

Collaboration to Develop Recommendations to Improve Trial Activation Timelines

Prepared by the AACI Corporate Roundtable Trial Activation Task Force



Introduction

The Association of American Cancer Institutes (AACI) represents 108 leading academic and freestanding cancer research centers in North America. AACI Clinical Research Innovation (CRI) is guided by a member-elected steering committee comprised of clinical trials office (CTO) medical directors and CTO administrators who help guide, implement, and disseminate the strategic plan, goals, and best practices across AACI cancer centers. To drive change and advance cancer center clinical research programs, AACI developed a forum for cancer centers to address topics of mutual interest with their pharmaceutical industry colleagues, known as the AACI Corporate Roundtable. There are 10 corporate roundtable members who meet at least twice a year with AACI leadership to foster communication and build relationships that lead to collaborative research best practices that benefit patients with cancer and their families.

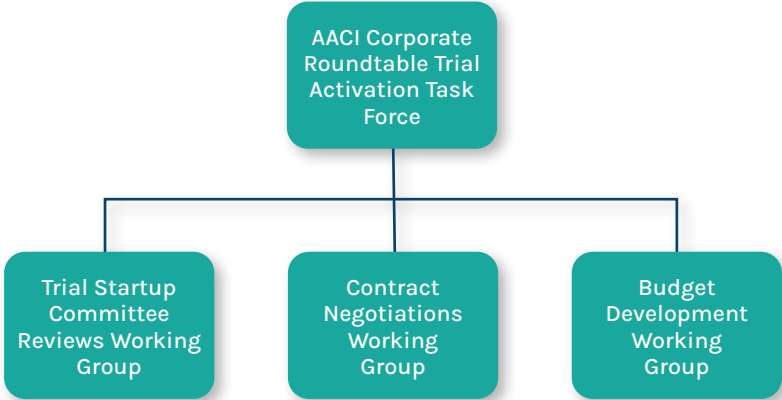
Prioritizing the health and safety of its members during the early months of the COVID-19 pandemic, AACI convened virtually for its 2020 annual meeting. The purpose of this meeting—which included AACI leadership and industry leaders representing the Corporate Roundtable—was to discuss operational challenges in cancer research that emerged during the pandemic, including effects on trial activation, lessons learned regarding remote staff and practices including remote site monitoring, and how to utilize telehealth for trial patients.

It was apparent to sponsors and cancer centers during this meeting that the time to trial activation needed to be addressed more purposefully, as lengthy delays to trial start-up increased costs for patients, trial sites, and sponsors. Participants agreed that transparency in communication is key to a mutual understanding of expectations and processes by the sponsors and cancer centers and essential to improving trial activation timelines. It was suggested that this group would be ideally suited to create recommendations to address trial activation pitfalls and identify process improvements. This led to the development of the AACI Corporate Roundtable Trial Activation Task Force.

This task force was composed of 33 members, including AACI cancer center members involved with trial activation, a representative of the NCI, and industry sponsor leaders in the trial activation arena. The task force's initial virtual meeting was held in the fall of 2020 to create the charge for the task force and identify additional stakeholders to develop recommendations. Five key areas for improving trial activation timelines were identified: 1) develop communication expectations for trial activation at the site and sponsor level; 2) explore the feasibility of industry creating a national coverage analysis (NCA) for industry-sponsored trials; 3) utilize master trial agreements to shorten contract negotiations; 4) use commercial online portals at trial sites to speed trial activation; and 5) better inform industry of the complexity of trial activation at academic cancer centers with NCI designation, including requirements of their Protocol Review and Monitoring Systems (PRMS) used for establishing the scientific prioritization of cancer trials, which can contribute to delays on the site side.

The AACI Corporate Roundtable Trial Activation Task Force chose to focus on three areas of activation: 1) contract negotiation, 2) budget development, and 3) trial start-up committee reviews. The task force was divided into three working groups to allow members with relevant interests and experience to work together (Figure 1). Each working group developed a charter to guide future discussions.

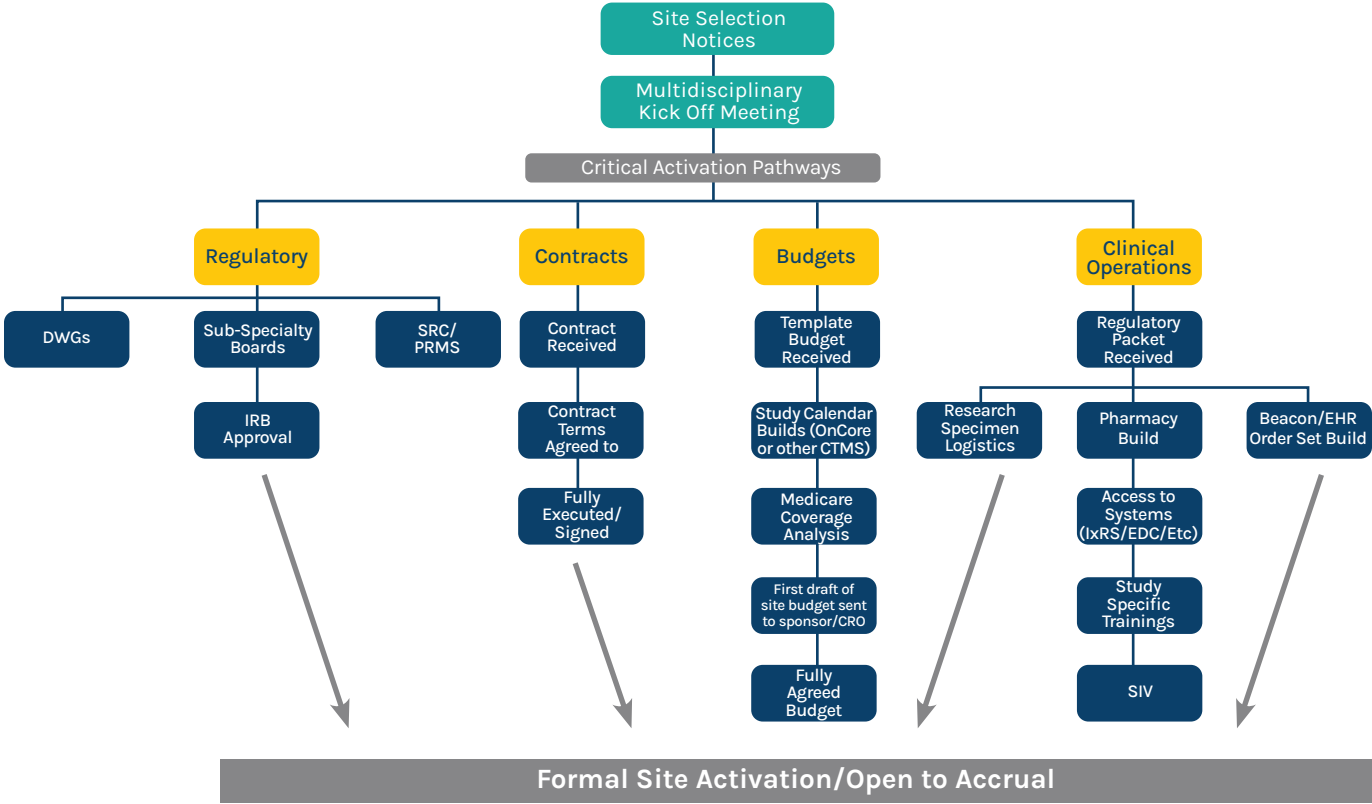
Figure 1. Organizational chart of the AACI Corporate Roundtable Trial Activation working groups



Barriers to Trial Activation

Each of the working groups held preliminary discussions to identify roadblocks to timely trial activation (Appendix 1). The challenges noted by the task force are found in Figure 2 and include budget and contract negotiations, frequent protocol amendments received during negotiation of the budget and contract, lack of responsiveness, lack of a start-up process “roadmap,” staff turnover, difficulties with technology and systems, and coverage analysis inconsistencies. Through discussion it was noted that the nuances of academic health systems and university requirements for trial activation were well-understood by sponsors.

Figure 2. Study start-up roadmap template



Disparities in Timeline Expectations

NCI-Designated Cancer Centers target a 90-day start-up timeline from the Protocol Review and Monitoring Committee (PRMC) submission to trial activation². There was a disconnect between when sponsors started the activation timeline internally versus when sites started the activation timeline. In fact, there are often many months of discussions and review before a protocol is submitted to the PRMC. Sponsors included time for these discussions in their tracked activation timelines, but sites did not, contributing to the disparity in trial activation timeline expectations. The internal trial review process at cancer centers includes review by individual physicians and disease-focused research teams, and often includes a feasibility committee review to ensure that the necessary resources are available to conduct the trial (e.g., pharmacy, lab, nursing). More recently, especially considering COVID-related staffing challenges, many centers have limited the number of trials in study start-up at any one time, leading to additional delays from when a protocol is brought to a site and when it officially enters the start-up process. Once trials enter the study start-up process, there are multiple steps involved, each requiring communication between sites, sponsors, and internal site committees. Communication was identified as a barrier to timely activation and suggestions were made to improve communication through clear definitions of start-up milestones and transparency regarding the start-up steps at sites.

The task force developed a trial activation process roadmap, **Figure 3**, to better define the requirements common across sites to be shared with industry sponsors to foster better understanding about academic center standard procedures during trial activation. Common time points and definitions from sponsors and sites were collected. The roadmap presupposed site feasibility work and official site selection. Figure 3 illustrates the roadmap and outlines four critical activation pathways, including regulatory, budgets, contracts, and clinical operations. Each area has milestones of the study site activation process. This is the first known external product of such a process or workflow. The hope is to establish agreed-upon time points for engagement and progress tracking between the study sponsor, participating site partners, and any other applicable stakeholders such as clinical research organizations (CRO).

Figure 3. Top challenges identified by academic sites and industry partners

| Top Challenges Identified by Academic Sites and Industry Partners |
|---|
| Budget and Contract Negotiations |
| Frequent Protocol Amendments Received During CTA Negotiations |
| Misalignment of Timelines and Prioritizations |
| Lack of Responsiveness with Communications |
| Lack of Start-up Process Roadmap |
| Staff Turnover |
| Difficulties with Technology and Systems |

Providing a process map outlining site-specific start-up workflows and realistic timelines to sponsors is a best practice recommendation. Study activation “kick-off” meetings should be held between applicable stakeholders, such as the sponsor, partner site, and the designated CRO where together they create site-specific start-up plans with proposed completion dates throughout the critical activation pathways. This roadmap review should optimally occur during the sponsor’s site qualifying visit or shortly after the site selection notification. This permits sites to determine if their start-up process allows adequate time for enrollment and the sponsor’s ability to proactively address obstacles to provide for efficient start-up timelines. Sites enter projected timelines into each roadmap section and post their completed start-up template on their website to share with the sponsor. Transparency in the necessary steps allows teams to focus on rate limiting steps along the timeline and aim to complete as many steps as possible in parallel.

Other key best practices were identified. Clear and frequent communication is essential, and escalations in communication shortfalls should be expected as appropriate and necessary. Sponsors should ensure relevant study materials, such as laboratory manuals and imaging manuals are included in the site’s regulatory packets. It was noted that sponsors did not realize that sites need at least draft manuals to assess feasibility of the trial at their site. Sponsors and sites should consider developing agreed-upon master consent form templates/sections to truncate review timelines. Sponsors and sites should implement staff retention strategies and contingency plans for staff turnover throughout the study and site activation process. There should be consideration of benefits of using a central IRB versus local IRB. A fully executed clinical trial agreement (CTA) should be completed before scheduling a site initiation visit (SIV).

Contract Negotiations

Contract negotiations were identified as another barrier to timely trial activation. The working group developed a 19-question survey, including 10 questions to be completed by the cancer center task force members and nine questions for industry task force members to determine barriers specific to contract negotiations. One of the key obstacles identified by the sites is that this part of the activation process is often outside the control of the sites themselves as contracts are typically completed by the university’s legal team or Office of Sponsored Projects. The sponsors noted that the various parties involved in contracts including point of contact for may differ along the process and that the CTO was not often aware of issues that arise with the legal teams. Discussion of intellectual property and participation of additional tissue collection at the sites are common challenges.

Proposed best practices (**Figure 4**) include the use of standard CDA process and provide as much information to sites as possible upfront to help them determine if the trial would be of interest to open, thus saving time and resources if the protocol is felt not to be a good fit for the site; the use of master trial agreements so that standard points would not need to be renegotiated repeatedly; and to stay involved in the communication between the legal teams of sites and sponsors and escalate questions.

Figure 4. Contract Negotiation Working Group key deliverables and proposed best practices

| Contract Negotiation Working Group Key Deliverables |
|--|
| Encourage master trial agreements to speed up budget development and contract negotiations. When master agreements are unavailable, the last CTA will be used as a starting point in the process. |
| Develop a master confidentiality disclosure agreement (CDA) for trial sites allowing them to determine their interest in opening a trial and eliminating the negotiation of unnecessary CDAs. |
| Recommend that sites make their trial start-up process available to sponsors, key contracts involved in the process, and their role along with expectations for communications and how to escalate communications when negotiations are stalled. |

The working group members discussed next steps for both sponsors and sites. The sponsors agreed to provide pre-CDA trial synopsis to the site principal investigator (PI) to facilitate trial site interest before presenting the site with the CDA. Often, the CDA does not provide enough information for the PI to assess portfolio fit and competing trials. Additional information prior to the CDA process will help sites determine if the trial is of interest, and if not, will prevent sites from undertaking the CDA process for a trial that will not be pursued. The suggested information to be provided pre-CDA should include the subject population to be enrolled (e.g., cancer type, stage, age group, number of prior therapies allowed, etc.), and the progress of sponsor trial enrollment (including projected first and last patient to be enrolled). Members highlighted this information as being helpful for the sites when deciding which trial they want to pursue or trials they do not wish to open, and sponsors should consider including this criterion in site feasibility assessments. Another recommendation was to incorporate master agreements and consider adopting the Accelerated Clinical Trial Agreement (ACTA).

The working group’s recommendation for the sites was to create an institutional fact sheet (noted in **Figure 5**) detailing their trial activation process for review of the CTA and contacts of staff involved.

Figure 5. Detailed trial site fact sheet

| Trial Site Fact Sheet |
|--|
| Primary start-up coordinator contacts name and email address |
| Descriptions of committees or workflows to describe the start-up process |
| Cancer center disease center prioritization review and scientific review completed the Protocol Review and Monitoring System (PRMS) |
| Feasibility review process |
| Other trial site committee reviews (e.g., tumor board, radiology review for imaging studies, radiation safety and biosafety committees, investigational drug pharmacy) |
| Institutional review board (IRB) review or central IRB |
| Medicare Coverage Analysis (MCA) |
| Budget development and contact information |
| Contract review |
| Site initiation visit |
| Study activation |
| Flow chart showing the entire process |

The fact sheet should also include a centralized email account that can be answered by anyone in the department. This would allow for an equal amount of transparency and help with the recent staff turnover. The task force encourages trial sites to utilize the standard site template and centers to make available to industry sponsors.

Budget Development

The third sub-group focused on the challenges for establishing a financial analysis of the trial costs included in the CTA and obtaining necessary approvals from sponsors and sites. At the initiation of the working group, the following nine items in **Figure 6** (not listed in order of importance) were identified as potential key deliverables. Within the clinical research community, trial costs are identified as standard vs. research care based on the procedures or services and frequency identified in the research protocol. Other trial costs noted in the CTA include labor wage rates, start-up fees, trial-related annual maintenance fees, and data collection costs. Members report that the process of securing an agreement on the budget can range from a couple of weeks up to several months. This timeline is unacceptable to the trial sites, sponsors, and, most importantly, the patients waiting for access to novel therapies that may be the only treatment available. The group’s aspiration was that cancer centers and industry could partner and establish a more streamlined process for establishing and agreeing on a trial budget in less than four weeks. The process ought to include an escalation route in cases when there is a standstill between the stakeholders.

Figure 6. Budget Development Working Group’s key deliverables and recommendations

| Key Deliverables | Recommendations |
|---|--|
| 1. Define the minimum required study package from sponsors that include the key components needed by sponsors, such as the final protocol, lab manual, and data to be collected in the eCRF | Minimum study package should include final protocol, laboratory manuals, investigator brochure, and budget shell. |
| 2. Establish the goal in business days for the completion of the budget negotiations | Assuming a study package (see #1) is provided to the site, the goal for consensus budget is 25 business days. This can be further improved (our estimate is 5-10 days less) if the sponsor provides the site a study-specific National Coverage Analysis (NCA) that will detail all procedures that are research (R) and not standard of care (SOC). Day zero is the receipt of the entire study package and the budget clock stops on the day that the sponsor has accepted the budget for the study in question. |
| 3. Establish escalation processes for when there is an impasse or the time allotted is exceeded | The site and sponsor need to identify a key member from each side to be the decision maker on study budgets. (For sites this tends to be a senior administrative leader over finances or in similar position). Schedule a call as soon as there is 1) an impasse in negotiations, or 2) the time allotted to reply has been exceeded. |
| 4. Establish data tracking tools of performance by cancer center and sponsor | It was a challenge to determine appropriate tracking tools that work for all sites and sponsors. As such, sites and sponsors are encouraged to utilize existing performance measurement tools to track efficiency of this process and use that for continuous process improvement. |
| 5. Determine rate-limiting steps to site budget approval | Sites organizational models vary, and levels of approval are needed to get a comprehensive study budget complete. Sites are encouraged to map out the process and identify all non-value steps added to address. Additionally, sites need to set expectations upfront with sponsors, in terms of what the site can achieve for turnaround times on budget. |
| 6. Identify ways to introduce greater transparency into the site budget development | For greater transparency, sponsors should work toward prepopulating site study budgets as much as possible. NCA provision will help, and sites can provide a packet of known/fixed costs to further streamline the process. |
| 7. Request sponsors provide a NCA for each study | If the sponsor provides the site a study specific NCA that will detail all procedures that are R and SOC, it will improve the timeline of budget negotiations. |
| 8. Standardize fees and site budget template format | Standardizing fees is not likely attainable due to the number of sponsors and sites, but if achieved would almost certainly improve the timeline for budgeting, likely by 50 percent or more. |
| 9. Recommendation vs. guidelines for a master rate sheet/fee schedule | The majority of study sites responded that a guideline for a master rate sheet/fee schedule tool would be beneficial. A challenge associated with the fee schedule was hesitation about committing to finances for a defined time period. However, if addressed in the contract language associated with the fee schedule, it could be possible and like #9 would greatly reduce the site budget negotiation cycle times. |

Members of the group wanted to define, through a survey, key drivers and gather a baseline of what will have the biggest impact on reducing activation timelines and determine the best budget package that can be handed to sites. The survey consisted of eight multiple-choice questions and was distributed amongst the working group members to complete in a two-week period.

When asked what the minimum is needed from a sponsor to begin evaluating a budget is the protocol, laboratory manuals and budget shell (document that contains procedures and personnel effort and the allocations at each visit) were the most essential documents necessary to develop a budget in a timely manner. This represents a challenge to both sponsors and sites as the laboratory manuals are typically not available at the time the budget template is provided to the study site.

The NCI’s National Clinical Trials Network (NCTN) has implemented a predetermined Medicare Coverage Analysis (MCA), referred to as a national coverage analysis (NCA) for their trial by providing a suggested coverage analysis for how third-party payors and the sponsor should cover each trial procedure². The process includes having access to a completed NCA when the trial site receives the budget and contract from the NCI for facilitating budget negotiations and helping all parties understand the allocation of trial costs. A representative from the NCI stated the protocol and consent form are used to determine the interventions, services, and tests required during the study.

Then based on the Medicare coverage determinations, National Comprehensive Cancer Network (NCCN) treatment guidelines, and Current Procedural Terminology (CPT®) codes which offer a uniform language for coding medical services and procedures a trial budget is created detailing standard or research care. The site's institutional review board (IRB) review can generate many questions regarding trial care by asking if it is standard vs. research. Having the trial NCA helps their review. As industry conducts the same trial at multiple sites, the concept of asking them to provide a NCA for their trial would help trial sites with the budget development and speed up negotiations.

While requesting a NCA of sponsors was not standard practice for most industry sponsors represented in the task force, creating a Medicare coverage analysis is essential for all sites, and having available a NCA from the sponsor helps to drive faster budget finalization cycle times.

Another key finding was that over 75 percent of the respondents stated that their turnaround times for the initial budget were greater than eight weeks. The most common limiting step for the trial site is creating an MCA which can take a minimum of four weeks to create and finalized. Additionally, the trial site's MCA is dependent on the site's internal departments to provide cost estimates and approvals. If the appropriate trial documents are not provided to the site, this process is delayed.

Members of the working group discussed the merits, challenges, and feasibility of each of the key deliverables noted in **Figure 6**.

While the working group met, surveyed, and discussed how sites and sponsors could collaborate to reduce processing time, there were specific items that became clear to both sides. All sponsors agreed they were willing to consider a utilizing standardized site budget template. This standardized approach would enable efficiencies from the study site perspective in having to only evaluate one format. Most study sites agreed a standardized budget template is beneficial and would help to decrease site budget negotiation cycle times.

One challenge associated with utilizing a standardized fee schedule related to hesitation about committing to finances for a defined period. However, this could easily be addressed in the contract language associated with a budget fee schedule. While having one master fee schedule would be ideal, the reality is that many of each site's nuances are needed to create a specific "master" agreement for their institutional needs. Knowing the hurdles helps everyone understand the delays and establishes a foundation to move toward the goal of a 25-day process.

Conclusion

Cancer centers and pharmaceutical partners have a common interest in opening clinical trials expeditiously. Steps in the process vary between sponsors and cancer centers. The AACI Clinical Trials Activation Task Force convened to critically examine the trial activation process and develop best practices to address common barriers to clinical trial activation. Important findings from the task force included defining the study start-up timeline, required documents, and steps in the study start-up process; outlining best practices and necessary information from sponsors in order to streamline budget and contract negotiation; and determining information needed from both sponsors and sites to understand a site's start-up process, required documents, and contacts. Both sponsors and sites agreed that clear and frequent communication is essential to expedite study start-up.

This manuscript represents the rich discussions and collaborations of sites and industry who share in the frustrations of activating trials. Through transparency and communication, we can continue to build relationships and define clear expectations, resulting in a shorter process with fewer delays.

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Appendix 1: Survey Questions to Gather Data for Recommendations

Two of three working groups created and disseminated surveys to either their working group members or to all three working groups to gather data on their targeted topic.

Cancer Center Survey Questions for Contract Negotiations Working Group

1. What is the name, title, and organization name of the survey respondent?
2. What Confidentiality Disclosure Agreement (CDA) bottlenecks do you experience when working with industry sponsors?
3. When working with industry sponsors and CDAs, can you suggest best practices you use to speed up negotiations?
4. Do you agree or disagree with the following statement? Providing the sponsor with a list of minimum requirements mandated by the institution (e.g., subject injury compensation, research data the site will own, indemnity, or confidentiality) before a contract is ever presented has helped accelerate negotiations.
5. Do you agree or disagree with the following statement? It helps accelerate negotiations by providing a global template for sponsors (e.g., a model contract that includes both our non-negotiables and their non-negotiables).
6. Do you agree or disagree with the following statement? It is helpful to have a list of reliable contacts from the sponsor to use when our institution has questions.
7. Do you agree or disagree with the following statement? Providing the sponsor documentation of the institution's process and contacts for reviewing and approving a clinical trial has accelerated negotiations.
8. Do you agree or disagree with the following statement? It is helpful to provide the sponsor with the documents required for budget development and submission to the IRB.
9. Do you agree or disagree with the following statement? Utilizing a master agreement or model contract (for a designated length of time) would accelerate negotiations with industry sponsors.
10. Have you participated in the Accelerated Clinical Trial Agreement (ACTA)? If yes, please list objections or barriers in the comments box.

Industry Sponsor Survey Questions for Contract Negotiations Working Group

1. What is the name, title, and organization name of the survey respondent?
2. What are Confidentiality Disclosure Agreements (CDA)-related bottlenecks you have experienced when working with oncology research sites?
3. When working with study sites and CDA, can you suggest best practices to speed up negotiations?
4. When working with pharmaceutical companies and CDA, can you suggest best practices to speed up negotiations?
5. When working with study sites and CSA/CTA, can you suggest best practices you use to speed up contract negotiations?
6. Do you agree or disagree with the following statement? Working on activation elements (budget, contract, and regulatory /IRB) in parallel is more efficient than doing so sequentially (one at a time).
7. Do you agree or disagree with the following statement? Working with central IRBs helps achieve patient treatment sooner.
8. Do you agree or disagree with the following statement? Streamlining pre-contracting activities (such as PRC/SRC, IRB submission, coverage analysis, etc.) is a best practice to streamline study activation.
9. Have you participated in the Accelerated Clinical Trial Agreement (ACTA)? If yes, please list objections or barriers in the comments box.

Survey Questions for Budget Working Group Members:

1. When a sponsor provides you with a budget, what is the minimum information that you need in order to properly evaluate the budget?
2. Assuming you have the budget packet you requested, what is a realistic turnaround time for your initial budget to be submitted to the sponsor?
3. How do you prefer the sponsor pay for each patient visit?
4. How do you prefer the sponsor pay for the following costs? Itemized Start-up/Total Start-Up/Itemized Annual Fees/Total Annual Fees
5. Is it helpful for the sponsor to provide prepopulated site budgets with the most recently negotiated costs included for your review?
6. Sponsor, are you willing to consider a uniform site budget template utilized by other sponsors to help streamline budget negotiations from a site perspective?
7. Is a master fee schedule useful for your study site?
8. Which method do you prefer to use when negotiating your study budget? Online Negotiation Tool/Email/Excel