Highlights and Summary of Part 4 Webinar:

Planning for Recovery: How Research Sponsors and Research Sites are Thinking Ahead to Restart Research

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"The old ways aren't going to work. A new approach is definitely needed, and it's that creativity and persistence that will help us cross the finish line for what we're doing here." --*Kathryn King, PhD, SVP Clinical Development, Aptinyx*

As part of an ongoing series, WCG hosted an April 8 webinar to address the coronavirus-related challenges facing the clinical trial industry. Speakers addressed specific sponsor and site concerns and offered insights into the post-pandemic future.

More than 4,500 individuals and teams listened live, and hundreds of them submitted questions. Most are answered below or in our always-expanding list of **frequently asked questions.**

Featured speakers:

1. **Kathryn King, PhD**
   Senior Vice President, Clinical Development, Aptinyx

2. **Alison Lakin, RN, LLB, LLM, PhD**
   Associate Vice Chancellor for Regulatory Compliance at University of Colorado Denver, Anschutz Medical Campus

3. **Jill Johnston**
   Study Planning & Site Optimization, WCG

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.**

Sponsor Considerations in the Wake of COVID-19

1 **Kathryn King, PhD**
Senior Vice President,
Clinical Development, Aptinyx

The four areas addressed below don't constitute an exhaustive list of what sponsors are thinking about, strategizing about and, in fact, are worrying about. It should, however, offer some practical advice on urgent issues and provide insights on approaches to how we might get back to work when the time comes.

1. Sponsor Considerations: Monitoring

This is very commonly done in collaboration with our partners and CROs. And also now in combination with sites in terms of what's possible for monitoring in our current situation.

Remote monitoring strategies: Think carefully about remote monitoring strategies. This is the time to seriously consider reduced and targeted source-data verification. It's also an important time to really think about strongly implementing risk-based monitoring strategies. Target efforts to the most important data, assuring its quality.

Look at what data requires source-data verification, what data requires quality review and really think about how you can leverage technology to be able to do those reviews.

It might seem impossible to do source data review remotely, but there are ways that protect patient privacy and data security. But it requires considerable effort on the site's part at a time when the staff may be unavailable.

Be creative and collaborative, think about the way that source data review and source-data verification might take place remotely. Carefully remotely monitor what is most important for the trial.

"So again I want to underscore strongly considering risk-based monitoring principles, thinking about the risks to data quality and interpretation of the data that you're generating and really leveraging that and the technology that's available to many of us in the studies that we're running to take a risk-based approach to monitoring in your remote monitoring strategies."

Benefits of centralized monitoring: The benefits of centralized monitoring are well known, but adoption has varied. It allows you to work remotely and to apply statistical methods for data quality that can be used to identify outliers--and also to identify protocol compliance. In our current situation, it can help identify deviations and variations to your plan, ensuring that

they are tracked and reported--and collected in your data set so they can be factored into the analysis.

Limitations of not being on site: Monitors need to consider the limitations of not being onsite. Source-data verification is not the same as source data review. There may be cases where there's information in the source that a monitor cannot see when they're monitoring remotely. Such limitations must be factored into data integrity and data quality consideration.

It may not be possible to do study-driven accountability. Depending on the importance of that in the protocol, depending on the specifics of your investigational product or device, it may be important to consider how that might be accomplished either remotely or once on-site monitoring is possible again.

Think about the burden that remote monitoring--for things like study drug accountability--might place on on-site staff given that they may not be in the office or they may be focused on patient care.

2. Sponsor Considerations: Remote Subject Visits

Safety and safety follow-up serve the interest of patient safety but also data integrity. Any strategy from remote subject visits should include a strong piece of safety follow-up; a strong emphasis on safety follow-up is incredibly important.

Efficacy: Think about how those remote assessments might impact efficacy and the way efficacy is judged in the protocol. "I would strongly recommend consulting subject matter experts who may be able to tell you what's possible even if it hasn't been published, for the way that different instruments might be able to be collected in a remote manner."

There will likely be flexibility among regulators given the current situation. And it may be possible to get things remotely that you hadn't previously considered. You might be able to validate a new method of administering an advocacy assessment. "Again, I would strongly encourage consultation with subject matter experts who can guide you through some of those processes."

Home health visits: It's understandable to see home visits as another way to handle remote visits. But with social distancing, with a risk to immuno-compromised patients, with risk to other vulnerable subject populations, those home health visits may not be appropriate. There are settings in which it will work, but proceed carefully.

Adjustments to data collection and analysis plans: In all cases with remote subject visits or different measures of safety or efficacy, it's important to appropriately adjust data collection--as well as analysis plans--to take into account the different ways that data may be collected and analyzed. This likely involves:

- Adding new fields in your EDC or case report form.
- Making adjustments to your statistical analysis plan.

Be able to assess the impact these remote visits may have had on subject safety and efficacy. Your data

management statistics colleagues can help you work through these issues.

3. Sponsor Considerations: During a Pause to Enrollment

"There are a number of things that our teams are working on now in order to allow us to restart in a good way but also manage some of the pressures that are placed on all of our partners."

Adjust payment triggers for sites: For instance, if you pay for a visit based on the source-data verification by a monitor, consider changing to a trigger--perhaps to the EDC data entered. The goal is to allow sites to be compensated for the work that they've done.

Carefully monitor expiry dates for study drug, lab kits and other supplies. Take this time to look at those dates, make sure that you've got supplies available where they're needed and again, plan for either ongoing patient visits if that's the case or a restart to enrollment when the time comes.

Think about protocol amendments and deviations: You must be able to communicate to sites, to IRBs, to regulators, exactly how a study has changed as a result of COVID-19 and specifically what other individual deviations might have occurred. It's crucial that we take care with documentation at this point, that the protocol amendment will be clearly understood by everybody who's using it. To have those documents available in real time is incredibly important.

Ongoing assessment of COVID-19: Consider geography with respect to decisions about continuing or pausing a trial--especially in terms of the regional impact of COVID-19. Think about what specifically is required for a study to restart. Think about the population, the ability to do remote subject visits or remote monitoring visits.

Communication is a priority: Sites must have all the information they need to operate. IRBs must be well informed about how a sponsor's choosing to operate in this time.

4. Sponsor Considerations: Sponsor Teams

Things are very different from the way that we were working in January or February of 2020.

Support and leverage work from home: Across the industry, this is something that we're pretty good at.

Assign back-ups for key processes: A team member might become ill or otherwise unavailable. Key processes might include SAE processing reporting, remote monitoring, assessment of clinical supplies, and responding to site questions and inquiries.

Document everything: We've talked a lot about protocol amendments and deviations, but a variety of other

plans are changing right now. It's important those plans are updated and documented and they're available to everyone who needs to know. We all know that if it's not documented, it's not done. In a dynamic time like this, that's more important than ever.

Encourage creativity and persistence: In a recent JAMA article, Drs. McDermott and Newman said that we would require creativity and persistence in order to get through this.[i] King agrees.

"To the extent that team leaders and sponsor team members can encourage that creativity and persistence, that's what it's going to take to get through what we're facing right now. So in everything that I've spoken about today, the old ways aren't going to work. A new approach is definitely needed, and it's that creativity and persistence that will help us cross the finish line for what we're doing here."

Where Next: Handling the Consequences

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Alison Lakin, RN, LLB, LLM, PhD
Associate Vice Chancellor for Regulatory Compliance at University of Colorado Denver, Anschutz Medical Campus

"I think now is actually the right time to be strategically thinking about how we efficiently, collaboratively and in a coordinated manner move forward with research, managing the safety as well as the clinical trial interests."

Potential Disease Landscape Considerations: *Impact on Planning*

"It's hard to imagine how this is all going to work. All of us have some level of a crisis management plan that we've developed over time, planning all sorts of eventualities. But I don't think we'd ever plan for this one."

Future waves of disease:

- There may be the need for ongoing social distancing, whether it's continuous or intermittent.
- Large regional hospitals will continue to be focused on clinical care more so than some other sites.
- Plan for a new normal: "I think we have to be thinking about ramping up in a more unstable world than we have been used to."

Understand the Local Environment: *Impact on Planning*

Site capacity will vary, because the pandemic may affect different sites and different regions in different ways.

Basic resources may be limited

Capacity at sites will vary by hospital type

- Regional hospitals may continue to be regional COVID centers:
- Radiological procedures and pharmacy services prioritized to clinical care
- Certain specialties will have limited capacity: pulmonary, infectious disease, surgery and anesthesiology
- Healthcare workers may be re-assigned longer
- Community-based hospitals and research centers may have capacity earlier--depends on healthcare worker impact
- Specialized hospitals--such as children's hospitals--may be able to respond to research more quickly

Currently Open Studies--Considerations

Now is the time to be working across the spectrum to ensure all parties agree on how we're continuing to do the research, what deviations need to be put in place and how long those deviations are going to have to continue. How are we going to standardize that approach so we don't impact data integrity and we can continue to answer important research questions? This requires good communication.

Continued adaptation: Sites are adapting to the new environment of COVID protocols for current studies. But what about tomorrow?

Future landscape: Are we standardizing to this adaptive version of the protocol? Are we returning to the original version? Or are we creating a new hybrid. If so, what does that look like and how do we operationalize it? This will likely be different for different cohorts.

These could be potential reasons to not open new enrollment. You want to see this cohort through with these adaptations before we think about adding in new potential participants.

When to Open to Accrual

Now is the time to think about how you're going to operationalize. Among the considerations:

Data integrity: "I think we're going to end up in a world where we're likely to have COVID positive and COVID negative participants." Will that affect the science? How do we address that? Will we need some changes to the inclusion/exclusion criteria?

Amendments: These adaptations may lead to amendments. We need to make sure the protocol and the contract, everything is matching up.

Site considerations:

- **New spaces, new relocations:** "Being a regional center, we probably are going to need to be looking at new locations to start to think about ramping up." That could mean optimizing satellite hospitals, clinical research units, freeing up the clinical spaces.
- **Reset with SIV:** As we think about moving from this temporary status to the next phase, there's a lot of value in having a virtual site initiation visit or an actual site monitoring visit. It's about resetting the parameters of what that next phase in the study would look like. "I don't think we can just say we're just going to continue as we did before."

When to Open to New Studies

There are numerous considerations here, many relating to site capacity.

Priorities: Lakin's facility continues to open studies. The focus is on COVID trials and trials considered to have a potential for high therapeutic benefit and life extensions. So there's ongoing work and then there is work that has been part of clinical trial work that's been put on some other level of hold or hiatus.

Workforce: Research teams have been deployed from the research side to the clinical side. There may have been hiring freezes and layoffs. Ramping back up may require workforce expansion.

Economic impact: Important, but too soon to estimate.

Consider new study designs to proactively address uncertain environment. Before we start a new study, we not only need the normal, anticipated protocol. We need to have an adaptive design already prospectively developed so we can more thoughtfully adapt to a limited crisis of a hotspot or some temporary change--"in a more considered manner than we did with the advent of this crisis."

Data and feedback on some of COVID study adaptations:
There's an opportunity to really look at the data and the feedback that is coming from some of these COVID changes to show what can be done and what the quality of the data is, particularly around virtual visits.

"I will say that, as an institution, we are doing a lot more telehealth than we ever did or ever contemplated doing before this crisis. And it is amazing to see how quickly people have adapted to it and how successful it has been in this environment. So I think there are lessons to be learned, but I would caution as well that as we move forward there's likely to be that need for social reconnection, particularly with participants and recognizing where they're at as things move forward."

A more informed population: I think we're going to be in a different place. The population globally as well as locally is likely to be more understanding and informed about the drug development process than they ever were before. So thinking about how we take that opportunity to partner and how we facilitate recruitment into new studies may need to be different from what we were doing before.

Each side needs to take a strategic look at how they build on their capacity to continue to manage in a fluctuating environment.

Lessons Learned That May Help Prepare for Next Time

Continue to expand electronic solutions: Many of the electronic solutions have been working better than anticipated, but there's still a lot of work we could do in

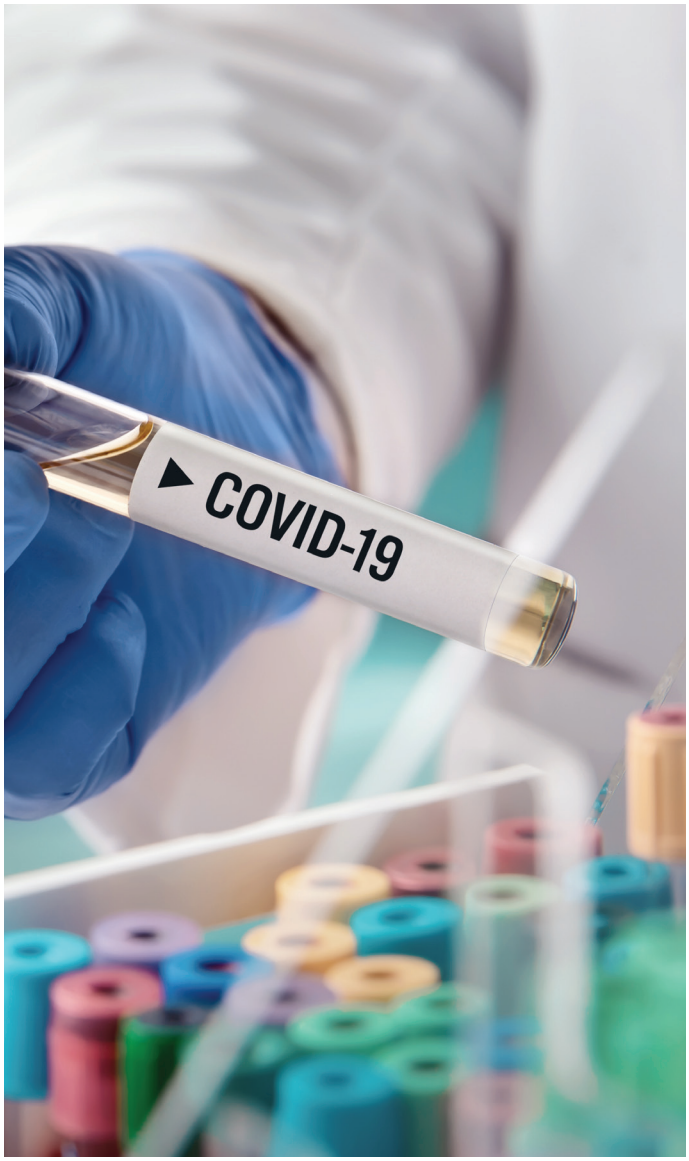
- standardizing an approach to e-consenting.
- making strategic decisions about telehealth and remote visits: "There's some efficiencies that we're seeing in this environment that I don't think people expected."
- electronic regulatory notebooks: If we're going to contemplate e-monitoring, that includes electronic subject binders.

Drug accountability: Think about how we can adapt drug accountability to electronic solutions.

Study the social and data integrity impact of the adaptations made during this period to inform future study design. "I think we can see some really interesting data starting to come out from these adaptations that we should be using for future study design, not just going back to the way things were."

Reconnect with the community: COVID forced us to connect with the community in a different way, to work in partnership on drug/device development.

"So while it's been a challenging hiatus, I think on a positive note, while I think clinical research is going to be a challenge to ramp back up, I actually think we have an opportunity to do it in a different way and to collaborate in a different way than we've done before."



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Jill Johnston
Study Planning & Site Optimization, WCG

Over the last three WCG webinars, we received many questions about recovery. They break down into three categories:

1. Recovery from COVID-19: Early Indicators

We don't expect a "Day 1" of recovery. It's going to be gradual and vary by region and localities. But we will have early indicators, including the following:

- Flattening of the curve in number of positive cases and deaths
- Availability of adequate COVID-19 testing
- Shelter-in-place orders being lifted and institutions allowing external parties to visit
- Physical signs in communities--opening of banks, restaurants, businesses
- "Certified Recovered" COVID-19 as an option being discussed in the media

We may also want to look at indicators in the clinical trials themselves:

- Increasing needs for study planning (leveraging data and outside sources)
- Start new site identification
- Launch new site feasibility
- Protocol IRB submissions

One of the things that we'll look at very carefully is any overlying epidemiological data at both the local and state levels, trying to get on-the-ground feedback from clinical investigators.

2. Recovery from COVID-19: How to Plan for It

"We really need to start to think about that now. It's not going to be one plan for the entire study or one plan for all of your studies at your site. It's going to be a rigorous portfolio planning prioritization of what you need for each of the trials, when those patients are going to be released to come back into the institutions. And then the second thing is what resources are needed both in people and equipment that might be needed for those institutions. Those plans are going to have to be addressed carefully."

It may also be helpful to look at a five-step plan framework:

i. **Plan and assess:** Do an inventory of a trial, what is needed, what are the resources needed, what are the statuses of the study, of the site, of the patients themselves, and how are we going to plan for that recovery? We also need to maybe create key areas of consideration at a study level: clinical supplies, regulatory impact, data flow, individual investigator sites and staff for those sites. Third-party vendors such as labs and imaging centers. And of course the management of safety.

ii. **Prioritize studies**, portfolios, resources. It's not going to be "open for business" everywhere, all at once. "We really need to think about how we're going to approach this."

iii. **Set trigger points.** If we see those early indicators locally, what is the next set of steps that need to take place, from a facility perspective, equipment, availability of supplies and people.

iv. **Take action**. Once you approach those trigger points, what are you going to do? Communication is key. Overcommunicate: Transparency is the name of the game here. Being open in communication and transparent about what's going on in all ways, with the sponsor, with the CRO and the site is going to be important to ensure we have multiple channels for engagement. Flexibility will be key.

v. **Measure and adjust accordingly:** We need to be flexible to adjust our plan. If you think you're moving forward locally with a specific site or institution, we may have to flex a little bit regarding how we're managing those patients. I think it's important to have a robust plan B, a plan C, and to be able to have that open communication as to when you have to alter it.

3. Recovery from COVID-19: Long-Term Impacts

We are not going to return to normal. It'll be a new and improved normal. Here's some of what that may entail:

- **Greater acceptance of new ideas,** especially around risk-based approaches to trials and the use of digital tools, including telemedicine and eConsent.
- **Progress on virtual and decentralized trials**
- **Advances in remote site management,** relationship support, monitoring, etc., as well as alternative ways to manage investigational product reconciliations and other onsite activities.
- **Direct-to-patient trials, drugs and clinical supplies:** We're starting to see a lot of questions around direct-to-patient drug and clinical supply shipments.
- **Greater need for flexibility:** Many alternatives to reach the same objectives.

- **A greater focus on the patient burden:** We've known about this for some time. "It's being seen and felt and it's going to have to be managed in a post-COVID world."

- **Increased patient comfort with virtual contact:** We're seeing a huge uptick of patients getting comfortable with e-contact virtual visits with their physicians. Some may not want to go back to a face-to-face interaction for every single visit. We need to think about that as an industry and figure out how we're going to move that forward.

We would expect to see more and more virtual clinical trials or procedures.

Questions from audience

Questions for King

Kathryn King, PhD
Senior Vice President, Clinical Development, Aptinyx

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Questions for Lakin

Alison Lakin, RN, LLB, LLM, PhD
Associate Vice Chancellor for Regulatory Compliance at University of Colorado Denver, Anschutz Medical Campus

Q **From the sponsor perspective, can you tell us, what do sponsors consider when they think about whether they can make parts of a trial or an entire trial be conducted virtually or remotely? What are those considerations?**

A

King: Often the way we've always done it is the way a trial gets designed. This has been a substantial wake-up call for many of us from the sponsor point of view--to understand the need to better integrate technology into our processes and the need to understand the pros and cons of virtual visits.

There's a real energy now behind understanding what the benefits might be and a clearer understanding of what the risks might be if we operate with a proportion of virtual visits or with better use of the technology that we have now. There's going to be an expectation that we continue to work that way because there will be speed and efficiency and certainly patient burden benefits that we're going to be able to measure here. And there will absolutely be an expectation that we carry that forward.

So I think it has to do with that creativity and perseverance that I talked about before and really a willingness to change to see what's possible. Again, in the current setting, it's really sort of painted us into a corner to force us to do it. But once we're able to show that it's been done, it will become the expectation going forward.

Q

Do you have any thoughts on that same question from the site perspective and maybe from the perspective of investigators or site staff as well. What is the opinion there about shifting to virtual assessments?

A

Lakin: I would echo what Kathryn said. At the site level, there's been a hesitancy to move in this direction--from both the clinician and investigator perspective. But we ramped up from doing 10 telehealth visits a day to over 2000 now in a day. And the feedback that we're getting is that people are finding it much more effective than they thought it was going to be.

There's still a relationship between, in these cases, the patient and the physician. I think that's holding true in the clinical trial environment too. So I think now that we've got the experience, I think people are not going to want to let it go. But I also think that there's a relationship that's established between participants and the clinical team. So it is being really strategic about how to build that relationship and to have that connection and how much of it can be done remotely versus locally. It's something that we have a real opportunity to study now and we should take that opportunity to collaborate and make that happen.

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[i] McDermott MM, Newman AB. "Preserving Clinical Trial Integrity During the Coronavirus Pandemic." *JAMA.* Published online March 25, 2020. doi:10.1001/jama.2020.4689