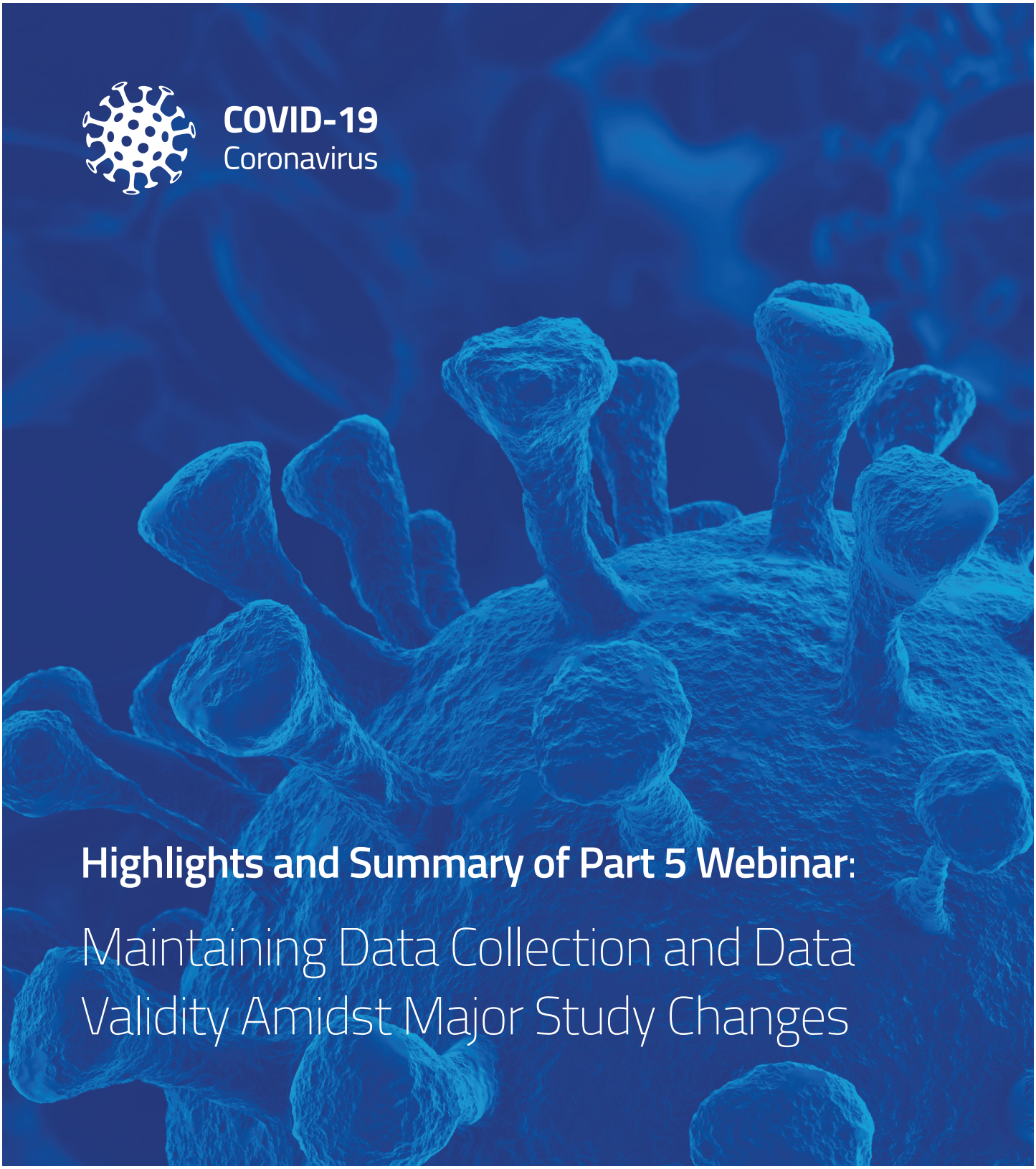


Highlights and Summary of Part 5 Webinar:

Maintaining Data Collection and Data Validity Amidst Major Study Changes

wcg™

What do we need to think about in terms of trying to continue important research, assess the validity of endpoints and what COVID-19 might do to our ability to draw study conclusions from the data we can collect?

That's the focus of a recent WCG webinar. It's the fifth in a series of WCG webinars that address the coronavirus-related challenges facing the clinical trial industry.

The webinar, held April 15, featured three expert speakers:

1. **Bernadette D'Souza, MD**
   Scientific Advisor & Consultant, Evolution Research Group

2. **Mark G.A. Opler, PhD, MPH**
   Chief Research Officer, WCG MedAvante-ProPhase

3. **Nathaniel Katz, MD, MS**
   Chief Science Officer, WCG Analgesic Solutions

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

You can find links to this webinar and an array of COVID-19 resources on our new **WCG Insights Program page.**

The ART of Managing Change at the Site Level

1 **Bernadette D'Souza, MD**
Scientific Advisor & Consultant,
Evolution Research Group

"The *ART* of Managing Change" refers to three necessary attributes to successfully navigate change: "A" for adaptability, "R" for resilience and "T" for trust. Adaptability and resilience are relatively clear. Trust refers to trust in oneself as well as all the other decision-making stakeholders.

Organizations have SOPs or crisis management plans for unpredictable catastrophes. However, no existing SOP can begin to help us through the disruption that COVID-19 has caused. This disruption is hard to quantify, and it's evident in all aspect of a clinical trial, from enrollment to supply chain to data collection and data analysis.

Amid the challenges and the chaos, three basic issues emerge.

1. **The safety of our staff and our research participants.** How do we provide that? How do we implement CDC guidelines?
2. **Best practices in uncertain times.** How do we gather and deliver accurate and validated data to our sponsors?
3. **Preparation for the future.** How will we be ready for longer-term changes in the design and conduct of clinical trials?

Let's break down these issues with challenges we've likely all experienced:

Screening for COVID-19: Someone from the site calls participants the day before a visit; if they have any respiratory symptoms or illness, we ask them to stay home. Same goes for the staff. "If you're sick, stay home." Gatekeepers to the clinic screen all patients, staff and potential visitors (of whom there are almost none). COVID testing will have to wait on the availability of the tests and CDC guidance.

- **Sterilization:** Evolution Research Group (ERG) follows diligent sterilization protocols before and after subject visits, and strictly enforces frequent hand washing.
- **No travel:** Meetings are remote, using Microsoft Teams and other technology.
- **PPE use** is required. In anticipation of mask shortages, staff and their families have made masks ahead of time.
- **Patient transportation** is provided to the site, minimizing exposure.

The need for frequent communication: Persistent and frequent communications keep sponsors and CROs aware of ongoing strategies for safety, current

capabilities and what sites are doing to keep studies going. It also allows sites to seek guidance as necessary.

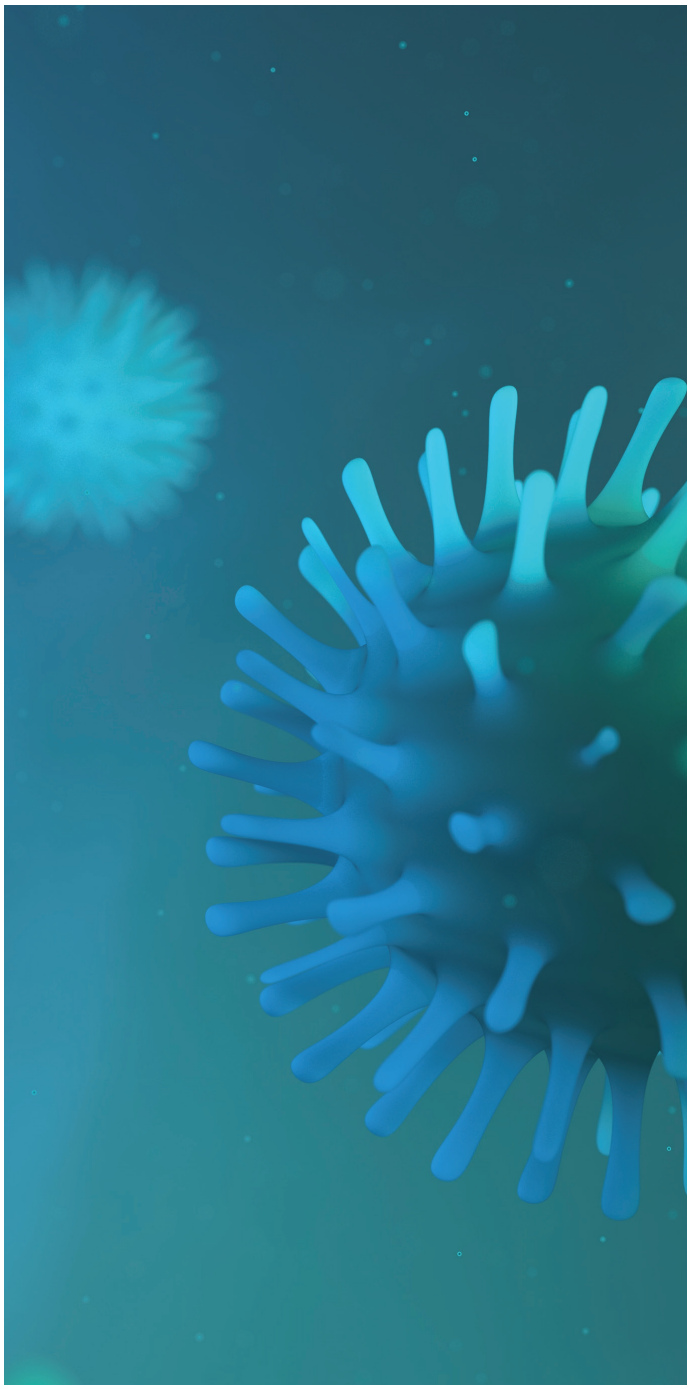
Because of the importance of keeping sponsors and CROs apprised of changes–especially missed data points and protocol deviations–many sites continuously stress the importance of documentation to the staff.

Remote assessments: FDA guidance drives the strategy for patients who cannot be on site. Questions remain, however: "At a site level, we would appreciate more guidance on acceptable platforms. Our concern is that the available things like Zoom, Skype, Google, etc., though used, may not be HIPAA-compliant, and if they're not, will our data be rendered invalid?" And what we know is: more guidance is needed.

Investigational product (IP): The chain of custody and accountability for the IP continues to lie with the PI. Based on the new FDA Guidance on home visits, "We all prepared to deliver IP, investigational product, as needed and have done that a few times."

Patients appear to be taking their medicine: On the CMS Summit call, a speaker presented comparison data of pre-COVID compliance rates and the six-week, post-COVID compliance rate. Even though there was a slight dip in the compliance, it came back to within acceptable range.

Facilitating the visit: We're assisting in remote monitoring. ERG has established a clear, remote monitoring visit policy to streamline and track this so the visits can be scheduled on the calendar and documents can be uploaded via a SharePoint online folder.



So Close, Yet So Far: Remote Assessment in the Era of COVID-19

2

Mark G.A. Opler, PhD, MPH
Chief Research Officer,
WCG MedAvante-ProPhase

How do we continue to keep momentum to keep our studies moving forward in an era of social distancing and reduced social mobility? How do we keep data flowing in? How do we maintain our obligation to our patients to continue to evaluate whether they continue to experience any changes in efficacy or safety from treatment assignment?

This high-level overview of strategies that we've worked on with various sponsors and other organizations during the early parts of this crisis may provide a blueprint of sorts.

If study participants or study staff cannot make it to the site, how do we continue to evaluate safety and efficacy? How do we collect data and preserve the study?

1. **Identify which endpoints** are accessible via remote methods.
2. **Select the right modality** to ensure collection is adequate for participants and staff. Can some endpoints be evaluated through clinical interview by telephone? Do other endpoints require a video connection in order to examine them? What's feasible and practical? It may be desirable to have high-definition, high-bandwidth video conferencing capabilities, but that's probably unrealistic if we're tethered to the patient by a smartphone. Part of this process is finding that right balance between the ideal and the practical.
3. **Obtain sources** to establish methodology; manualize procedures for remote use.

Once we have determined which endpoints we're going to go after and which modalities we're going to use to collect them, how do we then adapt them to this new world?

Part of that process involves manualizing procedures, coming up with a standard set of procedures: Create as much certainty as we can in a very uncertain time.

We must ensure that, when an investigator is performing remote clinical assessments, they have a very clear path for doing so and they know the steps and the processes that are involved as they begin that journey.

How do we ensure the validity of our outcome measures if we're evaluating them remotely instead of through traditional in-person methods? Are your outcome measures still valid if you go remote?

1. **Review the literature.** "You'll be amazed at the amount, sometimes, of prior work that's gone into trying to address these questions." Many of these questions have been addressed to some degree and guidance can be found in the literature.
2. **Consider conducting a "nested validity study."** Think of this as a sub-study within a trial to analyze the data and evaluate the extent to which it behaves or resembles the data collected through more traditional methods. A true validity study will compare side by side two methods of evaluation, often on the same patient. These tend to be small, carefully designed and very analytically rich studies. We may be forced to adapt some of these approaches, but it is something that I would do if my study were at risk.
3. **Keep a close eye on data.** It's more vital than ever to closely monitor the quality of the data that's being collected, and to evaluate it in as near to real time as possible. Look for anything that seems out of the ordinary. "If it were my study, I'd want to know about it soon so that I could make, shall we say, command decisions about how to proceed."

Another question that has come up a lot: Will regulatory agencies accept data that's been collected remotely as we move from in-person to telephone or video? Is this data still acceptable to regulatory agencies? Is there any precedent?

There *is* precedent. This is one recent example (there are several others): In 2019 the FDA approved a rapid-acting antidepressant, esketamine, based on data collected by telephone.

Case Example: Rapid Pivot to Remote Evaluation

An ongoing global phase 2 study needed to continue to collect data on enrolled patients in the midst of social distancing and shelter in place. The sponsor was about halfway through enrollment and many patients were already active in the study.

The sponsor decided to collect the primary, and least their key secondary, endpoints–and as many safety endpoints as possible remotely.

They followed the decision-making path outlined above and soon determined they needed to use video to capture and collect a primary outcome and some of the safety outcomes: Clinicians needed to be able to observe physical signs and symptoms.

They then asked the questions that many of you have asked: What level of security, what level of regulatory compliance are required?

Pandemic notwithstanding, this was a global trial and they wanted no doubt when it came to the question, "Is this data going to meet regulatory standards?"

They then chose a secure and compliant video solution, one that allowed clinicians to connect to patients, on the smart phones that they owned, in their homes. They deployed it in two weeks.

"I have to say, I was very impressed with both the decision-making process they went through and the rapidity with which they actually implemented this

solution once the decision had been made. Examples like this give me a certain amount of hope that we can continue to keep our studies moving forward, that there are both technology and process solutions that can be conducted, and that we can keep doing what we need to do to meet the needs of our studies and our patients."

Interpretation of Data from Clinical Trials Performed in a Changing World

3

Nathaniel Katz, MD, MS
Chief Science Officer,
WCG Analgesic Solutions

What we're going through now is unprecedented in its magnitude, but it's not at all uncommon for clinical trials to be affected by things that happen in the world. Many times, things that happen in the real world have an impact on the ability to collect valid data and on interpreting the results. So there is some experience with this, although, of course, this is the more extreme example.

Key issues:

1. **How to ensure that the performance of outcome measures is stable during secular change. (As used here, "secular" refers to events and changes that happen in the real world while we're doing our clinical trial.)**
2. **How to determine whether a secular event affected the integrity of the trial data.**
3. **If they did have an impact, how do you interpret the results of a trial?**

Validity/Performance of Your Measures

We know how to evaluate the validity of measures and their performance. Certain standard elements go into measure validation. The FDA Patient Reported Outcome Measure Guidance of 2009 provides a thorough review; that's where the examples below come from.

Performance Criterion	How to Evaluate	Example
Test-retest reliability	Monitor the test-retest reliability of critical outcome measures over time	Correlation between screening and randomization values of a depression scale time, should be around 0.8
Temporal consistency	Measure the variability of a measure over time	Daily pain variability should be around 0.7
Internal reliability of multi-item measures	Cronbach's alpha or other measure of inter-item correlations	The Cronbach's alpha of the WOMAC Osteoarthritis questionnaire over time
Relationships between measures	Concordance of two measures of the same symptom at the same time Relationship between two correlated measures	Pain on a 0-10 scale vs. pain on the WOMAC OA pain scale Pain and Physical function

You can use these same techniques during an ongoing clinical trial. You can look to see whether the performance of a particular measure is changing during your studies. If it is, you can address it without unblinding your data or introducing new biases.

Ongoing Quality Control

Example: Aberrant intra-scale reliability at a site indicative of poor measure performance

Many sponsors these days are using what are called risk- based-monitoring techniques or central-statistical monitoring techniques, and we were very heavily involved with that ourselves.

You can set up those same central-statistical monitoring techniques to monitor many of those different aspects of measuring performance mentioned earlier.

Let's take one measure at one site in a multicenter study. The WOMAC osteoarthritis scale is a 24-item measure.

Looking at the variability of all the items in this scale, we discovered significant episodes of zero variability. That means that at this particular site, some patients filled out the same number or the same answer for all 24 items on the scale. You know that that never happens with valid data, so you can monitor that over time.

Put another way, a bunch of patients over several weeks rushed through the questionnaire and put the same answer down for each question.

We contacted the site, retrained the staff, made sure they knew how important it was to interact with their patients and explain how to complete this questionnaire. Suddenly this behavior disappeared.

So this is just one way you could look at variability within a multi-item scale–which you would normally look at when you were developing the scale in the first place–for ongoing quality control.

Example: *Discordance between two similar measures monitored over time in two sites*

Another thing that we commonly look at when we're doing central-statistical monitoring is discordance between two similar measures that you can monitor over time.

What does that mean?

Let's say, for example, you're doing a depression study, and you have two different measures of depression that you're capturing at roughly the same time. If the patient seems to be very depressed on one measure and not depressed at all on the other measure, that's a problem. We call that "discordance."

This example looks at two different sites in a multicenter clinical trial being monitored for discordance. At the beginning, both sites were very highly discordant.

Over time, with some attention and retraining, that discordance improved to the point that "the data that we're getting from these sites is just exactly how we want it."

Discordance or concordance between scales can be monitored in real time to make sure that nothing weird is happening in terms of collecting valid data from sites. It can also be done on an individual level, a subject level, a regional level or a trial level as well.

These same techniques can be used to see if this particular perturbation–COVID-19 pandemic–is having a noticeable effect. If it is, we can respond to it in the normal way, even though these are abnormal times.

Analyses to Evaluate the Impact of a Secular Event on Study Results

You've done your study, you've got your database, and of course the question is going to arise: Did this massive perturbation that happened in the middle of my trial affect my result? You can assess that through a series of questions.

1. **Was the study positive or negative?** If the study was positive, then you're in a much different situation than if it were negative. But in either case, go to the next question…

2. **Did the between-group difference vary in relation to secular events?** Let's take the difference between treatment and placebo.
   a. Up to the point that this perturbation began, what were the results?
   b. As we collected data during the perturbation, did that change the between-group difference that was observed?
   c. What was it at the end?

These questions–which can be asked at the site level as well–enable us to get a sense for whether the treatment effect was robust.

That's why it's important for sites to collect data on how they and their patients are being affected in real time by these events, because that could potentially be used later on to answer this question, of whether these events affected study results on a site-by-site level. The following three questions are along those same lines…

3. **Did the characteristics of the study population vary in relation to secular events?**

4. **Did baseline symptom intensity change in relation to secular events?**

5. **Were the study results "robust" to the secular change?**

Recommendations and Considerations

Here are some concluding thoughts about how sponsors and CROs could use their existing infrastructures and techniques to prepare themselves for the accountability that will come later, when they are analyzing this data.

1. **Get the data.** People will be starting to get data in different ways–telephone interviews, home assessments, videos, audio recordings. It's much better to get the data than to not get it. Missing data is the worst possible situation to be in. "Better to get data and figure out later whether it's valid than to not have the data at all, in my opinion."

2. **Realign your central-statistical monitoring (CSM) techniques** so you can monitor for any changes in the performance of critical assessments. CSM techniques can be re-tooled to monitor whether the shifting modalities of administration of assessments are associated with changes in the performance of those assessments. If they are, you can respond as you would under normal circumstances.

3. **Be prepared to remediate** performance issues through training, re-training or other means.

4. **Assess sites.** Use these CSM techniques to determine whether some sites should be shut down, should have additional support, etc. Some sites may not be able to withstand the buffeting of these COVID-19-related events.

5. **Consider interim analyses** to determine whether your study really needs to continue. It may be positive already, or it may demonstrate futility of ever being positive.

6. **Begin to plan analyses** to evaluate whether treatment effects were impacted by these secular events. Prespecified analyses will be more persuasive in the end: "I think it's good to sit someone in a corner and have them begin to think about what those analyses will be down the road, so that we can be sure we're collecting the data now even if it's not currently in a protocol."

Audience Questions

Note: Many of the questions listeners submitted are already answered on our **COVID-19 FAQs page.**

Questions for McNair	**Lindsay McNair, MD, MPH, MSB** *Chief Medical Officer, WCG*
Questions for D'Souza	**Bernadette D'Souza, MD** *Scientific Advisor & Consultant, Evolution Research Group*
Questions for Opler	**Mark G.A. Opler, PhD, MPH** *Chief Research Officer, WCG MedAvante-ProPhase*
Questions for Katz	**Nathaniel Katz, MD, MS** *Chief Science Officer, WCG Analgesic Solutions*

Q **Several questions came in about whether protocol amendments are needed when onsite studies shift to remote visits**

A **McNair:** Yes: Those need to be submitted as changes in research. Our **COVID-19 Research Center** has information about how to submit those changes as well as FDA guidance on those issues.

Q **Several people submitted questions while you were speaking and asked for information about the regulatory compliance video solution you mentioned in the case example you talked about. Could you give us a little bit more detail about what that was?**

A **Opler:** Of course. That was a repurposed technology we have used in the past for independent or central evaluations. This is, if you will, a democratic twist on that platform. We re-engineered it so it could be used by site investigators to contact their patients remotely. Certainly anyone who wants further details on the platform and other information is welcome to contact WCG. We're delighted to help you out as best as we can.

Q **We've talked about some of the scientific concerns around moving to remote assessments, ensuring validity, etc. From a site perspective–and a real logistics perspective–what are some of the things that you and your team have encountered when you have tried to move to doing remote assessments and studies?**

A **D'Souza:** Let me address this question from personal experience. We had done these kinds of remote assessments for sponsors.

I'm sure there's some perception change from the patient's point of view, as well as from the people who are administering the scales. Talking about the logistics of that, we did run into some problems. Our subjects would say, "No problem. Yes, I'll take this appointment, and so and so can call me. I'll be at home."

When the call is made, the person's not at home, or they're cooking dinner or doing something else but think they can handle the call.

Sometimes the minutes have run out on their phone. And oftentimes we had patients who gave us the wrong number. And so, for me, the point when all of those things happened is we had some pretty tight streaming windows and, oftentimes, because we couldn't finish the screening procedures and assessments, we would lose these patients as potential subjects. Sometimes we would rescreen them. But it ends up being a lot more work. I don't know if, when designing these things, some of these logistic things are taken into consideration.

But on the flip side, I've been pleasantly surprised with how well subjects had been able to handle some of these technology changes, and they have been pretty good about doing this. I know some indications may be better for remote assessments, but some other assessments that require a lot of the subjective evaluation may need to go a little slower.

In the end, if the point is to get the right patients in, or better patients in, and the study can be completed, I'm all for it.

Q **What additional documentation should sites and sponsors be trying to attain now–documentation that can support these future analyses, that can address the potential impact of the COVID-19 disruptions on the study results?**

A **Katz:** I don't think there are any specific guidances on that. What comes to mind for me is capturing information that would have an impact on the patient's response on questionnaires or participation in the study.

For example, the patient gets sick; that would interfere with the patient's getting to the clinic and would be important. Or the patient's not sick, but they're quarantined. Or they're not quarantined, but there's a transportation stoppage and they can't make it to the clinic. Or some other circumstance prevents them from performing an assessment even remotely during the visit window.

All of that should be captured on a subject level but also on a site level. If a site, for example, has changed its procedures or has to shut down for a period of time and move through a tele-health approach for a period of time, those site level data should also be captured.

I think we tend to forget about the value of capturing qualitative data as well. If the patient reports something that they think might be influencing their disorder–perhaps they have a mood disorder which has been perturbed by current events–then simply capturing that qualitative information in progress notes (if you don't have a specific a form to fill out) is much better than just letting that information go and trying to reconstruct it down the road.

Q **Mark, you talked about nested validity studies, and the possibility of doing nested validity studies within the clinical trial to assess whether the assessment tool remains valid.**

If there is an ongoing study that is using either a paper- or iPad/tablet-based questionnaire in-clinic that has to move to doing those assessments by telephone, would a nested validity study be something that is appropriate to try to do in that type of study to assess whether that data will be useful?

A **Opler:** Certainly a lot of what Nat covered addresses some of the analytic techniques that you'd want to apply in that situation. The essential research question there is, can we change modality from pencil and paper to (if I understand the question) telephone administered? Is the data still valid? Does the questionnaire still perform the same way?

The answer is yes. I think you've got to collect the data, as Nat said, and I think you need to do your best to analyze it to determine the extent to which the change in modality and the change in condition changes how you interpret it and its usability.

The challenge there is, quite simply, we can't do a well-controlled traditional validity study looking at this changed means of administration. We have to do the best with the data we have.

I think the use of central statistical monitoring, as Nat described, is a great approach. I think it can be done with, at most, minor modifications. Even if you choose not to modify your approach to data collection, I think we all still have to address the impact of, as Nat described, the secular change that COVID-19 has forced upon us all, to make sure that the quality of our data is good, and that the results of our studies are still interpretable.