Highlights and Summary of Part 3 Webinar:

Evaluating Study Status and Leveraging Data Monitoring Committees to Make Study Decisions

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As part of an ongoing series, WCG hosted an April 1 webinar to address the coronavirus-related challenges facing the clinical trial industry.

Our 2 featured Speakers discussed modifying ongoing clinical trials response to COVID-19. They addressed an array of subjects, including safety, the role of DMCs/DSMBs, and the lasting impact of COVID-19 on clinical trials. What follows is a summary of their remarks.

Featured speakers:

1 **Jonathan Seltzer, MD, MBA, MA, FACC**
Executive Vice President, WCG &
President, WCG ACI Clinical

2 **Janet Wittes, PhD,**
Founder and President,
WCG Statistics Collaborative

Lindsay McNair, MD, MPH, MSB, *Chief Medical Officer, WCG,* moderated

We have summarized key points and observations from each speaker, followed by questions addressed during the Q&A portion. You can find links to this webinar and an array of COVID-19 resources on our new **WCG Insights Program page.**

Seltzer: Novel, but not Unprecedented

Sites are being closed. Trials are being delayed. Some investigational products are harder to come by. And we're seeing many, many protocol deviations. These are, without a doubt, crazy times. But when we step back and think about it, a lot of this has happened before. We've had temporary halts on trials, problems enrolling patients, lack of access to investigational drugs, etc.

Right now, our first goal is to keep study participants, study sets and study personnel safe. That's above all, and if it means that we can't do clinical research for a month or two because it's unsafe, that's fine. We've all faced that before.

We need to look at the studies that we're doing. If we haven't got all the data, how do we know whether it's worthwhile to collect it? Should we put people at risk to get that data to keep the trial live? Are there other ways to get the same data?

Different types of trials require different types of solutions. Should we shut down all clinical trials? No. Should we keep them all going? No. So much depends on the type of trial.

Phase I safety-only trials: Typically, they have a small sample size and can be ramped up and completed quickly--sometimes in a matter of days. So maybe if you're in an environment where you don't have COVID-19 yet or you are way past the peak, you can probably conduct phase I trials. But that's not absolute; for instance, it may not be the case in phase I oncology trials.

Symptomatic endpoints: These studies look at things like pain, fatigue, anxiety. You may want to continue that trial, or you may feel it's not that important to go all out to finish it.

Disease-modifying endpoints: How much will we interrupt their lifestyle were we to interrupt the clinical trial?

Curative endpoints: These include gene therapy trials, device trials, etc. Will you need a different strategy there?

What is the most important safety information?

Severe events, serious adverse events (SAEs, expected and unexpected) and adverse events (AEs) of special interest. AEs of special interest may be trial-specific, patient-specific or even COVID-specific. There may be special interest events: Maybe a mild elevation of liver symptoms is not terribly important in the run-of-the-mill trial, but for specific trials or specific patients that may be very important to capture; the trial sponsor should be able to define AEs of special interest.

Remote safety evaluations: Many of these safety evaluations can be done via phone, video, etc., but let your IRB know. Make sure you're trying to capture things you can actually capture: If you're evaluating a rash, it's very helpful to do that on video rather than just asking a patient on a telephone.

Common questions about COVID-19 and AEs/SAEs

- A participant is positive for COVID-19 but is asymptomatic--is this an AE? *Yes.*
- A participant is positive for COVID-19 and has mild to moderate symptoms but is not hospitalized--is this an AE or an SAE? *It is an AE.*
- A participant tests positive for COVID-19 and is hospitalized. Is this an SAE? *Yes, this is an SAE and the patient should be followed until resolution. If the patient dies, that is an SAE, whether the patient was hospitalized or not.*

Wittes: Looking at the Axes

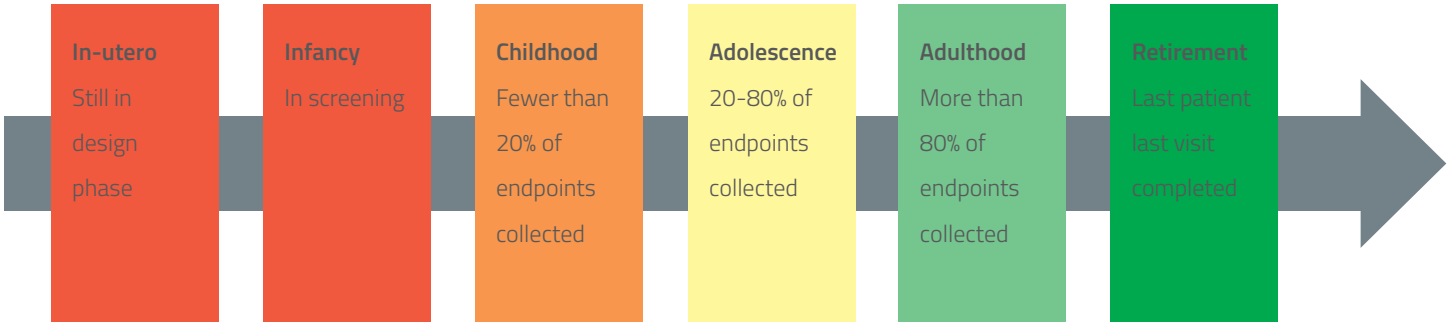
"My first message to all of you is of course be safe. [...] You and your entire team must think about how to change your behavior and how to change the trials in the face of this disease."

Think of the trial as having a lifespan. Each has an in-utero period (the design phase), an infancy (screening phase), childhood (fewer than 20% of endpoints collected), adolescence (when 20% to 80% of the information has been collected), adulthood (more than 80% collected) and retirement (completion of last patient's last visit).

If your trial is in-utero or in its infancy, this probably is not the time to start recruiting. Similarly, if it's in retirement, it's probably time to stop the trial. Just make sure you have those data that are central to the interpretation of the study--safety, efficacy, primary endpoints and important secondary endpoints.

What about adolescence (20%-80%)? It depends on the nature of a particular trial. Among the questions to consider:

- Where is the trial taking place?
- Does it require a visit (e.g., imaging studies)?
- What's the design?



Here, you want to consider three other axes other than time:

- **Type of patient:** Are these basically healthy patients who don't have to be in the study? You can pause that study easily--at least compared to other studies.
- **Type of drug:** Is it a well-studied drug already given to thousands of people? If it's a new chemical entity, you may have to think very hard about the consequences of discontinuing a trial.
- **Purpose of the trial:** Is it symptomatic? Is it curative?

Seltzer: Deciding Whether to Modify the Trial

Balance benefits, risks: Consider benefits of remaining in the trial. Is it curative or disease-modifying? Weigh that against the risks. You don't want to send people home to die of heart failure vs. taking a 10%-20% risk of symptomatic COVID.

If the trial goes on, think about how to minimize risk.

Prioritize Safety-Data Collection

What needs to be collected? What doesn't?

- Necessary data: Continue collecting, as usual, SAEs and AEs of special interest as specified in the protocol. Collect COVID-19-specific AEs of special interest.
- What can you collect less frequently? Possibly vitals and lab data as well as some AEs. If you have x-rays on the schedule think about whether you really need them.
- What can you do at home? For example, can you get an ECG from home? An Apple watch may be good enough to monitor arrhythmia.

These decisions are very trial-specific.

Maintaining trial integrity: If you can't use the data from the trial, you've wasted everybody's time. So, we want to figure out how we can maintain trial integrity by maybe taking our foot off the gas pedal of gathering so much data.

But this must be handled, documented and reported correctly.

Wittes: Handling the Statistical Analysis Plan

What we have been talking about thus far are operational changes to the trial. And some of these are major changes, talking about changing the way we collect the data, changing how much data we collect, maybe even changing who is collecting the data. Maybe changing the timing of the primary endpoint, all kinds of things we may be changing. And they have direct implications for a statistical analysis.

Talk to each other, and don't forget the statistician: We must make sure that the people who are making these operational changes, the people who are making the clinical changes, the people who are making the changes in the database, and the statisticians working on the statistical analysis plan, are really talking to each other.

Very often there's this unfortunate separation between operations on the one hand and statistics on the other.

Read your statistical analysis plan: This applies not only to statisticians. The operations people, the clinical people, the database people--everybody involved in the trial--needs to understand what's in that statistical plan. You need to understand how the operational changes arising from COVID-19 affect that plan. Those could be very, very important.

For example: We have a study that is taking measurements. The outcome is at week 24. But the patients come in at week 20 and 22 and 24. The operations people said, "We can't make people keep on coming in. They're only going to come in for one of those." The statistical team said, "Okay, we will define 20 and 22 and 24 as the same point. We'll call it point 24." That's an example of the interplay between the operational changes and the statistical changes.

It's extremely important to explain in that analysis plan why the changes are being made: If regulators see changes that seem arbitrary or unexplained, it's very difficult to defend. The sensitivity analysis must be thoughtfully redesigned, because we now have studies with a pre-COVID-19 part, a part that's during COVID-19, and perhaps a post-COVID-19 part.

Make plans for missing data: The typical missing-data analyses, which are central to lots of plans, are now going to be different. They must be thought out very carefully and, again, discussed with the entire team.

SPAs during COVID-19: A special protocol assessment (SPA) is a tacit agreement between the FDA and the sponsor that if the approved protocol and statistical analysis plan are followed precisely and the product shows benefit, the product will be approved. Science can change, of course, but basically, it's a conditional compact.

But what happens to the SPA when COVID-19 leads to protocol changes?

One approach is to ignore the SPA and say, "I will just do my study the best way I can. I understand I'm violating the SPA, but I can't preserve the SPA given the changes I have to make."

The other way is to think about the crucial parts of that protocol and the statistical plan. Then write a supplement to the statistical analysis plan.

- Beware of changing the primary outcome or the primary method of analysis
- Carefully justify changes or additions you are making

Seltzer: Who Decides on–or Recommends–Changes?

Three entities can recommend changes:

- **The institution/site:** They may recommend that it's unsafe or they can't support clinical trials.
- **The study sponsor:** They run the trial, they're in charge of them, they have the legal responsibility. So ultimately, it's all up to them.
- **The DMC (aka DMSB):** If you have a data monitoring committee (data safety monitoring board) consider consulting it. Both the FDA and EMA allow for consultation with DMCs about study modification.

Wittes on DMCs

Remember: In phase III trials, DMCs are typically unblinded. They may have already viewed efficacy data. **So, avoid giving them responsibilities that will render the trial invalid.** It may be tempting to go to them and ask, "What should we do with this trial?" An open-ended question like that could affect the validity of the trial.

You may form a DMC if the trial does not have one or expand the scope of a current DMC, but that DMC must follow standard procedures. But, don't be too tempted to give them too much responsibility, because they must follow standard procedures if you want to preserve the integrity of the trial.

Practical Q/A for Working with a DMC

Questions for Seltzer

Jonathan Seltzer, MD, MBA, MA, FACC
Executive Vice President, WCG &
President, WCG ACI Clinical

&

Questions for Wittes

Janet Wittes, PhD,
Founder and President,
WCG Statistics Collaborative

Q **Who should initiate DMC/sponsor questions?**

A **Seltzer and Wittes:** The sponsor

Q **What types of questions can the DMC help answer?**

A **Wittes:**
- Help to define AEs of special interest
- Perform new interim analyses (with sponsor guidance), assuming the DMC has the necessary expertise; they may have the ability to look for futility or for overwhelming benefit
- Help to define impact of COVID-19

Seltzer: EMA on DMCs

The European regulatory framework is less well-funded than the FDA. So, they have a little more dependence on outside committees and were very specific in their guidelines about things that a DMC may recommend.

- **How to re-start usual trial operations** and additional measures when completing the trial after the pandemic (e.g., validation of outcomes that were measured differently).
- **The need to adjust the trial sample size** and additional analyses (to be included in the statistical analysis plan) to investigate the impact of COVID-19 to understand the treatment effect as estimated in the trial.
- **Proposals to deal with any identified potential sources of bias** such as missing values, newly identified intercurrent events or other unforeseeable required changes to trial elements.

Seltzer and Wittes: Final Thoughts

Study participants and study staff must be kept safe. If studies haven't started or are almost finished, you may want to consider terminating them--or at least any further patient visits.

To ensure safety, changes will be needed in most trials, but the trial must be interpretable at its end. Strategies to ensure interpretability will differ by type and duration of trial, the patients and test product.

We believe if your studies haven't started or are almost finished, you should strongly consider terminating them, terminating any further patient visits. You might want to do data collection, but the patient visits should probably terminate if you're in a COVID-rich area.

Audience Questions

Q **You talked about study modifications as a result of COVID. Could you give us an example of a decision that you've made regarding study modification during the pandemic so far?**

A **Seltzer:** I'll use an example of a strongly disease-modifying therapy. We were looking at two global trials. One had barely started, and we recommended a complete hold on any enrollment until the COVID goes past its peak in Europe, and then start and begin the trial there.

The other one was ongoing and had quite a few patients in it. We suggested a complete hold in Europe. We suggested that in the U.S., where they were able to get home help to do study visits to do that, and collection of data only through telephone in Europe. And we defined for the sponsor the key pieces of safety information that we felt were essential to maintain the integrity of the trial.

Q **Everybody is thinking about how to modify study visits to decrease the number of in-person visits because of COVID-19. But what about in the future when we think about this for flu season, for patients who are at high risk of flu? Are we going to take the same precautions then that we are now taking around COVID?**

A **Seltzer:** In the past, people have talked about "trials without walls" and doing things like we're doing now. I think we'll have a lot of data from this period: We'll see what works and what doesn't work. The silver lining might be that we'll develop some best practices for future clinical trials. We all know that one of the reasons people don't enroll in clinical trials is the burden of coming in so much. So we may be able to actually improve the entire process with what we learned through distances and additionally protecting the safety of our patients by keeping them out of hotbeds of infection.

Wittes: I'd like to echo the last few things that Jonathan said. If we learn to do trials in a simpler way, less visit-intensive, less data-intensive, that would be really good. The other thing we could do is, when we write a protocol, actually think up front about what people do, not only in the case of pandemics,

but volcanoes and earthquakes and tornadoes--a section on what centers should do when some of these things happen. So a combination of protocols that identify that these may happen and what centers should do. And finally, the whole clinical trial community should do some self-reflection: Are we collecting too much data and are we demanding too much of our participants?

Q **This is a two-part question. First, if a visit is done by telephone instead of in-person, and some of the procedures that were scheduled for that visit could not be completed (e.g., specific eye exams or physical tests), would that be considered a missing visit or missing data?**

A **Wittes:** I do not consider that a missing visit. That's a visit with incomplete data but incomplete for structural reasons that are operational. That's an important piece that needs to be collected. For instance: If somebody doesn't have a slit-lamp exam because he doesn't want one, that's completely different from not having one because the visit is done by telephone. I think it's really important to modify the databases in such a way that you can identify what part of the missing data relates to operational issues due to COVID-19, and what part of it was volitional because the patient wouldn't do the exam or something like that. Because in analyzing data, one type of missing information is informative and the other kind is an act of God and therefore not informative in the same way.

Q **The second part is this: If a study plan had already outlined its processes for dealing with missing data or partial data, can they leverage those existing plans to deal with missing data because of COVID-19, or does that need to be modified because this is a different situation?**

A **Wittes:** I think it should be modified, or at least one should think about how to modify it. That's because when statisticians deal with missing data, we're typically very conservative and assume that data are not missing at random. We assume the data is missing for some reason that has to do with the patient, or the treatment. The analysis is a little punitive there because it assumes that things may very well be worse than what they seem.

Seltzer: That's a great suggestion. In fact, the best practice in general for clinical trials. I would say--as someone who does a fair amount of safety monitoring--we do the same thing. For instance, if somebody has a missing visit, we'll often assume maybe they don't feel well, maybe they're having adverse events--not because they missed the bus. We tend to look at things very conservatively and in monitoring. I think that we should consider the regulators might also look at it that way in the future. I think it's a good habit to continue after this pandemic passes.

Appendix:

The **FDA identified** key factors to consider in modifying a trial, which Dr. Seltzer shared with the webinar.

- Assessing whether the limitations imposed by the COVID-19 pandemic on protocol implementation pose new safety risks to trial participants, and whether it is feasible to mitigate these risks by amending study processes and/or procedures.

- Assessing the continued availability of the clinical investigator/sub-investigators to provide oversight of the trial, and properly assess and manage safety issues that may emerge.

- Assessing whether there will be sufficient clinical trial support staff given the evolving COVID-19 situation and its impact on staff availability. Are there appropriately trained staff that could be available to handle the expected tasks? Is there adequate equipment and materials for clinical trial support staff?

- Assessing whether clinical investigator sites will remain open to trial participants for required in-person assessments or whether the clinical investigator has the ability to provide required in-person assessments at an acceptable alternate location(s), or whether such protocol-specified in-person assessments can instead be conducted virtually.

- Assessing the continued availability of clinical trial supplies and continued operations of vendors, especially related to supply of the investigational product and/or to clinical trial supplies that are essential to maintaining appropriate safety monitoring or other key trial procedures. This should include consideration of product stability (shelf life) if the treatment schedule is revised, or if the clinical site is unable to properly store the product for the needed duration.

- Assessing the continued availability of, and support for, information technology systems and any other technological tools that are needed to support the trial. Are current contingency plans adequate for the types of disruptions that might be anticipated? What other plans can be put in place to minimize any potential disruptions?

- Assessing whether there will be continued operations of, and adequate communications with, IRB, IEC and Data Monitoring Committee staff, if applicable, to support trial needs.

- Assessing whether it is feasible to conduct the trial in light of any COVID-19 public health measures implemented by Federal and State authorities to control the virus.