Clinical Trials, COVID-19 and the Road Ahead: Building Flexibility into Your Operations

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We hope you and your families are safe and healthy. Many of us are sitting at our desks (at home) adapting to the changing landscape as quickly as possible. In order to operate now and to maximize how effectively we emerge from this crisis, it is important to strategize. This was the topic of the 4th webinar in WCG's weekly series. Our Update sets forth key operational takeaways for your non-COVID-19 studies to help you adapt your ongoing studies and plan for the future.

Planning Now

Why is planning now imperative? Remember that we will not be flipping a switch and having everything return to "normal" when the pandemic subsides. Thinking about what you can do now to adjust to the changed circumstances will serve you well.

1. Monitoring Strategies:

a. Leverage Technology.

b. Collaboration. Sponsors and sites need to collaborate to determine how to conduct source data review and source data verification.

c. Centralized Monitoring Benefits:

i. Enables sponsors to apply statistical methods to data quality in order to identify outliers, protocol compliance and protocol deviations.

ii. Important contributor to data quality.

iii. Can help ensure that deviations are tracked and reported.

iv. Allows for remote work.

d. Centralized Monitoring Limitations:

i. Drug and device accountability may not be possible. Consider how to facilitate this remotely or after on-site monitoring becomes feasible.

ii. Source data review and source data verification are not the same. There may be information the monitor cannot see when monitoring remotely. Factor this into data integrity.

2. Remote Subject Visits:

a.Subject Safety. We previously wrote about subject safety here.

b.Efficacy Assessment: Consult subject matter experts who may be able to advise on how to collect different information remotely or how to validate a new method of efficacy assessment. Safety is first, but efficacy is an important consideration for enrolled subjects.

c. Home Health Visits: These may or may not be appropriate depending on the patient population, stage in development and other risks that may be presented.

d. Data Collection and Data Analysis Plans: Adjust these plans, including:

i. Add new fields to EDC and CRF.

ii. Assess impact of remote visits on safety and efficacy.

iii. Consult your data management and statistics colleagues.

iv. Adjust statistical analysis plan.

3. During a Pause to Enrollment:

a. Adjust payment triggers: WCG recommends paying sites based on EDC entry rather than source data verification by a monitor so that there is no payment delay.

We caution you to keep in mind that payments to the site are traditionally conditioned on the sponsor having first resolved data queries with the site. Query resolution plays an important role in demonstrating that the sponsor is paying fair market value for services rendered (Federal Anti-Kickback Statute compliance). Removing the query resolution requirement as a condition for payment means that the sponsor will need another mechanism to recoup monies paid if the data turn out to be unusable and/or queries cannot be resolved.

b. Plan for ongoing subject visits or restart to enrollment.

c.Manage expiry dates: Closely monitor the expiration dates for drugs, devices, lab kits and other supplies. Ensure that you have adequate materials for now and for restarting enrollment when the time comes.

d. Protocol amendments and deviations See our Update on FDA Guidance Q&A.

e.Ongoing evaluation of whether to continue or pause the study: Continually assess how to manage your studies depending on a variety of factors such as patient population, geography, ability to do remote monitoring and visits, local conditions and global trends.

f.Communication: During a pause to enrollment (where enrolled subjects continue treatment and visits) or a pause to the study (where all subjects and activities stop), communication is a priority because sites and IRBs need to know how to operate; sponsors need to know what is happening; and study subjects need to be

informed. Listen to what barriers exist and what challenges sites are facing so that there can be careful and creative collaboration.

4. Sponsor Teams:

a. WFH: Support and leverage work from home opportunities.

b. Backups: Assign backups for key processes, e.g. SAE processing and reporting; remote monitoring; assessing clinical supplies; and responding to site questions.

c. Document everything – "If it's not documented, it's not done." 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. We previously wrote about Making Safety Decisions here.

d. New ways: Encourage creativity and persistence (while complying with the regulations and focusing on subject safety) because the old ways won't work.

The Road Ahead

1. Potential Disease Landscape – Impact on Planning:

a. Gradual: The re-opening of studies and sites will be gradual.

b. Prioritize: Sponsors and sites will have to prioritize which studies open first.

c. Waves: Future waves of virus spread at national, regional, state or local level will lead to:

i. Some level of social distancing – continuous or intermittent.

ii. Hot spot management – unpredictability.

iii. Regional hospitals continuing to be impacted longer, limiting capacity for research.

d. New normal: Business will not return to normal; instead, we're going to be planning for a "new normal."

2. The Local Environment's Potential Impact on Capacity:

a. Regional hospitals may continue to serve as regional COVID-19 centers:

i. Could slow return to elective surgery.

ii. Radiology and pharmacy services may be diverted for COVID-19 treatment and may not available for research studies.

iii. Certain specialties will have limited capacity, e.g. pulmonology, infectious disease, anesthesiology and surgery.

iv. Healthcare workers may still be reassigned to COVID-19.

b. Community-based hospitals and research centers may have capacity for research earlier.

c. Ramping up will be in a more unstable environment than we were used to.

d. Local context: Be aware of local context because each site will be different – even in the same geographic area.

3. Currently Open Studies:

a. Do not start by opening to enrollment. See this cohort through with the adaptations.

b. Site adaptations: Each site will likely have adapted in different ways.

c. Finish current cohort: Sponsors need to decide how best to complete their studies for the current cohort enrolled.

d. Different cohort outcomes: The group of subjects who went through the height of the pandemic will have different data collected and may have different outcomes than those that did not.

e. Protocol: Sponsors will need to decide whether to use the adapted protocol, return to the original protocol or create a hybrid protocol.

4. When to Open to Accrual:

a. Update documentation: Before new enrollment, all study documents must reflect for new approach based on feasibility assessment, COVID-related safety considerations, data integrity and approved amendments to protocol, informed consent, HIPAA authorization, clinical trial agreement, CTA budget and other contracts, as needed.

b. New locations: Consider ramping up at new locations within the site such as satellite hospitals and clinical research units.

c. Refresher: Consider a new site initiation visit or site monitoring visit to reset parameters prior to enrollment.

5. When to Open New Studies:

a. Capacity: Ensure that you have the capacity (work force, equipment and supplies) before starting up new studies.

b. Subject safety.

c. Adaptive design: Consider new study designs that would proactively address potential continued disruptions:

i. Anticipated vs. adaptive design.

ii. Adaptive design can make it easier to adjust to a limited crisis, a hotspot or a temporary change.

d. Incorporate lessons learned, such as expanding electronic solutions, addressing adaptive solutions for

investigational product accountability, and the social and data integrity impact of the changes made to address this crisis on future study design.

e. Readiness to pivot: Proactively build flexibility into the study process.

6. Early Indications of Recovery from COVID-19:

Recovery will be regionally driven. Dates will not be concrete. Early indicators at local level:

a. Flattening of the curve (number of positive cases and deaths).

b. Availability of adequate COVID-19 testing.

c. Shelter-in-place orders being lifted.

d. Institutions allowing external parties to visit.

e. Physical signs in communities (opening of banks, restaurants, businesses, etc.).

f. Feedback from sites (patient coming back for standard of care, elective procedures restarting).

Sites are not likely to be ready to restart at the same time. It will be different for different sites, which is why open communication with sites is key.

7. Five-Step Plan for Restarting Studies:

This will not be a one size fits all approach.

Step 1: Plan for restarting your studies – assess clinical supplies, regulatory impact, data flow, patient population, geography, remote monitoring and visits, local conditions and global trends.

Step 2: Set Priorities – expect relatively slow, localized restarts.

Step 3: Set Trigger Points – know the steps you'll need to take globally and locally when you start seeing early indicators of recovery.

Step 4: Take Action – when you reach the trigger points, take action to restarting your studies. Remember that communication and transparency among the site, sponsor and CRO are critical.

Step 5: Measure, Adjust and Move – determine how to measure whether or not plans are working. Have flexibility to adjust the plan. Create robust backup plans. Communicate openly regarding changes.

8. Potential Long-Term Impact on the Clinical Research Industry from WCG:

a. Will we return to a "new and improved normal?"

b. Will there be an increased acceptance of new ideas (risk-based approaches, digital tools, telemedicine, etc.)?

c. Will there be an increase in virtual/decentralized trials?

d. Will there be a move to remote site management and site monitoring?

e. Will there be an increase in direct-to-patient trials, investigational product and clinical supplies?

f. Increased focus on the need for flexibility.

g. Increased focus on burdens to study subject.

Good communication across the parties is key to handling current studies appropriately and to work for future studies. Now is the time to plan ahead and to be thoughtful in doing so.

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

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