COVID-19 and Clinical Trial Agreements: Advice for Sponsors for Now and the Future

04-26-20 • alert • katherine leibowitz

The pandemic has spurred sponsors, sites and IRBs to collaborate at light speed to adapt to the evolving health care and regulatory environment. How should sponsors adjust their clinical trial agreements (CTAs) and budgets to reflect operational changes and minimize risk? CTA revisions should address the current crisis and enable the parties to respond nimbly to any future disruption caused by a resurgence.

This Update explores key modifications that sponsors should make to their CTAs for ongoing studies and for studies post-crisis, with a focus on non-COVID-19 studies. For studies relating to COVID-19, the CTAs should track the protective language and requirements of the Public Readiness and Emergency Preparedness (PREP) Act in order to take advantage of the liability immunity conferred and may need to address other matters.

Depending on the study, the product, and the site and local circumstances, the points below will range from "must haves" to "nice to haves" to "for future studies only."

Site Responsibility for Shift to Satellite and Clinic Locations

For sites where the CTA signatory is a large, regional institution, the site may shift study activities to smaller locations such as satellites or clinics. The CTA should include flexibility for the site to shift locations and should ensure that the site's obligations extend to those locations, including those locations' facilities and personnel, particularly if the locations are separate legal entities from the site signatory. By "site obligations," we mean everything ranging from indemnification to insurance, subject injury, confidentiality, intellectual property, on-site and remote monitoring, audit rights and more.

Compliance with Laws

CTAs normally obligate the sites to comply with all applicable laws and regulations. These typically include the FDA regulations (e.g. 21 CFR Parts 11, 50, 54, 56, 312 and/or 812), HIPAA, state privacy, security and confidentiality requirements, and more. Sponsors may want to modify the "applicable laws" section to include the Centers for Disease Control and Prevention (CDC) guidances, federal, state and local declarations and requirements relating to COVID-19, or a broader requirement relating to pandemics or public health emergencies. Further, sponsors may need to address enforcement discretion announced by HHS regarding HIPAA compliance under certain circumstances (e.g. telemedicine, drive-through testing and more).

Subject Injury

Sponsors should carefully review their CTA subject injury clauses to see how broadly they are written. An overly broad subject injury provision could arguably encompass COVID-19-related illness and complications even though proof would be very difficult. A subject injury clause that limits the scope of sponsor's obligations to "injuries caused by the investigational product" vs. "injuries caused by participation in the study" (Subject Injury Scope) can lead to very different outcomes. While the exact wording of these phrases varies, if the Subject Injury Scope is broader than "injuries caused by the investigational product," a sponsor may be taking on liability for COVID-19-related treatments.

Standard Care

Under normal circumstances, if a subject comes down with the flu while at the hospital, the flu is treated as an adverse event and addressed through standard care. Subjects who contract COVID-19 should have their illness handled in the same manner.

Insurance Coverage

While Medicare and private insurance appear to be committed to covering the costs of COVID-19 diagnosis and treatment, whether there will be gaps in coverage remains to be seen. Initially, hospitals were expected to shoulder the costs for uninsured patients, but the Trump administration announced on April 22 nd that it would help hospitals pay for treating uninsured COVID-19 patients. With the financial stressors at play right now, some sites and subjects may look to sponsors to cover costs associated with COVID-19 treatment. Given the circumstances, are the Subject Injury Scope and corresponding carveouts (see below) in the CTA adequate?

Scenarios

These may sound unreasonable, but consider the following scenarios: In the course of negotiations with research institutions, we have had a handful of sites tell us that the purpose of expanding the Subject Injury Scope to "injuries caused by the study" is to cover a situation where, for example, the subject falls off the curb and breaks a leg when leaving the institution after a study visit. We have also seen sites require the sponsor to cover the costs of emergency treatment for a heart attack experienced by a subject on the operating room table during an implant of an orthopedic device in the spine where neither the site nor the sponsor was at fault. It may not be a far stretch from these examples to a subject contracting COVID-19 at an on-site study visit and expecting coverage by the sponsor.

Study-specific Concerns:

i. What if the subject population is immunocompromised and therefore more susceptible to COVID-19?

ii. What if the study drug or device makes the subject more susceptible to COVID-19?

iii. While unlikely, what if the COVID-19 screening using a nasal swab causes a hemorrhage followed by a cascade effect?

Proof and Reputational Harm

Of course, there is the problem of proof. How will a site prove that the subject contracted COVID-19 during the study visit? There is also reputational harm. Under normal circumstances, most subject injury situations settle. Sponsors want to be good corporate citizens, and generally, they want the problem to go away as quickly and quietly as possible. But sponsors have not had to consider the likelihood of subjects contracting an extremely communicable disease that can be fatal, is easily and silently passed on and for which there is no cure…while at a study visit. Nor have they faced site-wide, screening-related concerns.

Carveouts

In addition to narrowly tailoring the Subject Injury Scope, Sponsors should carefully review the carveouts from their subject injury obligations. Common carveouts include site negligence, failure to follow the protocol or applicable laws; preexisting conditions; natural progression of the study disease and more. Going forward, should carveouts (and corresponding language in the indemnification provision) include bacteria, viruses, epidemics or pandemics?

Additional Limits on Site Responsibility

If the site is a public institution protected by sovereign immunity and state law caps its liability for torts, then even if the subject injury clause is narrowly tailored, as between the volunteer study subject and the sponsor, whom would a judge require to shoulder the responsibility? The state's joint and several liability doctrine could also leave the sponsor responsible. Additionally, the PREP Act may shield the site. Sponsors need to consider what happens if the study site has limited liability or goes bankrupt.

Indemnification

See the subject injury discussion above and review the CTA indemnification provision for consistency with the subject injury scope and carveouts. Otherwise, any effort made to narrow the subject injury clause may be undone by the indemnification provision.

Sponsor Insurance

Check insurance policies for coverage of COVID-19-related illness and related complications. No-fault medical expense coverage for subject injury and clinical trials insurance policies likely do not provide coverage unless there is a link to the study product. General liability or property insurance might offer coverage, but these policies have not been tested in this way. Keep in mind that shifting to remote monitoring may spur sites to request proof of cybersecurity insurance.

Audit and On-site Monitoring

If sites shift the study to satellites and clinics, the CTA should ensure that the sponsor's audit and monitoring rights cover those locations. Sponsors may not be able to access these locations if they are separate legal entities from the site signatory.

Remote Monitoring

The CTA and budget should address remote monitoring. Remote access to the site's electronic health record (EHR) systems could enable robust source data verification (pre-crisis, this was sometimes accomplished by the monitoring sitting with the study coordinator at the site), but this is hard to implement on the fly because of HIPAA issues, difficulty providing access only to the data that the monitors need and other concerns. For now, sites, sponsors and CROs are scrambling to implement remote monitoring solutions that include, at a minimum, limited remote monitoring for safety issues. The FDA Guidance that we previously reported on, including the Q&A section, was recently updated to include more detail about remote monitoring. In Q13, FDA explains that remote monitoring should focus on the review of critical study site documentation and source data, and that the study monitor should focus on study activities that are essential to subject safety and/or data reliability. FDA suggests several options, including establishing a secure remote viewing portal, remote access to the EHR, and uploading certified copies of source records to the sponsor's EDC system or other secure cloud system.

Considerations for the CTA:

CTA Body

Confirm that the CTA does not impede remote monitoring by the sponsor and its representatives. For example, some CTAs state that the site will provide only de-identified data to the sponsor. Because dates of service are HIPAA identifiers, this type of language is impractical, as it does not enable proper research. The sponsor and its representatives need access to protected health information (PHI). At a minimum, the CTA must not prohibit the site from using and disclosing PHI to the sponsor and its representatives.

CTA Exhibit

For greater flexibility, add CTA language that addresses remote monitoring at a high level with instructions to include additional terms in a CTA exhibit that could be modified over time by mutual agreement of the parties.

Remote Monitoring Agreement

Some sites will provide separate "remote monitoring agreements" to bind the sponsor to terms. A remote monitoring agreement may be a contract that the parties sign. Alternatively, the site may present it as a "clickwrap" or "browsewrap" agreement that requires each monitor to click "I agree" before first accessing the site's system or as a link on the sign-in screen for the remote monitoring portal. Sponsors should review standalone remote monitoring agreements carefully, particularly for risk mitigation provisions that conflict with the carefully negotiated indemnification, limitations of liability and other provisions of the CTA. Because the sponsor may not have an opportunity to review any clickwrap or browsewrap agreement before a monitor clicks "I agree," the CTA should include language that rejects any contrary language contained in a standalone remote monitoring agreement.

CTA Budget

Shifting to remote monitoring may impact costs for the study sites. The parties will need to amend the CTA budget accordingly. For fraud and abuse purposes (e.g. anti-kickback, False Claims Act), the sponsor should not pay outside of the written study budget. CTA budgets now and post-crisis should include a mechanism to enable the parties to pivot to different payment structures if remote monitoring is periodically activated or terminated.

Principal Investigator and Staff

Sponsors should consider the potential unavailability of the principal investigator (PI), co-investigators, subinvestigators, study coordinators and other study staff due to illness, diversion to COVID-19 treatment or other public health emergency reasons. This issue goes beyond the standard provision that enables the sponsor to terminate if the PI leaves the institution because the dearth of personnel could make it difficult to continue the study.

IRB Correspondence

The CTA should already obligate the site to provide the sponsor with copies of all IRB correspondence relating to the study or the study product. The sponsor should consider requesting copies of IRB policies related to public health emergencies as they become available.

Termination and Study Pause

Sponsors should review the termination and suspension provisions of the CTA to allow for study pauses and possibly early termination. For example, how long should a pause last before a party can terminate? Other considerations include supply chain problems that impact the study product or other medical supplies, site study personnel unavailability due to diversion for COVID-19 patients or illness, and the inability to collect study data due to safety risks to subjects. In the event of early termination, sponsors should recoup advance payments for subjects that have not been earned.

CTA Budget

The parties should revise the CTA budget to adapt to study changes prompted by COVID-19 and to anticipate future disruption. For example, the budget should reflect changes relating to data collection procedures, number and

nature of study visits, remote monitoring costs, impact on participation payments to subjects for visits removed from the schedule, shifts from on-site visits to telemedicine, additional costs to study subjects who may lack cell phones or Internet services for telemedicine, study staff resources and more. Further, if the trigger for sponsor milestone payments changes from data query resolution to entry of data into the EDC system, there needs to be a mechanism for the sponsor to recoup the payment if the data are unusable or queries are not resolved. For compliance purposes (anti-kickback and False Claims Act), the study budget needs to be agreed upon in writing in advance and must reflect fair market value for services actually rendered. Building in flexibility to adjust payments for changing circumstances needs to be done properly from a fraud and abuse perspective.

Force Majeure

If the CTA has a force majeure clause, review that clause for triggers and impact on performance obligations, including termination rights and payment. Force majeure clauses are fraught with potholes: they are highly dependent on state law; they are difficult to enforce; and they can undermine a party's ability to take advantage of a better remedy under state common law doctrines of impossibility, impracticability and frustration of purpose (although not all states recognize all of these doctrines and/or employ them very narrowly). Force majeure clauses are difficult to use properly (e.g. leading to claims of anticipatory repudiation), and courts have historically been quite skeptical of force majeure claims because the default rule is that promises must be kept. Any force majeure clause should be carefully drafted under applicable state law. Many litigators recommend instead that the contract directly identify intolerable contingencies and build remedies into the contract that would become available if those contingencies occur. For example, identify the event that would make the sponsor not want to pay or deliver study product, and make performance expressly conditioned on that event not occurring or explain what happens if that event occurs.

Miscellaneous Operational Changes

Sponsors should think through the operational changes made to the study conduct and protocol and reflect this as needed in the CTA. For example, if home health care providers will take the place of on-site visits or the investigational product will be shipped directly to the subject's home, the CTA should build in responsibility by the site for these activities and personnel.

Agreement to Address Changing Environment in Good Faith

While the obligation to act in good faith always exists for contracting parties, consider including language obligating the parties to work together to modify the CTA to address changes in the medical, legal and regulatory environment.

PREP Act Immunity

For COVID-19 studies, the CTA should track the language and requirements of the PREP Act to take full advantage of the immunity from liability that it provides. For non-COVID-19 studies, consider whether the PREP Act could impact the subject injury or indemnification provisions.

Other Contracts to Review

The revolutionary changes to clinical trials operations stemming from COVID-19 will have a trickle-down effect on other study-related contracts and documents both during and after the public health emergency. We will eventually reach a "new normal" that will require the ability to pivot quickly for subject safety, data integrity and other reasons. Sponsors should consider the downstream impact of the current crisis on all clinical trial transactional documents, recognizing that some documents may be more heavily impacted than others.

Documents include:

1. Informed consent
2. HIPAA authorization
3. Remote monitoring agreements
4. Data monitoring committee (DMC) agreements, including DSMB and CEC
5. CRO master services agreements
6. EDC vendor services
7. Core lab services
8. Supply chain agreements
9. Physician consulting agreements, including medical monitor, national principal investigator, scientific advisory board, etc.
10. Other ancillary services documents supporting the conduct of clinical studies

Regulatory agency guidance and industry webinars have stressed the importance of documentation. This crisis has required all stakeholders to devote immediate attention to patient safety and to document their decision-making process carefully. Equally important is proper contracting around the changing study obligations and associated risk.

Many operational changes engendered by COVID-19 may continue for months or longer. Clinical trial agreements and related documents need to be flexible and resilient enough to enable the parties to function now and to conduct studies in a potentially bumpy future. It is critical to review and update agreements so that they reflect the new and developing reality.

The above recommendations represent our thinking in "real time" and will likely evolve as the situation progresses. We can help you adapt your documents to the "new normal," including evaluating the risks and drafting to mitigate them. We will continue to monitor the unfolding situation and encourage you to check our News & Insights for updates.

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

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