Impact of COVID-19 on Clinical Trials

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What will happen to my organization's clinical trials?The answer will vary based on the type of site, site location, protocol visits, endpoints and other factors.We are sharing insights based on the WCG (WIRB-Copernicus Group) webinar from March 18, 2020, and on research institution discussion groups.

Institutional and commercial IRBs are posting guidance on this topic. Some IRBs have paused all in-person research interactions with human subjects. Others are continuing studies that have direct therapeutic benefit to participants, as long as in-person activities are minimized. The definition of "direct therapeutic benefit" varies by IRB. See our related post of links to IRB clinical trial policies on COVID-19.

The WCG webinar, Clinical Trials in the Era of COVID-19: The Changes You Need to Make Now , drew over 4,500 people. WCG received hundreds of questions before and during the webinar. The speakers were Arthur L. Caplan, PhD, at NYU Langone Medical Center; David Borasky, MPH, CIP, at WIRB Copernicus IRB; Suzanne Caruso at WCG, and Michael Cioffi at WCG.

Given the breadth of issues raised, this content is in bullet point format. We will elaborate on certain issues in future posts.

Separately, FDA released new guidance on March 18, 2020 entitled, Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic (press release with link to guidance). The webinar was consistent with this guidance. We will elaborate on the guidance in a future post.

Overarching questions addressed in more detail below include:

Should we continue the study?

Will our study sites continue our study?

If yes, what study changes do we need to make?

If no, what steps should we take?

These are complex questions with no easy answers. They present ethical and scientific challenges that will be different for every study. The webinar, IRB positions and discussion group commentary provide significant food for thought and action items.

Is our study coming to a grinding halt? Not necessarily.

What key factors impact whether or not to continue the study?

– Type and location of study site (e.g. front-line response to COVID-19 surge vs. smaller or rural area) and

– Type of study (risk-benefit analysis).

Should we continue our study?

The webinar began with Dr. Caplan's presentation about moral and ethical considerations of continuing current studies.

Moral and ethical issues include:

– Exposing subjects and their companions to COVID-19 when they attend study visits.
– Exposing study monitors to COVID-19 while on-site monitoring.
– Resource allocation: should investigators, nurses, study coordinators and other site personnel be working on the study instead of on COVID-19? What about hospital facilities?
– The harm to the subject if you terminate the study regimen.

What are the deciding factors?

Risk/benefit analysis:

– What phase is the study?
– Does the study have a potential direct benefit for the subject?
– Would the subject be harmed if he/she were cut off mid-stream? Do the benefits of coming to the hospital, potentially exposing the subject/companion to the virus, dealing with the hassle factor of diverted resources, etc., outweigh the harm caused by the subject not receiving care?
– For example, is this a Phase 3 study, and we know the subject is benefitting from the treatment of their cancer?
– What about supply chain integrity?

Terminate non-direct benefit studies:

Dr. Caplan recommended stopping the following studies, and this is consistent with industry commentary:

– Studies that have no direct patient benefit.
– Observational studies.
– Pragmatic trials.
– Phase 1 clinical trials.
– Animal studies.
– Studies where the demonstrated efficacy is minimal.

Continuing beneficial research:

During the Q&A, Dr. Caplan observed that Phase 3 and perhaps Phase 2b studies where patients were receiving

substantial efficacy for a life-threatening condition could continue. Should the study discontinue the placebo arm? He felt that this would be a question for the DSMB, not the IRB, although we think the IRB will need to be involved. Studies with moderate to serious benefit might continue, but many, if not all, research institutions located at the frontline will pause in-human research.

Subjects:

Are study subjects willing to continue?

Availability of site resources:

– The investigators, study coordinators, nurses and facilities – are they available or being diverted to handle COVID-19?
– Supply chain – will you be able to supply the investigational product and associated materials?

Sponsor risk management (this was not addressed in the webinar, and we have not seen this in institution discussion groups)

– If the study continues, what happens if a subject comes to the hospital for a visit, becomes infected with COVID-19 and dies? Should the informed consent process address this as an anticipated risk? What does the CTA's subject injury clause look like (e.g. injuries caused by the investigational product vs. injuries caused by participating in the study)? Would the sponsor's subject injury or indemnification obligations cover this?

Who makes the decision?

– The site? The sponsor and the site? The IRB? While Dr. Caplan indicated that the decision rests with the sponsors and institutions, not with the IRB or FDA, we think the IRB will be involved.

– Should a sponsor engage its data monitoring committee or another independent advisory body to help make these determinations (and document them…)?

Documentation is critical:

Sponsors should carefully document all decisions, including whether to continue the study, how to continue the study, changes to the protocol and informed consent, and more. When the dust settles, you will want to have a good paper trail.

What changes should we make so that our study can continue?

For all of these changes, sponsors need to heed FDA regulatory, privacy, IRB and scientific validity concerns.

Remote monitoring:

Switch from on-site source data verification to remote monitoring.

Protocol visits:

Decrease the number of protocol-required visits at research facilities.

Remote visits:

Replace in-person study visits with phone calls or telemedicine, if feasible. Many IRBs have already mandated this. This change would require addressing:

– privacy issues and
– scientific validity/rigor concerns. For more subjective testing, like quality of life assessments, remote visits may impair the integrity of the study.

Labs:

For objective measures, like imaging and blood draws, replace hospital visits with visits to commercial/consumer labs.

Direct product shipment:

Ship investigational product directly to study subjects, if the patient can self-administer, and if permitted by state and federal regulations.

Site logistics support:

Consider easing the burden of certain logistical responsibilities of study sites by engaging independent providers to handle time-consuming services typically rendered by study personnel that are easy to outsource without impacting study integrity, such as calling subjects with updates, rescheduling visits, confirming visits, etc., as the study coordinator may be overwhelmed or routed elsewhere. But note:

– Sponsors should not provide these services through their employees. They must be provided by an independent body (apparently, WCG offers these services).
– Follow IRB requirements regarding written communications with study subjects.
– Be mindful of fraud and abuse compliance (e.g. Federal Anti-Kickback Statute). You must reduce the CTA budget exhibit accordingly by written amendment so that the sponsor is not paying the site for services that another entity is rendering instead. This can be accomplished without a long, drawn-out formal amendment process but must be in writing.

Communicate early and often to investigators and study staff:

Be proactive, not reactive, on the communication front, but do not overwhelm. Some sponsors are sending daily news reports about the study with 2-3 bullet points on their plans.

What study changes need IRB approval? When? Is after-the-fact ok?

IRBs have to approve changes to previously-approved research, such as reduction of the number of study visits, shift to telemedicine, provision of investigational product, and other changes that may impact participant safety or the integrity of the research.

IRBs do not have to approve changes in advance "where necessary to eliminate apparent immediate hazards to the human subjects." 21 CFR 56.108(a)(4).

How are your IRBs handling COVID-19-driven changes to the protocol and informed consent? Many are relying on the "immediate hazards" exception to prior approval and require reporting within their policy timeframe (5 days is common).

Protocol amendments and deviations:

There is no consistent standard across IRBs regarding protocol deviation reporting.

– For WCG, you do not need to report a deviation unless it negatively impacts the risks to subjects or it has a negative effect on study integrity.

Follow each IRB's requirements.

Be proactive if possible: if you can amend a protocol now to accommodate anticipated deviations, this may save you from having to report deviations later.

Many IRBs may try to be flexible regarding amendments and their format during this time. The key is to provide enough information for the IRB to assess the changes and their potential impact on study participants. Options may include:

– Formal protocol amendments.
– Letters of amendment.
– Memos of protocol clarifications.

For some IRBs (including WCG), sponsors can amend the protocol temporarily (e.g. for duration of pandemic). You can indicate that when you submit the amendment. Best practices for sponsors will be to have a paper trail with the IRB for reversal of the amendment after the pandemic subsides. Further, sponsors may not want to tie themselves to a reversal, as this situation will change the conduct of clinical studies.

Informed consent revisions:

What do subjects need to know?

– The regulations require informing subjects of significant new findings that may relate to their willingness to continue participation. 21 CFR 50.25(b)(5).

How quickly do you need to contact subjects?

See above on moral/ethical issues and subject injury/indemnification.

Do subjects need to be "reconsented?"

– In the interest of time, consider less burdensome ways to address this, as informed consent is a process.

Are other options feasible and reasonable, such as phone calls, video calls or electronic consent?

Follow regulatory and IRB guidelines regarding electronic consent, including HIPAA.

Documentation is key:
Record what was done, who conducted it, and the time and date. Subject signatures may not be required but may be best practices.

Miscellaneous:

– If a participant refuses to return to the site for follow up visits, should he/she be removed from the study? Dr. Caplan said yes. IRBs are providing guidance on this.

– Do IRBs need to review written communications to the subjects? Yes, but you may be able to rely on the "immediate hazard" exception and report to the IRB immediately afterwards.

– Check institution COVID-19 screening requirements and associated HIPAA issues for all subjects who will continue in-person visits.

Data Integrity:

How will you handle data that is missing because subjects did not attend follow up visits?

Changing from on-site visits to remote assessments (e.g. phone call) to collect efficacy data has scientific and regulatory considerations. Certain types of assessments are not amenable to remote collection.

– WCG strongly recommends consulting with your FDA division responsible for review regarding any protocol modifications regarding the efficacy endpoint, including how you are collecting data.

– WCG advises that your clinical study report summarize missing endpoint data, changes to visit schedules, patient discontinuation, etc.

Address statistical considerations.

Adapt your study protocol.

Comply with FDA and IRB requirements.

What steps do we take to pause the study?

Participant safety:

How do we taper subjects?

How do we follow up for adverse events?

How do we obtain follow-up study data?

Regulatory, IRB and business considerations.

Restarting the study after the pause/deferral/halt:

– Plan for this.

– How do you ensure participants know what their study responsibilities are, such as when they will re-engage with sites?

– How do you prepare staff to take on patients as they return?

– Smaller sites may have participants and staff return sooner than larger sites.

– How will the protocol change (again) accordingly?

– When talking about pausing the study, consider not using the term "suspension," as that has regulatory implications.

Document everything carefully.

For regulatory, compliance and business purposes, you will need a clear paper trail for after the dust settles.

IRB policies:

See related post of links to IRB policies on clinical trials during COVID-19.

We will be addressing specific issues in more depth in future posts as we continue to monitor, analyze and advise on the developing situation.

If you have any questions or would like more information about these developing issues, please contact the following:

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