Clinical Trials during COVID-19: Making Safety Decisions

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As we adjust to evolving circumstances, this Update focuses on safety issues relating to non-COVID-19 studies. We highlight select topics from the last two WCG (WIRB-Copernicus Group) webinars on clinical trials during COVID-19 and provide our insights. We reported on the first WCG webinar here.

Data Collection: Do you already have enough data? Can you cut back?

Part 3 of the WCG webinar began with a discussion about data collection and safety reporting. WCG stressed the prioritization of safety data collection, noted that some data required by the protocol may be amenable to less frequent collection, and reminded everyone to be careful about patient safety and study integrity.

Questions addressed included: Do you have enough reliable data now so that you can stop the study? Is it feasible to eliminate collection of any data? Can you use telemedicine in place of on-site study visits?

Our Insight:

We recommend approaching the answers to these questions with great caution, both in terms of patient safety and trial integrity. Subject safety is paramount (front end). Consumer safety will be paramount when the product is on the market (back end). Planning simultaneously for the front end and the back end to address COVID-19 can catch study sponsors between a rock and hard place.

Missing data:

Scenario 1: It is not hard to imagine a scenario where a study subject is injured and sues the sponsor, sites, CRO, DMC, etc., claiming that the investigator failed to notice and collect key adverse event or safety information during a study visit because for, patient safety reasons, the visit was changed from an in-person, on-site visit to a remote visit via telemedicine, possibly over a scratchy Internet or phone connection. The subject would argue that, had the visit been in person, the investigator would have collected that safety-related information.

Scenario 2: The above scenario involves unintentionally missed data due to the lack of a "hands-on" visit. What about "intentionally" missed data due to a change in the protocol driven by COVID-19? Sponsors may legitimately conclude that having certain visits or collecting certain study data points are not worth the risk of exposure to COVID-19. The FDA guidance that we wrote about here observes that switching to telemedicine would likely result in certain protocol-required procedures not being conducted and that sponsors should evaluate the potential safety impact and how to mitigate the risk.

These scenarios could contribute to study subject and consumer injuries. On the front end, injured study subjects might sue during or after the study. On the back end of the pandemic, a group of injured consumers might claim that the inadvertently or intentionally missed study data was critical to FDA's decision to approve or clear the product (class

action, anyone?). Depending on the approval pathway, certain types of lawsuits may be preempted (e.g. PMA device), but is that something that sponsors want to risk?

What about discrimination or underrepresentation of minorities? Would switching from on-site study visits to telemedicine discriminate against subjects who cannot afford a smartphone or computer? What if the Internet or cellular connection is bad? How will that impact safety issues now or later?

Safety-driven changes to protect against COVID-19 may lead to safety problems after the pandemic for subjects and consumers. Sponsors should document all decisions regarding data collection and study visits carefully, including the rationales, steps taken and entities consulted. To do the right thing now for study subjects and to protect subjects and consumers, it is critical for sponsors to work with the sites, the IRB, the DMC (see below) and FDA to reach and justify these decisions. This process can help sponsors reach optimal decisions in what are admittedly suboptimal circumstances and create a paper trail justifying the decisions should they ever be questioned.

Data Monitoring Committees (DMC):

"The DMC advises the sponsor regarding the continuing safety of trial subjects and those yet to be recruited to the trial, as well as the continuing validity and scientific merit of the trial." FDA Guidance on DMCs. WCG explained that if you have a DMC or wish to form one, the DMC can be consulted about study modifications for safety issues and study integrity. WCG suggested doing this carefully, including making sure not to give the DMC responsibility that could invalidate the study.

WCG addressed questions a DMC might answer and stressed the following in terms of DMC makeup: DMC members need to be able to meet quickly and decide quickly; and the DMC should have a strong chair, a statistician (or access to statistical expertise), and a member who understands the FDA (and foreign) regulatory obligations.

Our Insight:

We expect DMCs to play an important role in the difficult safety decisions sponsors may need to make due to COVID-19.

We remind you that the DMC is an independent oversight committee. The members should not have financial or other important ties to the sponsor or other trial organizers. Their only involvement in the study design and conduct should be as members of the DMC. DMCs need a process for assessing conflicts of interest, and individuals with serious conflicts of interest should not be appointed.

Adverse Event (AE) Reporting for Study Subjects

For study subjects who contract COVID-19, WCG recommended the following:

1. **Not hospitalized – report as adverse event (AE).**
2. **Hospitalized – report as serious adverse event (SAE).**
3. **Death – report as SAE.**
4. **IRB notification in certain instances; maybe not if you have the same infection rate in both the investigational and control arms.**

When addressing AE reporting, we recommend considering whether your informed consent form (ICF) should list the risk of contracting COVID-19 in the "general risks" section.

Statistical analysis plan (SAP):

When considering changes to the SAP, WCG advised sponsors to make sure that the following groups are all speaking with each other: operational, clinical, database and the statisticians. Separation between operations and statistics is common, and if you're making major operational changes to your SAP, the whole team needs to be talking.

Sponsors will need to analyze the impact of missing endpoint data on study integrity and adjust the SAP accordingly.

What about product shelf life and storage? Extending the study duration in order to lower the impact of missing data needs to be weighed against the shelf life of the investigational product and whether the study site will be able to store the product properly for the needed duration.

As we previously noted, per the FDA guidance, sponsors should consult with FDA when making changes to the data management plan or SAP.

Additional Insights:

Document everything: all decisions made, rationales, steps taken, and individuals and entities consulted. The goal of documentation is to show that you made reasonable decisions with good intentions and with careful thought in response to a crisis.

Communications between sponsors and study sites should be effective, efficient and often. Ditto for communications by sites to subjects, although less often.

The state of clinical trials right now: Our overall impression from various sources is that, on the one hand, clinical trials face serious challenges including subjects and staff testing positive for COVID-19; investigators and study staff being diverted to treat COVID-19 patients; subjects refusing to attend on-site visits; monitors not accessing study sites; and supply chain problems for the investigational product and other supplies.

On the other hand, this is not the end of clinical trials. Study status depends on the study, the site, the region, the nature of the disease, and the investigational product, among other things. Many studies are pausing enrollment and switching to telemedicine, where feasible. Some new sites for ongoing studies are being initiated. New studies tend to be placed on hold. Site contract analysts and budget compliance personnel are reviewing and negotiating clinical trial agreements and related documents – albeit from home – in anticipation of the pandemic easing. While COVID-19-related studies and COVID-19 itself takes precedence, other research is continuing, and should be planned for accordingly.

We will continue to monitor the situation as it unfolds and to share our insights with you..

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

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