing is involved with and and also can reach out to regulatory project managers in the primary review divisions. And attorneys may also wish to refer to the FDA guidance on conduct of clinical trials during the October 19 pandemic. And like I said, it was updated yesterday and it has guidance very relevant to this discussion. So I'll now turn it over to Rich to get get into our first theme of the discussion. OK, great. Thanks very much, Mike.

And so I guess so Mike and I are going to alternate back and forth during the course of the day and each take a different theme. I also just want to add, I was remiss in my introductory comments just to thank I CTM executive directors office profusely. Mary Bea, Linda and Carlotta have just been tremendous and flexible and incredibly responsive to. To be able to set up this technology, actually. We switch technology at the last minute and they've been incredibly flexible so that we can handle what's now, I guess.

One hundred eighty eight people on the line at the same time. So thanks so much. So the first theme is data quality. How do we maximize data quality during clinical trials conducted during the pandemic period? And there were four questions. I'm going to try to very briefly read them because I want to make sure that everyone is well represented and that folks from FDA and the panelists, Bob and Dave, also hear things about how people are thinking. So what information can sponsors collect?

How can rapid adjustments to things like virtual Pietro's clinical clinician reported outcomes and performance based outcomes be executed to collect information related to this while remaining compliant? Another question we have a double blind, placebo controlled trial that is currently ongoing and have recruited about one third of the total number of subjects due to cobh at 19. We are anticipating collecting data remotely for a number of safety assessments such as part of dyskinesia at Kathie's year, etc. and FSC scales as well as some patient reported outcomes like the caregiver global impression of change.

The protocol is being amended and we will submit to the agency it is reasonable to with some of it. It will be collected at sites in person with face to face interviews, and some will be collected by remote means. We would greatly appreciate your thoughts about approaches to assessing quality of data while the study is going on. Third question for active trials as trials go remote and shift measurements to match. How can sponsors best justify and document the changes to new measures and compare data from current remote assessments from previous trial data with different assessments?

This is rich talking back question also as a data analytic component and we're gonna get to that actually in the seventh section at the end. The fourth question is if the subject is read the piano and Rader is completing the digital scale on subject. The half. Do we need confirmation from the subject that their answers were correctly marked? So for different questions. A general theme of data quality and how to handle that. We would love to hear from the folks at FDA about their perspectives on this issue.

Thank you. So maybe I can kick off its land attacks on the office of medical policy. You know, I think that there are two issues here. The one is the discipline's specific issues related related to these pianos. I'm not a psychologist or psychiatrist. I'm an infectious disease officer. I would totally defer to Dr. FARCHIONE and the others in her group and Mike. But I think one of the issues that sort of seems to override is that data quality is probably really a very important consideration when we're looking at a very big concern when we look at non-inferiority studies.

So just as a general theme that's occurred to me, I think if you're looking at a superiority study, there's probably less of a constraint. And if you're looking at a non-inferiority study where increased variability around an assessment obviously needs to drugs to look the same. But in terms of the content for simplicity, I would turn over to the other panel members. So this is typical of our training. So I think that, you know, as I look through these these four questions, what I what I kind of see generally is a theme of how much information do we need to collect to document the differences in assessment across some across the trial and.

I think that in. They want to see the questions on the screen. Details have those to put them up there just for. I don't know if that's on one of the slides, but we do we do have them. I don't know if Mary B or Carlotta could, then they could get that up there. But in any case. You know, all of these changes we know are going to introduce variability into into the study. And it's a completely unprecedented situation that until we actually see what comes out of it, we're not really going to know how much of an effect all of these changes are going to have.

So to me, the most important thing would be to try to capture with as much granularity as possible where what the deviations I don't want to call them deviations. Because if you're submitting protocol amendments to allow this to happen, it's not really a deviation anymore. But where are these differences occurred? What the differences from the usual practice are. And you know how so? So in it, for instance, you know, adding just and an extra data entry point about, you know, home verses like, you know, remote versus in-person assessment.

And, you know, if you had to make any modifications to the instrument itself to adapt it for remote segments. And, you know, honestly, as far as a question about is completing the digital scale on the subject's behalf. You know, it probably wouldn't hurt to have the subject confirm that their answers were marked correctly. Again, you know, the more detail that we have, if there is some sort of. And I expect to see that there's going to be perhaps some group differences between the folks who were assessed in the usual manner versus folks who were assessed during the pandemic in a different manner.

And, you know, whether that's related to the method of assessment or just the state of the world, who who knows? But the more detail that we have, the better we're able to judge what the impact is on the overall trial. Next to this is Mike Davis. And yeah, I think I I reviewed the FDA Cauvin 19 clinical trial guidance again to kind of assess the changes and one theme that one theme in that guidance is just that we're encouraging flexibility and we know that you can't do everything that you would be able to do if there wasn't discovered pandemic going on right now and be flexible and reasonable and try to do the best you can to accomplish what you were previously trying to do and then documented.

Why? Why you did what you did, what you did. And then in the clinical study reports, as well as the data sets indicate, when things are changed from during this period, from previous and after to this period. So then later we'll be able to analyze and assess, assess really where what went on. And so just thorough documentation was is a theme. And and it just allows of flexibility to kind of do the best you can, given the circumstances.

Thanks. Thanks. Thanks, everybody. Thanks, Mike. So I think a couple of these names are going to run throughout the different questions that we have, particularly the analysis. One, how do we compare this period to the period before and hopefully the period after the crisis? And so we'll we'll get to that later. Mike, why don't we move on to the second theme of remote method validity for remote assessments?

Sure. So so the next time of remote assessments method, there are three questions we received. One is the first is that ongoing studies may be at risk. Should at home orders become wailing over the next 18

months, which is read about some suggesting this possibility in the news and this may make it necessary to conduct assessments remotely in the context of trials not being initially set up for such assessments. Should sponsors be planning to replace such patients for which the primary endpoint is impacted?

Or do you see flexibility in accepting a variety of assessment collections because of overcovered? And the next question is if a trial switches during the ongoing trial to remote assessments, why is it a benefit to switch all assessments to remote and not on a state by state basis? The data will be mixed anyhow. And this this question was as a follow up to comments made by the doctor, spoke Jyoti and Ranter on the protocol. Next, if an ongoing study is returned from face to face assessment, administration to remote administration, are the FDA experts recommending or mandating that all trials centers have to switch from base to base to remote, meaning it would not be acceptable to switch only a certain percentage of sites over to remote assessments?

And so I put the first question, I think, which at a good idea that we could ask Dr. Berger to provide his academic perspective on the validity of a remote post implosive assessment since he has been very about and in this topic. It is working. No psychology committees that he is on.

Well, thanks so much, Mike. Can you folks hear me? Bob Builder speaking.

And thank you so much for inviting me to join in. And I want to apologize in advance. I have to leave at noon to go to another combat related meeting. But the work that was described earlier was done together with Inter Organizational Practice Committee that had psychologists from the American Psychological Association, a bunch of the other clinical neuropsychology organizations, to try to rapidly develop some provisional guidance. And anything that I say, there's more detail contained at I OPC online.

And I'm happy to send links out to anybody who is interested in that. Talk about any details. I think that the bottom line of this work is clinical neuropsychologist around the country are trying to figure out what they do is that there is quite a lot that can be done. You know, we've surveyed the existing literature, which includes about 22 studies and some analysis. And the sort of potentially surprising news is that that the difference between in clinic and online, you know, Xoom based assessments or remote assessments or telling neuropsychology assessments, the hedgies G was about point 0 3, meaning that's like one thirty third of a standard deviation difference between the in clinic and on line version of a test.

Overall, there were very few of the untimed tests that differed by more than one tenth of a standard deviation from there in clinical scores. So overall, the news was really good. The verbal tests were almost identical to the clinic versions with creativity. The visual spatial stuff was done really quite well. And nowadays there are really good platforms to enable the presentation of stuff that you would have in the clinic to be able to present it to somebody at all. The caveats.

All this, of course, include first and foremost technical issues. So limitations in bandwidth, screen size, camera options, etc. These have to be pretty carefully evaluated. Fortunately, I think for clinical trials, a lot of those can be overcome. There's also some age limits that may be factors. The validity data really

exists primarily for people under the age of 75 above age seventy five. There is less consistency in the data so far. And then another key factor is how to use and engage other facilitators.

During the course of this war, but overall, that a key issue that came up was that if you can, is really what Tiffany and Mike were saying earlier, if you emulate as closely as possible the original conditions and can document what you've done that is any different and particularly that you can document what the examiner is doing at the time, that's critically important. One of the counterintuitive things that we noted is that many of the web based assessments, you might think that, oh, this would be the perfect time to start doing web based assessments and there are vendors out there who provide this kind of service.

Unfortunately, the evidence for those is so far not as good as it is for some of the other more classic neuropsychological tests that are done in clinics. So I think that the bottom line is that the more standard stuff that can be done using a zoom contact or other, you know, web based contact that replaces the in clinic visit as closely as possible seems to be quite valid, replicable and useful.

Thanks, Dr. Bell. I wonder, as the round about Tina, would you be willing to talk a little bit about that second question about that? I'm switching all the assessments to remote now side by side and the faster it sort of relates to the other questions and that the results. If some states have one type of assessment, somehow or another, a different percentage of the sites, depending on which jurisdictions the studies are being conducted in, I'm just kind of.

But yeah, some like before you pass it over to Valentino, maybe there's a Tiffany, maybe you could just say one thing really, really quickly about that. I mean, I think that the main thing that folks have to realize here is that when we're making this recommendation for all the sites, you know, to try to be consistent and make everything remote, the primary motivation there is patient safety at this point in time. Doing in-person assessments just is not safe.

You know, everywhere that you know that the vast majority of no, even clinical physician appointments, you know, primary care doctors, whatever, they're all switching to remote visits as much as humanly possible so that we can try to continue social distancing and try to keep people safe. That's the primary motivation here. So but as far as the data, you know, I'll go ahead and I'll throw that back over to Valentino, because I think she wanted to make a comment in terms of the estimated.

No. Well, we're well aware. Can you hear me first? Do you hear me well? Yeah. Well, we weren't aware that some safety measures are differently implemented in different territories. And I likes to point out that we tried with this call to reach out to my former EMI colleague, which we hope to have some of them, at least in future interactions. And just to have an idea of what is what is required up there to keep this consistency.

But as far as what we know now, we know that there are different safety requirements. But whenever possible, I would make some example as to how to make increased consistency easier. Some of these languages, you can find it on the KUA name, the guidance frequency, if there are some circumstances in

which the assessment at the site level is down. Whether with a child and the parent tried to reproduce the same situation when you do the remote assessment.

We've had some sponsor coming to us with multiple options for remote assessments like placements of video and phone. So two options. So we try to keep consistency and choose one option. So the two across the site. Also, there are cases in which options include the possibility for raters to complete digital scales online and on behalf of the patients. If if something like this happens, please try to get confirmation. And also try to collect data. This actually happens.

And then there are very obvious examples. Just to say, tried to make sure that in-person assessment, remote assessments are seamless, be consistent in terms chosen methods. And that is essentially our you know, you can find rest of the language and the guidance is essentially out of common sense. Thank you. And perhaps somebody from some gas, from some medical policy, for example, I think if you look and and picky about decentralized trials and health and how some some sites will be doing, one thing just get kind of dealing with the heterogeneity of the different approaches.

What do you make of it?

My guy. Can I just mention one very minor thing before then? And I just want I just what I mentioned is the higher principle that as an agency we do recognize that, as Stephanie mentioned, this is really abnormal times and that there might be not just, you know, comparing the body, ABN Demick to boost pandemic. I think during the band Demick that we're going to see a lot of variations within the same clinical trials sometimes. And it might be appropriate to do a little site assessment to some subjects and remote assessments within the same trial.

And I think it minimizing the differences is the key here as our guidance highlighted. And I just want to mention that we do recognize the need for this variability within the specific context of the clinical trials.

Thank you. Thank you for those comments.

Mike, this is Rajha. I just wanted to add there have been a couple of questions with the same theme about children. What about what about a pediatric clinical trials? And I wondered if Dr. Builder or any of the FDA panelists had a comment about that specific case. I've been commenting a little bit, just as Bob Builder in the chat place, there's not really data for neuropsych stuff on kid assessments.

Just adults and and then the older seventy five group, that's where we know there's more inconsistency. But with kids, there's really not enough data. Okay, so this is a secretary has found the office make a policy. Can you hear me? Yes. Yes. Here, a little bit quiet, though. I think if he could maybe try to get closer to the mike. Where am I know better?

OK, so listen in on the sense of questions from the first set of a group of queer students and now the second group of questions, I kind of take a step back and think a put it put it myself in in the position of the investigators and the sponsors.

Everything that we do is really connected to the context of use within the context, specific contents of use. And so that's when I tend to keep in mind there are general considerations. But are you really able to do what you need to do in the protocol by modifying the protocol, by amending the protocol, by documenting the deviations and be able to really transition from the in person to a remote activity, keeping in mind, keeping an eye on everything, a participant safety in the first place and evidently preserving as much as possible and making a robust effort to preserve it as much as possible.

The data integrity, data quality of the trials in all of these. The agency recognizes that there is there will be variability, there will be a change in the way that things are conducted in the best case scenario. We would all want to go on one type of assessment, say done all in person or transition all of them remotely document everything that has happened at the site level. A date participant level on the connection with Collet 19 in the case report forms in this study report document that is two extremes of best case scenarios, if you will.

The reality is that there may be sides that need to do a combination or a side should be doing all remotely. Other side should be doing the opportunity of doing in person is still available depending upon the area of the country. If the call at 19 has decreased significantly, which is not the majority of the country. So it really comes down to this study specific situation. The assessment of the sponsor and the investigator can conduct and documentation of day actions in relation to convert 19 scientia specific patient specific level and understand that the variability will infect the data.

And that data analysis needs to be equally conducted to essentially understand the range of variability in the dataset.

OK. Thank you, Isaac. So I want to move on to the next step, which is about remote assessment methodologies and not that the rich.

Yeah. Thanks, Mike. And there have been some great questions coming in on the chat and we're going to try to address those as we go forward. I do think that some of these things will get a little redundant and that will open up some time to address those questions. One of the ones that came in particular, I think from Stephanie Festa was relevant to this discussion, which was about what? About doing remote assessments of movement scales such as tardive dyskinesia with at Kathie's year with the balms and so forth.

And I think that perspective on is it possible to do that? And will those types of remote reading scales have content validity and. Let me read these questions related to content validity as those designing the first one. And by the way, this is Ritchey as those designing and implementing clinical trials adjust to the current situation. There is a question, especially in CNS of the quarantine state and the impact of a global

pandemic in general on assessment results. For instance, people are more depressed, our treatments working differently as a result of less outside time, access to clinicians or family, etc.

. How is the FDA considering these impacts? And obviously you have two things happening at the same time, potentially remote assessment and the impact of a changed affective state for the entire world. And how do we do to separate them from one another? Second question, very similar. How are psychological stresses being accounted for during analysis? We do an analysis looking at these things and will they still be valid? Is there third question is, is there a value in collecting data regarding whether patients are sick with at 19 and potentially adjust accordingly?

And then for again, same kind of theme. The influence of social stress came up on our last call as a potentially confounding effect on measuring symptoms. Do the FDA experts have an expectation that a trial explicitly has to assess social stress, or is this just an imperfection that we need to live with? Fixed number one question. I can see, for example, to add a social stress outcome measurement to protocols as attempt to quantify its impact. Fixed number 2.

Would it be acceptable to increase the level of clinical judgment in an outcome instrument that measures depression such as the modest or back to allow the rater for separating the disease type depression from the tactical clothes offered in? If yes. Should no guidance for the administration of an outcome originate from the scale author or test copyright owner rather than on a trial by trial basis? So before I open it up to the FDA panelists, I wanted to call specifically on Dave Walling, who does run a site and has been interacting with patients quite a lot before and after covered 19 and currently.

So he may have a comment about the changes in the emotional state of these patients and how it may be affecting their scores on rating scales. Dave?

Yep. Good morning, everyone. Can you hear me OK? Yes. OK, good. So so, yes, we are still seeing patients based upon we're based in California, so we do have a shelter in place. However, health care is excluded from the shelter in place. So we do continue to see some patients really based upon sponsor guidance. There are some studies that are still saying patients should be seen in the clinic and there are others that allow for some remote assessment.

And sometimes it depends on what exactly is being done at the desert. But what we are seeing with with subjects coming in is definitely increased anxiety. I was meeting with a schizophrenia patient yesterday and as I was talking with him and asked about paranoia, he explicitly talked about how the covered situation and how that was impacting him. And I really didn't think it was overall increase paranoia. But but what I thought it was, was anxiety related to what's going on.

I mean, he actually had a gas mask on during the visit. The other thing that we're also having to to assess, both with schizophrenia, depression and other disorders is the issue of social isolation. In schizophrenia, we expect negative symptoms. We expect the subjects to socially isolate them. Same

thing with depression as well. We do see that and we're seeing we're having to differentiate and document why we think it's social isolation related to konbit and why we think it's social.

It may be social isolation related to the disease process. And I think for us, we're having to document a lot more because we have not gotten guidance from sponsors and from from rating companies exactly how we should be dealing with some of this. So we're just docking. We're rating as we see it and we're documenting what what we notice in the subjects that are. There are a few other things that we're definitely seeing, and this is certainly affecting rating scales.

You're seeing a lot more sleep disturbance. So a lot of subjects that are coming in, both depression, schizophrenia even and some of our ADHD subjects, we're seeing sleep disturbance that we're noting. And I've also seen this on our inpatient unit. We do some inpatient studies for acute schizophrenia where we've had patients complaining. It seems like more a sleep disturbance. I do see patients in the hospital watching the news nonstop. So that's probably contribute contributing. And then, you know, other areas, such as lassitude, their ability to get up and do things is certainly impacted as well because they can't really go out and do things.

And we're asking them, you know, have you been doing your normal activities? Have you been participating in things? Have you been seeing family, friends, things like that? So it's definitely taking an impact overall on the patients that we're seeing. From my perspective, I'm trying to document everything that I think is covered related. And, you know, I've even wondered as I was seeing the subject yesterday, I was wondering, should I give her a score that I think is a non-covered score and then also give a covered score because it certainly would have made a difference on some of the items.

So hopefully that answers your questions, right?

Yeah, that that that's great to have your perspective on that. And it, of course, raises the question went to a couple of people have mentioned on the chat. So so what do we do about those scores from some regulatory perspective? How do we how do we. What do we adjust for? So if you didn't give two scores, you know, A, this is the score that I felt was the patient's stay within. And this is the score that kind of account for the change.

How should people address that, given my we are going to talk about the data analysis part later, but how should be the Raider address that from the regulatory place.

Thank you so deliberately. This is always a British number three a. Something really interesting, which is, is there value in collecting data regarding whether patients in current trials are sick with chronic 19?

Basically i--just analysis blonde's was hard on in my opinion really is important. As was said before, to document all the information related to this study, participants in connection with Corlett 19. So that is a very is a yes question you need to document, because as we just heard, there is a major impact. As

David was saying, it's a major impact on the behavioral patterns of the participants. Connection. Begovic, 19. And that one. Introduce variation.

Do your study employees. So that information has to be capture. There is a quality. This asked aspect to all of this assessments and there is a quantitative aspect that is put in place when statistical analysis with the analysis is also conducted to assess the validity of their assessments after the impact of their ability. For example, due to Covic 19, thesis has to be done on a case-by-case basis. As I said, contacts of yours aren't specific case study.

Essentially, information needs to be documented. Do we need to conduct subgroup analysis? If you think it's worth indent for this study in question, again, it's on a case by case basis. I can see their data as well. If you have the sample size and you do Dr. Joe statisticians and your house there, the design is statistical design plan and you can have the sample size and the confidence in their answer, nor the parameters that can add validity to the subgroup analysis by all means, especially Dudi.

So documentation indigo's took of it 19 and 8 would pass faster. Thank you.

Thanks. This is Mike Devastator. Third to kind of go out disaster response. We received a question the chat window about asking a question asking how much their life or the current experience has affected the subject during the study. And it's also kind of relates to question for our lost on whether there is an expectation that you have to explicitly assess the social stress and which there is no sort of FDA prescription that you need to do this. But and in discussion, Rosario's, Lytro, Papadopoulos and colleagues from Clinical Outcomes Assessment State thought that perhaps what one thing people could consider would be some sort of post study interview, a survey, because to try to learn from subjects how how this may have affected their experience during the clinical trial.

It legit logistical issues as well as on those symptoms that they experienced during this period. And it's it's tough to know exactly what would you do with that information by collecting it and including it in the clinical study report and presenting analyzing how these how the pandemic affected affected the data and the results of the trial. It could be potentially helpful and review. Peter, we all need to understand is, is this is the new normal? There will be an initial potential variability to the data sets and then recalibration of the data sets that can be present in many senses.

I wash off because everything will be done in the midst of covered 19 if the study start to be continued. And that is something that the quantitative base of statistical analysis to be conducted can determine whether or not that is the case. OK. Thank you very much. Mike, why don't we move on to the next set of questions, realizing that not all of these questions have gotten answered and and ask, but there are some more good questions coming in in the chat window.

We're going to try to get to those later. Thanks, Mike.

Thank you. So the next item is a remote assessment methodology. So getting more into the practical, practical concerns. And I first want to read several related safety assessment questions. So question here is to what extent, if any, can telemedicine technologies be utilized for safety assessments such as physical examinations, EKG is clinical laboratories, etc. and that telemedicine overrides receptacle inspection, not isolation of palpation. Remote is cages seem possible. Labs probably require sending a full botanist to a home for collection question.

B How would remote video assessments assess items that require the reader to actually touch the subjects such as Devaluate Cartwell cartwheeling and kind of piggybacking on that? So if, say, if a subject is at home and and has somebody else at home, I was just kind of thinking about logistics. Would it be acceptable if a like a family member, under the instruction of the writer said, like, move your love, move your loved one's arms and you let us know if you feel any sort of resistance or so it can come to kind of try to think about how people might try to do these sorts of assessments.

How are people addressing labs and so do assessments where drought has limited human safety data. And next. To what extent can position objective assessment that just fuels our measures? One joke our physical physician grab an assessment of condition, be made using virtual platforms. Such a space time. The second question is with major recent security concerns with some of the most popular video tours, no presume how is FDA considering a remote video to us and either any recommendations on approved technology solutions for video, audio or video recorded visits?

So I'd like to see we have it video from Beth CNN.com/Rick. She's been very involved in health technology and I want to see it. Would you have any comments about these questions?

Sure. Thank you. My is Beth Caskey from the Office of Medical Policy. Can you hear me okay?

Yes. Okay, great. So telemedicine that we are very fortunate that we are in an age where telemedicine is now an option, since we have limited ability to go into many different sites.

And realistically, a lot of these factors depend on what the study is and what the study outcomes that you're assessing. There are many things that you can do at home, but realistically, there are many things that are just limited because a physician does need to actually do the assessment. As Mike mentioned, there are many opportunities where our caregiver might be able to work with the patient and the physician through the video chat to be able to do the assessments and provide some feedback to that to the physician.

Let's see. Let's see what else the the lab and safety.

Yes, of course. The safety aspect is always most important.

And that is probably where this relies on a lot of safety monitoring from afar, which of a lot of that falls to the study staff. And most of these really do just end up being case by case basis. And then the last part,

the security concerns that the FDA is primary focus when it comes to security is the part 11 regulations require or guarding electronic record security. And a lot of these technologies may or may not fall within the scope of being part eleven compliance.

Some of the remotes video tools actually are regulated by senior each as medic medical devices. And I do believe they've published some guidance on this topic that is out there as well. So a lot of it really is just common sense and making the best of the situation that you can. And I actually want to ask Dr. Rawling. Could you give any comments about your experiences and how it reciter doing its physical assessments of these disorders, safety assessments that were previously done in the clinic?

So so as of now, most sponsors have had us do any visits that have safety assessments. They've actually had us do those still in the clinic. So we're bringing the patients in. But we we checked temperatures before they get in the band to come to the clinic. We don't put more than one passenger in the van at a time where socially distancing the patients when they come into the office. The doctors, when they're doing the exams are, you know, gloving up, putting that sign, things like that.

So we're taking all of the precautions that we can. But as of right now, none of the sponsors have had us do physical exams, blood drives and things like that from afar. May I sit here? I wanted to bring down the attention to everybody of everyone is when it comes to last clinical trials and the use of telemedicine.

I got the impression the second question A to D relates to just having the participant on one side and the investigator or the staff personnel on the other side. In reality, there are opportunities to expand that if there is a need to conduct physical examination. So to to actually touch the participant. There is the possibility of having a mobile study nurse or a local health care provider. And the telemedicine session is going to happen with the assistance of these individuals, along with the participant on one side and the investigator or detailed personnel on the other side.

This is to account the need for the physical or the physical examination that is not possible when it's just the patient or the participant, the investigator or the trial personnel on the other side. In all of these, the information needs to be done in a standardized fashion so that there is mitigation of variability in procedures. Thank you. Thank you. And and just reviewing some of the comments that are coming in in the chat window about this one when one team is that changes in assessment methodology training.

It will be very important for the Raiders per say investigators, as well as potentially for a patient or family and caregivers or others at home about just how things may be changed, changed during this period.

In the documentation, as we have been saying, is critical in all of this so that we can assess the data quality and the impact of the variability on on the assessment in particular. So this is rich. So I had a question for four FDA folks and including Mike. Is that for some of these technologies? It it seems that things need to be done substantially different. So there are ways of assessing extra of symptoms, tardive dyskinesia remotely. It's been done before.

Test retest reliability is pretty good. The standard validity studies have not been done. But it seems that in in the context of these trials that there is the opportunity to do the validity studies because you have the pre Cauvin time period.

And then the post called the time period when remote assessment of movements and disorders and movement symptoms would be collected. Would that be a strategy? That would be.

You know, acceptable. This is bad. I think that is very reasonable. And then as Mike and Isaac were just talking about it, it's the training and the kind of the planning and how that is executed.

But you're right, it is a good opportunity where you can draw the distinct lines and hopefully things will return to normal sometime in the future and you would have the ability to carry on and continue to make those comparisons. So you're right, it is a good opportunity. So I think here we're looking at why the most important one, the safety. We're looking at the inequality for that. Interestingly, we measure that based on study outcomes.

And. If you are measuring an endpoint with a specific assessment and you have to quantify that assessment because of College 19, that has to be documented. And we were discussing among ourselves the extent of the modification to that particular assessment. And still they consider that assessment or are we talking about the implementation of another assessment that is equivalent and that can essentially measure the same endpoint? All of these considerations need to be put in place, need to be documented. And there has to be a validation.

Last you were discussing. Because there will be changes and those changes have to be understand, understood by everyone.

Thank you. Well, Mike, I'll make a comment on this, and I'm sure it also have something to say as we do see these type of proposals coming through, that, you know, some items within a particular assessment need to be changed or there are doubt some from the point of view of the sponsor as to whether, you know, the instrument needs to be validated against a remote assessment. I think, you know, that there is no rule that that stands for everybody but reaching out to the reviewers decision.

I think where were the ayanda is so that we are aware of of the implications from from a clinical point of view. It's I think is the best strategy and we will apply. We discussed this internally and it's too bad that Elektra Papadopoulos not here with us. But there is that there will be a judgment applied in a case like a.

And I'm trying to find so elektro sent me some some of her kind of thoughts about these about these questions and and she and just her thoughts are that she doesn't anticipate asking first and foremost validation study or comparability study for changing the assessments. And and she but she says Daco kind of just use outrageous use judgment and be flexible during this period. She says that if a sponsor switches from impersonally mode assessment. But otherwise, essentially the same assessment. And they observe a robust effect even despite all the challenges.

She doesn't think from her clinical outcome assessment group they would ask for a formal validation study or comparability study and they would use their judgment. It's just that it's not not like a box tracking exercise, but just be reasonable about it.

And this is this is Tiffany. Just to to weigh in there, I think that one is just to piggyback on that and also to kind of respond to their comment in the chat about it at the end. Others are strident on the point that there should be no interest in me. I want to make it really clear that we're not being strident about that at all. This is a matter of trying to be more flexible, acknowledging this unprecedented circumstance that we're all in at this point in trying to do the best we can with the circumstances at hand.

Right. So if it's not safe to do an in-person interview, then, you know, we want you to put patient safety first ahead of, you know, anything else is there. And so when we ask you to do a remote assessment where possible. That's where our flexibility is coming in. In that, like Mike said, you know, the idea of having to go through and do a formal validation, comparing in-person to remote assessment and all that, realistically there just isn't time or or, you know, it's just not possible under the circumstances to to rebuild your entire plane while you're flying it.

So when that data comes in, it's going to be challenging for us to be sure, in terms of seeing what the effect of all of these shift are on the study outcome versus, you know, how much of it is in differences in terms of factors and differences in, you know, social stressors versus whatever. You know, it's again, that is why we're asking just to collect as much information as possible about the circumstances, the changes and circumstances.

But again, kind of do it a validation study or something like that, that it's too much for us to ask and we understand that. Thanks, Tiffany.

So I want to go over to Rich to go into the next day about technology access, which is also kind of a trust issue, but can have it can have impacts on changing the subject. Who might be able to provide the data during this period? Rich. Yeah, great.

Thanks, Mike. And before I get to that, I did just want to make a comment is that I know there's been a lot of questions in the in the in the chat as well as in some of the previous discussions about different technologies. And I I I really would urge everybody great caution when reading, you know, media articles about the dangers, because I think some of them are just in accurate. So, for instance, we had many concerns from participants that using Zoom today was problematic because it was going to get Zubov then and and that it was going to be bad for everybody and it was hackable and so forth.

And that's just not true. You know, Zoom has a as a platform that is much more secure than that. And this is gets done all the time. So I wanted to leave some room for a comment from FDA about that, because I think hearing from me people, my sluff it off and hearing from FDA, they wouldn't. And in fact, there have

been FDA recommendations along those lines about what are the acceptable security comply and HIPA compliant methodologies.

So I just leave that there. But I'll move on to some of these other issues, which I think are more pertinent to our discussion, which is that some CNS patients might not have access to the technologies. And what should we do to that about that? So the question one is in response to a previous question about the percentage of participants in CNS clinical trials who own devices that can be used from remote assessment such as iPods or smartphones. The question was raised about the challenge of knowing how to implement the platforms needed for video conferencing.

CNS trial subjects more commonly have high school education or less internet young and so may have less technological expertise. To relatedly, if patients do not have computers at their homes or residences, what other available options are there for remote assessments? And then third, in patients who are particularly low functioning. What recommendations would you make?

So I don't think that we're asking necessarily FDA for recommendations about what brand of product to use. But I think a consideration of how do you feel? How do you how are you going to look at data when some patients are going to have remote devices and others are not? Thank you. This is Bath, I can start and others can chime in. It is definitely a important consideration that some subjects will have availability to technology and others will not. And then their ability to use that technology.

So one thing the sites can do is write very explicit training procedures that these sites can then use to train any subjects because there is a large discrepancy in subjects ability to use the technology. So you do have to assume not no one can use it well and have the procedures in place to help them in terms of availability of technology between different subjects. That is a large concern. I've actually heard a lot that is a concern for a lot of this.

Remote teaching for schools and schools have had to be very creative somewhere, providing the technology. Some are providing Internet access through school buses are being left in various neighborhoods. So part of it does go back to the study staff to brainstorm what are some of the resources in that particular area that a subject might be able to take advantage of. Can I add one more thing, Mike? This is a Cardosa, right, from medical policy, and I've heard this concept actually from a European colleague recently.

Is that when you look at such software, we should look at them more as a baggage, not just as a single Blackcomb software. Especially when you think about it in the context of a clinical trial like you can provide AIDS training, AIDS along with the software, that can be something as simple as a link to a YouTube video. It goes all the way to having a chat, you know, to allow people to participate and understand the technology a little bit more.

So I think the context that the ecosystem persay of the tool itself have to be considered in its totality and not just in single software. Thank you. We have been saying for all these questions, everything goes on a case by case basis. And the same goes for these set of questions.

This is a studied, specific situation. The sponsors need to assess technologies and the participants and they know who may or may not have access to technology tap dances. We all would like to have a technology that is reliable that we can use with confidence, that we can use in the emergency situation and that we can continue to use in after agency situation as needed. We also want to have all participants accessing technology and information. The question for the sponsors and all the participants is can do if participants don't have the technology.

Can you come up with ways of providing that technology to the participants?

Those that don't have it. This is rich again. So in those cases, I can imagine that the implementation of that strategy may take a while. And in those cases, would you expect that studies would collect remote data as quickly as possible and then try to get the devices to those who don't have them? Well, it depends again. The study in question is the studies. The study is pretty thick.

The technology may be quicker not to implement something that will lead to us consultation with investigators and their technology providers. Just see the feasibility of implementing this in a reasonable fashion for the participants who may not have the technology.

Thank you. Mike, do you want to move on to the next the next segment on data analysis? I do think that that's particularly important. It's come up several times in our discussions about other issues. Is that how how will data be analyzed given this unusual honor? You know, I see some of the comments in the chat room from especially folks who were methodology minded. Many in this society or a statistically minded, they are saying, wait a second.

You know, you this is not a well-designed study. You're collecting data with one methodology over a period of time and then you're switching when other things in the world have changed. And so I think the data analytic approach for that really needs a lot of consideration. So, Mike, you want to take over it? Oh, sure. Yeah.

So be right. Before we get into this, I just want to turn over quickly to Dr. el-Zawahiri. We've had some comments related to safety and documentation.

Yeah. Thank you. Just very briefly, I know as we discussing the exploration of the technology we stress in our guidance and similar to what Tiffany was saying, that a careful risk assessments have to be done. You know, we have to consider not just the safety of the participants, but also we know, for example, with this stuff, mobile, nursing and local health care providers. And I think the risks to anybody who's interacting at this point within the clinical trial itself, we have to be careful about that.

The other just minor thing, too, when we discuss documentation, when we've discussed this over and over again in this call, when we say documentation is not just a symbol jolting down off of an incident per say, but also consider adding an explanation specific, especially when things are linked to call that kind of consider those who are going to read it and how they're going to link the issue you're discussing to little bit. If it's related to that, that's only thing.

Thank you. Secondly, can we also emphasized the importance of in all of these assessments or considerations to keep in mind, which is the paramount driver, the privacy of the participants when it comes to doing this remotely?

Yeah, definitely. That's a good point. So this is Mike Davis. So, yes, we can get into the analysis question. Looks like we've got about 15 minutes left on the car. And so the theme of this theme is that how should we analyze the data when the measurements are impacted by Coga €90 conditions? And the questions are simple, which additional statistical analysis should be conducted after database like to ensure the data collected by both methods can be combined with all your valid results.

Next, many psychiatric scarers were created an area where Face-To-Face ministration was the norm. There are some scales which have not been Daladier for administration by telephone or through other remote means. How should sponsors handle the analysis of assessments which had to be captured remotely during the pandemic with an instrument that has not been validated in these situations? Next, could one run a subpopulation analysis to investigate the impact of social stress? Do Kolbert's subpopulation player and now during the crisis time.

Next, I want to that we use remote versions of outcomes and ongoing trials for evaluation of patients during TOPPIN 19 will be requested to compare patient's characteristics with the aim to discard any type of difference between those patients with access to technology with those without a questionnaire. So I think that patients with a lower economical level might have less possibilities to have any type of evaluations, therefore more missing data. And finally, what date would you use for an analysis of Colberg data being impacted by kobrin 18?

It's very practical. And I assume, though, the question is asking, is there a certain date range that they should specify in the data sets to say this data is impacted by over 19 or not? So I think we were actually just abducted, elektro Papadopoulos was able to join the call. And I wanted to give her to make a few comments related to from her perspective, from the Clinical Outcomes Assessment staff about these questions, as well as some some comments about the updated guidance from yesterday.

Question Tribe specifically is about remote assessment, so.

Hi. Yes, and I'm sorry I couldn't have joined earlier, but it sounds that, you know, that that discussion has been very informative. And I wanted to just reiterate what, Mike, what you said earlier about, you know, the your comments about validation studies and comparability studies and, you know, our willingness to,

you know, not ask for all of these studies when when when really we need to approach this much more pragmatically. And so so I thought you stated it very well.

And the other thing I wanted to point out was yesterday was published an update to be covered, 19 clinical trials, guidance, which included a question and answer. Question number twelve. Which discusses remote assessments of interview based condition reported outcomes. And also it also refers to performance outcome assessments. And so a lot of people on this call, it was really very much a team effort to, you know, to put together some of these thoughts and a lot of the people on this call from FDA who had been involved with that.

So I urge you to to look at that. And in addition, there is some advice being put out by the Critical Path Institute, the Pierro Consortium of the Critical Path Institute on remote implementation and the patient reported outcome arena. And we can we're happy to stand the link after the after this call.

So what would ever FDA panels be able to comment on just this sort of analysis questions from a general approach? So we just in internal discussions, I know that by statistics group is actively thinking about these and working on it internally. And it's still a matter of matter of discussion. But what anybody from the FDA be able to provide any comments about analysis. Maybe I can just stick my neck out and maybe we'll just share a couple of my thoughts as Leonard Sax.

So I guess one of the things that actually occurred to me with an earlier question when we heard about the fact that you could make two parallel assessments, one taking into account period and one not. I mean, one of the things that's sort of fairly standard in analysis is to do sensitivity analysis where you can use a worst case scenario, where you use the extreme in one arm and the other extreme in the other arm, and then you balance it in various ways.

So I think there are ways in which we would probably be able to stress the data that we obtain to just make sure we're getting a robust conclusion on drug effect. But again, I'm not a statistician.

It's just something that is a tool that we often use examples. I think here I think, well, I'm not a statistician either. That's my disclaimer.

But we have discussed during this call today different options include the sensitivity analysis, including the subgroup analysis for a deep impact of GABA on the data per say at the end of the day. I think this is really a study specific. There is not a universal set of recommendations that we can come up with.

Each sponsor with this does this dish shaam investigators and the group look at this this past study.

We need to really assess this carefully because there are multiple ways of doing statistical analysis to understand the evaluation of closet within the study and the outcome of the study in itself. Hi, this is Rich Keith again. So soon, given that there are multiple ways to approach that. Should should folks who are running these trials, sponsors reach out with their plans and run them by for a response. I certainly know

that FDA doesn't like that, you know, tell tell folks what to do, but would rather look at what people are planning to do and then comment on whether it's acceptable or not.

So should folks develop their plans and, you know, with, you know, pre-specified analysis of how they're going to deal with the current situation and then run those plans by FDA representatives? And forgive me, but what would be the mechanism for for doing that?

If they should just is Mike Davis. So I want to quote it like I hope that the people on this call can hear the FDA is really kind of considering these issues and things like how exactly should you do the analysis plan are very, very complicated questions. And so on page 8 of the current FDA clinical trial, October 19 guidance, it states if changes in the protocol lead to amending data management and or statistical analysis plans, the sponsor should consider doing so in consultation with the applicable FDA review division.

Prior to locking the database, sponsor should address a statistic statistical analysis plan protocol deviation is related to covering 19 will be handled for the pre-specified analysis. That definitely recommends that sponsors be in touch with the review division and that would be the primary protocol to appropriate the regulatory project manager for a given application. And and as I reviewed in our division, we work very closely with our statistical colleagues on these sorts of questions.

Thank you. Mike, if I can make a comment, I I I've heard from sponser some questions related to how to address these changes in the context of the ICAC 9 addendum and then to the same line of the response that you just gave. You know, we we are little discussions internally. We were well aware that there are Intercrime events that change in Modibo administrations about coups as well as missing data that will have to be handled. However, we don't think it would be irresponsible from our side to suggest one way of doing this or another at this stage.

One thing that would be very useful for both of us would be to start as soon as possible and as soon as your death. It's become a complete, in fact sharing data and proposals with us. So it will be a learning from both sides. And now we absolutely open to to your proposal and your strategies. Think 17A. And I look at the clock, looks like we have about four minutes left. I want to before we kind of wrap things up from the work of God.

I want to give Dr. Khair ElZarrad opportunity if he had any kind of final remarks or comments, his thoughts based on the call. Thank you, Mike, and again, appreciate you, including us in the bruschetta, activity and to for having this dialogue. You know, Stephanie alluded to again, is this really all of us moving into this territory and trying to provide as much understanding of flexibility together and trying to see how this is going to impact us moving forward as well?

We were all listening and we're all communicating, as as Mike mentioned, the divisions open. We have the clinical trial mailbox that we will come. Any comments on. And we said we put the right people to trying to do our best and asking those questions. So we will come those to continue this dialogue. And

beyond that, please keep your eyes on our guidance. And we're we're trying to make sure we're updating them accordingly to the needs of our stakeholders.

Thank you all again for this.

Thank you. I want to turn it back over to Rich.

Thanks, Mike. And we really appreciate everybody's engagement in this process. First, I want to thank the ISCTM and the Mary Bea, Linda and Carlotta of ISCTM certainly thank all of the folks from FDA. They're incredibly busy dealing with this crisis, just like all of us are. And to take the time, an hour and a half, actually two hours, because we we've got together ahead of time, take two hours out of their busy day.

Is it just shows how devoted they are to to addressing these health concerns and to try to get all of us to be a bit able to do clinical trials as best we can under the circumstances. Thank you very much. Thanks to Bob, who is left and thanks to Dave Watling for participating. And thanks to everybody who has engaged with us. The comments have been tremendous. Lot of the ideas that we read are really a testament to the collaborative nature of ICBM and to the great spirit of people to do these things.

So thanks to everybody for for joining. I think that we we did talk about the potential of having a later call to get the perspective of European regulators as well, to determine if there are some different ideas. We also recognize, you know, my Mike and I have talked about the fact that. It's an evolving, emerging situation as well as covered comes and hopefully goes. And so we recognize that we may need to have another one of these in in the short term as well as maybe in the medium term as well.

Any any more comments from you, Mike, or shall we adjourn? No.

I guess to turn over to the panelists. Tiffany, but I also have a final remarks. No, nothing for me other than, you know, again, as everyone else. I'd like to thank our ISCTM that you guys always do an amazing job. So thank you.