Highlights and Summary of Part 1 Webinar:

Clinical Trials in the Era of COVID-19: Changes You Need to Make Now

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Hospitals and academic research centers are shuttering clinical research and assigning clinical staff to deal with the COVID-19 pandemic. Trials that don't provide a direct benefit are being suspended.

These and other unprecedented changes have generated questions from sponsors, sites, CROs and others in the clinical research space.

WCG hosted a webinar March 18 to answer--or at least provide informed insights into--these questions. Approximately 4,500 individuals and teams dialed into the webinar. Hundreds of them submitted questions before and during it. Most are answered below or in our always-expanding FAQ.

Featured speakers:

1 **Arthur Caplan, PhD,**
Professor of Bioethics,
NYU Langone Medical Center

2 **David Borasky, MPH, CIP,**
Vice President,
IRB Compliance, WCG

3 **Suzanne Caruso**
Vice President,
Clinical Solutions, WCG

4 **Michael Cioffi**
Senior Vice President, Clinical Solutions and Strategic Partnerships,
WCG MedAvante-ProPhase

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.

Ethical issues arising in clinical research amid the COVID-19 pandemic

1 **Arthur Caplan, PhD,**
Professor of Bioethics,
NYU Langone Medical Center

Patient Autonomy vs. Minimizing Harm

The principle we want to follow all the time is patients first, but during this pandemic, minimizing harm to large numbers of other people must override the traditional respect for patient autonomy. In a pandemic, we have the duty to protect the community--the community of healthcare providers, the general public, our colleagues and peers in the workforce.
In practical terms, this means

- **Keep people out of the hospital:** That's why elective procedures have been canceled: We don't want to expose people to a risky environment.
- **Minimize exposure and transmission:** We want to minimize exposure and transmission of the virus by not having people come together when they don't have to.
- **Protect resources:** We don't want study participants and those who accompany them diverting resources unnecessarily.
- **Focus clinical staff:** Free up all healthcare personnel for clinical duties.

Don't abandon those who are benefitting

If the first principle is to minimize harm, the second is to not abandon those who are reasonably benefiting in research.

For example, if someone were in a late Phase III trial and we knew they were benefitting from treatment, we would want to assess the risks and benefits of going to the clinic or hospital vs. those of not getting care. The essential question: What is the likelihood of benefit in continuing to participate in the trial?

Do not pursue the goal of new knowledge that lacks potential for rapid clinical use

We want to reduce the impact of the pandemic, so we're not trying to conduct research unless it will absolutely benefit the person and stopping it would harm them.

That means ending studies with no potential direct benefit, such as observational studies, pragmatic trials, Phase I studies, animal studies. "We have to cut those back. They're not going to directly benefit, in any imminent way, the battle against the virus, so that's the kind of thing where I think we're probably morally obligated to stop."

Primacy of Patient Safety

When we *do* initiate new research, what we're trying to do is protect the patient's safety, health and welfare. That the top priority.

The risk profile of patients will vary across different studies and clinical trial sites. Among the things to consider when determining whether to proceed with a trial:

Sensitivity to "windows": Decisions about whether to initiate something involve sensitivity to the windows that patients may face if they have a disease that's really taken them down rapidly. "Somebody may say, 'I've got something that could help them. I was about to initiate that.' There could be an argument for trying to do that, but I think those situations will be very rare."

Consider integrity of supply chain: Are you going to be able to access agents that you want to administer? That may be difficult as companies divert what they're doing to pandemic work.

Keep travel restrictions in mind: Patients may not be able to get to the site.

Record all protocol deviations: This applies to new and ongoing trials. Failure to do so threatens data integrity.

Maintain consent: Obtain consent from all subjects.

Maintain IRB notification: If you want to initiate a trial, have a conversation with your IRB chair first.

Address the "therapeutic misconception": Patients may not understand that, especially in early-stage studies, the risk often exceeds the benefit. The therapeutic misconception doesn't go away in a pandemic, so we must address issues of infectivity and disabuse patient subjects of their efficacy beliefs.

Compassionate Use

Some companies are offering compassionate use, and each has its own requirements. For example, Gilead's inclusion criteria for remdesivir include mechanical ventilation, and its exclusion criteria include multi-organ failure.

Among the considerations for compassionate use:

Consider integrity of supply chain: Are you going to be able to access agents that you want to administer? That may be difficult as companies divert what they're doing to pandemic work.

Know the pipeline: Because the company controls access, it's important to keep tabs on the news and on media to see what's in the pipeline for new drugs and new trials.

Contact the company: It's important to keep in mind that the company is the first point of contact, not the FDA, and it's the doctor, not the patient, who needs to make that contact. Be ready to come up with standardized medical information in the manner the company requires.

Control expectations: We want to prepare the patient and the family for the possibility they will be turned down. What will be their next move if they are turned down?

Notify the FDA: If you do get approved, notify the FDA. The agency provides access via its website and a 24-hour phone number. (This may change; it's a political battle right now.)

Notify the IRB: If it is an emergency, you can proceed--you don't want to get bogged down in red tape--but notify them within five days.

Record what happens: This isn't research. I understand that. But if you have adverse events, if you can record the dose that you used and other facts when you try something, it's very important that we learn whether something works or not, and the only way we can do that is through "real world evidence."

Emergency Changes to Research, Protocol Amendments and IRB Review

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David Borasky, MPH, CIP,
Vice President,
IRB Compliance, WCG

The WCG IRBs are receiving an unprecedented volume of questions from, among others, sponsors, CROs, research sites and institutional sites. The questions fall into one of two categories: Process questions and study-specific ones.

The philosophy that we're following, from the perspective of the WCG IRBs, is that we're totally aligned with the new **FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic.** In general, the regulations provide IRBs with a great deal of latitude and flexibility.

The bottom line for WCG is that the IRB isn't going to be a roadblock to making changes that are essential to maintaining research that is

- Ethically appropriate and maximizes safety of study participants, research teams and the general public;
- Scientifically valid;
- Compliant with the regulations.

That context and the new guidance undergird the rest of the discussion.

What Needs IRB Approval?

Changes to previously approved research need approval, including

- **Changes in study procedures,** such as elimination of or reduction in number of study visits, the shift from on-site study visits to some sort of telemedicine or home healthcare or some combination of those things. It may also include the collection of safety labs offsite, sending a phlebotomist out or sending people to types of central labs, etc.

- **Changes in provision of investigational product,** such as changes in how it might be administered to study participants who can no longer come into the site. (Federal and state laws may come into play here.)

- **Any other changes** that may affect participant safety or the integrity of the research.

Reach out to your IRB and start talking about this. The WCG IRBs have created a special form for submitting COVID-related changes.

We do not require a full-blown protocol amendment be submitted. We have accepted letters of amendment, memos of protocol clarifications, we have accepted change-in-research forms--we're trying to be very flexible. It doesn't matter what the title or the format of the document is as long as it contains enough information for the IRB to assess the changes that are being made, the implications for the study and potential risk to participants.

When is IRB Approval Required?

We received many questions about when IRB approval is required. Ideally, from a regulatory standpoint, the answer is "before implementation."

However, the regulations also anticipate situations in which changes can't wait for IRB approval. Immediate changes may be needed for the best interest of those involved--something that remains fluid.

Changes made without IRB approval should be submitted as soon as possible. WCG's IRBs expects them within five days. We understand and expect that research sites and sponsors will be working to implement some changes very quickly--being nimble, putting something in place and then coming to us.

"We are certainly working really hard to make sure … that the IRB is not acting as some sort of a roadblock that's preventing important changes from happening in the research studies."

Informed Consent

Informed consent has become a hotspot for questions. The key one is this: *When we make all these changes, what does it mean for informed consent?*

Keeping in mind that consent is a **process,** consider the following:

"Re-consent" is not a regulatory term: "Re-consent" has just become part of the research vernacular.

Regulations require consent initially and, when applicable, when significant new findings may affect the participant's willingness to continue participation. Second, consent is a process.

But thinking of what we call re-consent, new information can be presented in different formats, including

- Revised consent document
- Addendum to consent
- Memo or other communication to subjects
- Orally by phone, video call or in person

What's required are well-thought-out and reasonable plans for making sure that research participants are aware of what's going on, know what changes are being proposed, and understand those changes will affect them.

It should be presented in the simplest way possible: The Secretary's Advisory Committee on Human Research Protections, or SACHRP, has offered new guidance. The bottom line is this: *When there is a need to present participants with new information, IRBs should encourage use of the least burdensome approach for the participant.*

What about protocol deviations?

We've been receiving a lot of questions about protocol deviations. Historically, there's not always a consistent standard across the IRB world in terms of what's expected in these circumstances. But we're seeing such a spike in deviations now that are really having to take place because of the issues created by the pandemic.

When to report: Protocol deviations do not need to be reported to the WCG IRBs unless they negatively impact risks to participants, or have a negative effect on study integrity. For example

- ***Do not* submit** if the scheduled visit is out-of-window because participant is in self-quarantine (unless, of course, there were safety implications).
- ***Do* submit** if one or more participants will be immediately withdrawn from IP without tapering or if safety labs will not be conducted because facility is closed.

Submit prospectively: If anticipated, submit prospectively to IRB with plan for mitigating risk. Consider submitting potential deviations--and a mitigation plan--prospectively. It is probably a good idea to prospectively reach out to the IRB to discuss what you anticipate coming and figure out how you're going to mitigate that risk.

Document and explain: If the current situation puts you out of compliance with a site's SOPs for conducting research, then the site can be proactive and write a deviation memo or a note to file describing the deviation and the circumstances and, again, have that filed away for future monitoring or a future inspection so it is clear these things were done to manage a particular issue at a given point in time.

What's not a deviation: If you are proactive in making changes to your protocols and build in flexibility or the ability, for instance, to do home visits, then those changes would no longer be deviations that have to be tracked.

IRB Scope

IRBs don't typically review and approve clinical monitoring plans. IRBs don't need to approve or review plans to move to remote monitoring. "I think if there's a very study-specific scenario or a reason why a sponsor is concerned about that change in approach, we can talk to them about it, but we don't expect those to be submitted as their own changes on a regular basis."

Supporting Your Participants and Managing Retention Challenges

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Suzanne Caruso
Vice President,
Clinical Solutions, WCG

We've all seen that the infrastructure that supports clinical trials is not always available. Here are some of what investigators and study staff are reporting:
The bottom line for WCG is that the IRB isn't going to be a roadblock to making changes that are essential to maintaining research that is

- Closing down departments to ensure room for COVID patient care
- Reallocation of staff--especially nurses--supporting clinical trials to primary treatment and care
- Time to take calls from clinical trial participants diminished
- Increased administrative burden for rescheduling and offering new options
- Non-essential staff being asked to work from home
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Throughout all this, everyone is trying to be as flexible and transparent as possible. Everyone is trying to communicate as much up-to-date information as possible.

Several trends are already emerging.

A move to virtual trials

Virtual clinical trials are uncommon, so "How can we

immediately transition to a virtual trial?" is one of the hottest topics today.

Our sponsors are making sure study coordinators have virtual support. These virtual assistants, often nurses, can take on the administrative tasks and work closely with patients, keeping them informed about changes, providing patient education and answering questions.

These assistants are third parties and not employees of the site or the sponsor. Having an independent party that's part of the study, knows what's going on in the study, and may know that they are reaching out to the participants of that study has really been helpful.

New communication and engagement strategies

Sponsors are implementing various new strategies to support communication to clinical trial teams. They are reaching out through

- Questionnaires
- Site calls
- Weekly newsletters
- Webinars across all sites for investigators, staff and participants

Amending protocols to reduce unnecessary visits

A common question is "Should we amend the protocol?" Beyond what was discussed earlier, there many conversations about looking at the protocol and identifying visits that may not be essential to getting to the primary endpoint. The goal is to minimize the need for participants to be around other people.

Shipping investigational product

We're hearing many questions related to shipping investigational product, when appropriate, to patients. We have been able to ship investigational product for years. It varies by country, however: In the U.S., you may be able to ship to the house, depending on what the actual compound is. Outside the U.S., you may have to ship to a depot or a pharmacy.

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Preparing for Re-engagement

We're hearing questions about what happens when trial participants can start coming back to the clinic. How do we plan for participants to re-engage with sites? One study coordinator told us about a sponsor

that sends short daily reports to investigators and investigator staff sharing the most recent information and the sponsor's plan of action.

Flexibility and Transparency

Overall, we're seeing among sponsors greater flexibility and transparency, and a willingness to engage in new communication approaches. People are calm because they have information.

Ensuring the validity of your data as you shift to remote measurements

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Michael Cioffi
Senior Vice President, Clinical Solutions and Strategic Partnerships, WCG MedAvante-ProPhase

When talking about ensuring data validity in virtual trials, two important issues come into play: the remote assessments themselves and lost data.

Remote Assessments

As we move to remote assessments and virtual clinical trials, it's important to look at the scientific and the regulatory considerations around collecting efficacy endpoint data remotely. It's not as simple as saying, "We normally do this and record it; we'll just call the patient and we'll do it over the phone and we'll get the same data."

Regulatory considerations: Privacy--especially in light of The EU's GDPR--is a key regulatory issue. The ability to move that data in and out, knowing who's conducting that assessment and where it's being conducted must be considered in a global trial environment.

Scientific considerations: Scientifically, remote assessments are an even greater concern. Take, for instance, a somewhat benign measure--quality of life. Will someone reading that assessment to the patient and collecting the patient's answers suffice? Is that scientifically valid? What if the person doing the assessment ad-libs the question or places unnecessary emphasis on a part of the question?

These are some of the issues we must consider before saying, "We can collect this data remotely from a patient." Here are two examples.

- **Psychiatry:** Many endpoints are clinician-rated assessments that must be done through a very structured interview. Take SCID, the structural clinical interview for DSM disorders. It's typically done in the clinic with a clinician administering it. However, the literature strongly supports that can be done telephonically and by modalities that maintain the scientific validity of the scale. And that's also true for measures like the MADRS in neurodevelopmental disorders.

- **Fine motor skills:** Assessing fine motor control can be especially challenging, especially when we may have to do it by video. While technology to support remote assessments exists, it's essential to consider the various challenges and approach them with scientific rigor.

There may be differences in a registration study vs. non-registration study. In a non-registration study, we may be able to be a little more flexible.

Missing Data

We heard earlier about IRB implications for adaptations to the protocol, but what are the actual implications to your clinical development program? Some of this is included in the new FDA guidance.

Efficacy assessments: The FDA addresses efficacy assessments and recommends strongly that consultation be done with the actual division that will be responsible for review regarding any protocol modifications for the collection of the efficacy endpoint. *That includes virtual assessments or alternative methods of collection for specimens.*

Document everything: Document the reason efficacy endpoints ae not collected. Be sure to state whether the limitation is actually imposed by the COVID crisis. Document any changes to the visit schedule, or patients who may have discontinued, or primary endpoint data or safety data that may be missing due to the COVID situation. This should be summarized in a clinical study report; this will help FDA reviewers down the road.

I think all of these things are very important considerations when we look at the impact of COVID and what that's going to do to us and how we're going to have to change and adapt to what we're doing, whether it be our collection of the data through remote assessment, or how we are going to handle missing data as a result of patients not being able to complete assessments.