Accelerating Clinical Trial Activation: a Collaborative Framework for Managing Pre-Activation Protocol Amendments

Prepared by the AACI Corporate Roundtable Trial Activation Task Force

INTRODUCTION

Clinical trial activation remains one of the most critical, and challenging, steps in bringing new cancer therapies to patients. Over the past several years, cancer centers and research partners have invested substantial effort in improving start-up efficiency through enhanced planning, clearer role delineation, and more standardized processes. Despite these efforts, activation timelines continue to be frequently disrupted, particularly by pre-activation protocol amendments.

Since the Association of American Cancer Institutes (AACI) published its 2023 Trial Activation White Paper, the study start-up process has continued to evolve. Protocols are increasingly more complex, often including multiple cohorts, adaptive designs, and expanded eligibility criteria. At the same time, sites are navigating heightened regulatory and compliance requirements, staffing constraints, and competing priorities, while striving to deliver novel therapies to patients as efficiently as possible. In this environment, pre-activation protocol amendments, especially those that impact consent forms, operational workflows, budgets, contracts, and treatment plan builds can require modifications that contribute to significant delays prior to trial activation.

In response to these ongoing challenges, AACI, which represents more than 100 leading academic and freestanding cancer research centers in North America, formed a Trial Activation Working Group in January 2025. The working group was comprised of 15 AACI cancer center members, including three from AACI's Clinical Research Innovation (CRI) Steering Committee, and evolved to include AACI Corporate Roundtable industry and research leaders. Early discussions highlighted that trial activation encompasses multiple components, and that meaningful progress would require focusing on well-defined areas of the start-up process. To drive practical change, the group agreed to focus on discrete elements of activation that influence timelines, selecting pre-activation protocol amendments as its first area of focus. Through survey data and facilitated discussions, members shared real-world experiences identifying points of process breakdown, areas of flexibility, and opportunities where clearer guidance could improve efficiency.

This white paper reflects these discussions and experiences, providing an updated perspective on trial activation in 2025, with an emphasis on pre-activation protocol amendments. The paper outlines common challenges, highlights best practices implemented at selected institutions, and identifies opportunities for improved communication and coordination among stakeholders.

By focusing on a trial's pre-activation period, when decisions can either prevent or compound downstream delays, this paper aims to expedite a piece of the timeline while respecting regulatory requirements, operational realities, and the shared goal of opening trials for patients as efficiently as possible.

STATEMENT OF POSITION

This working group offers recommendations that coalesce around three guiding principles. First, that the impact of pre-activation amendments will be substantially improved by collaboration among stakeholders, including sponsors, Contract Research Organizations (CROs), specialized clinical trial execution vendors, Institutional Review Boards (IRBs)/Research Ethics Boards (REBs), and trial sites. There is recognition that an individual stakeholder's ability to effect lasting change is limited. Second, offering practical and actionable changes is the best route to meaningful improvement. Third, lasting change must be built on strong, cross-stakeholder relationships, supported by proactive, transparent, and continuous communication.

SUPPORTING ARGUMENTS

Previous scholarly work has evaluated and quantified the impact that amendments have on oncology clinical trials. The Tufts Center for the Study of Drug Development (Tufts CSDD) has conducted some of the most comprehensive assessments of the impact of amendments on clinical trials. In an extensive 2022 survey, Tufts CSDD found that trials average more than three amendments during the life of the study, with an average of 260 days required to implement an amendment (Getz, 2024). The percentage of studies with pre-activation amendments in the 2022 survey decreased compared to the 2010 and 2015 surveys, yet remains substantially high, at 24 percent of all studies.

In prior works, data was gathered on the direct cost to sponsors to implement an amendment, estimating daily cost at $40,000 for Phase II and Phase III trials, with amendment costs ranging from $141,000 to $535,000 (Smith, 2024). Complementing this, Tufts CSDD reports that the average cost to develop and gain approval for a new drug is approximately $2.6 billion, underscoring the broader financial stakes within which protocol amendments occur. This highlights the substantial financial impact of amendments on overall study execution, which do not include site expenses and other indirect costs.

Several sites have recently shared efforts to address the processing of trial amendments (Kukulka et al., 2025 and Ugrenovic et al., 2025). These approaches primarily focused on detailed process mapping across departments and the establishment of dedicated roles or teams to manage amendment implementation. While these strategies enhanced internal coordination, they required additional site infrastructure and associated costs and notably did not incorporate direct collaboration with external stakeholders such as CROs, sponsors, or IRBs. At Moffitt Cancer Center, Ugrenovic et al. showed a decrease in the number of amendments in process; however, neither study reported measurable improvements in activation timelines, limiting insight into their impact on trial start-up efficiency.

In fall 2025, this working group received 43 responses from AACI members to a survey seeking to better describe the impact of pre-activation amendments. In addition to answering survey questions, AACI members were asked to share best practices focused on improving pre-activation amendment implementation. (See figures below for key survey results.) Survey results demonstrate that pre-activation amendments remain a pervasive and operationally burdensome challenge. Over 40 percent of sites reported allocating dedicated resources to manage amendment implementation. Sites most commonly received between 3–5 or 6–10 pre-activation amendments per month. Critically, these amendments were associated with substantial delays in trial activation, most frequently adding 4–6 weeks, with nearly 20 percent of sites reporting delays of 10 or more weeks.

Figure 1. Pre-activation amendments received per month, by site

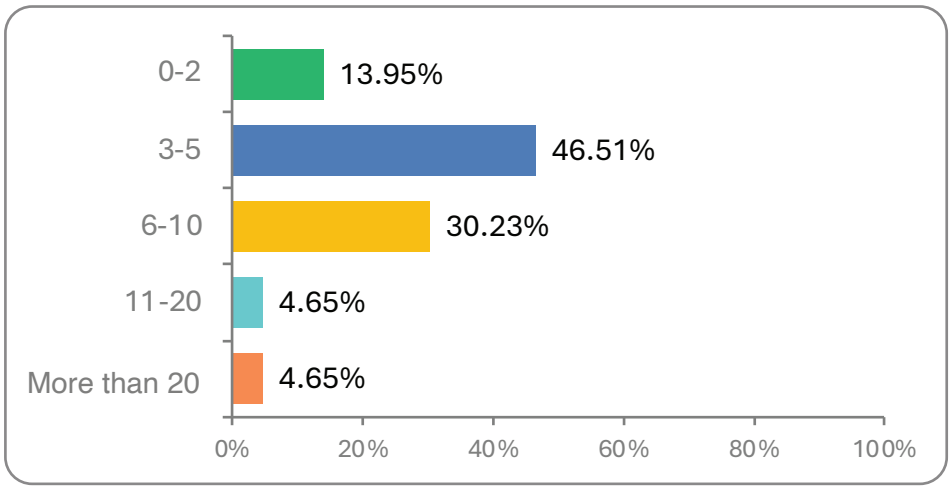


Figure 2. Sites with a dedicated role for implementation of pre-activation amendments

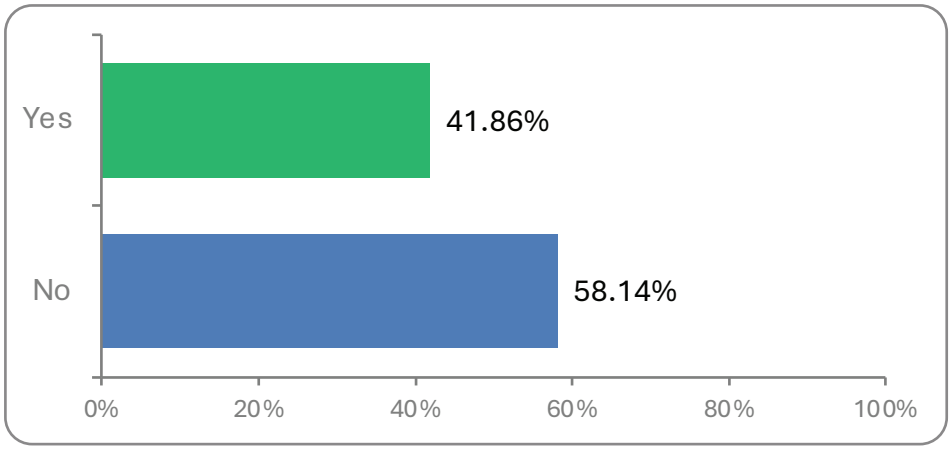


Figure 3. Biggest burdens sites face when processing an amendment

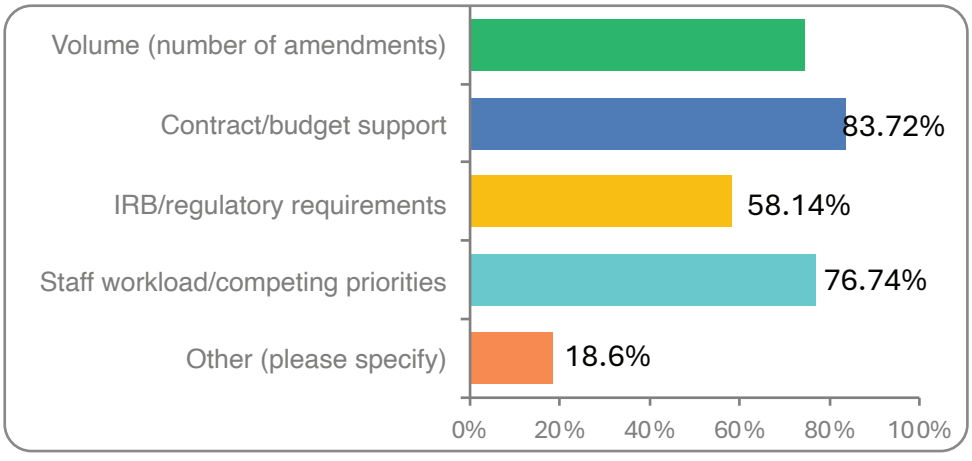


Figure 4. Sites that have a target goal for completing amendments prior to trial activation

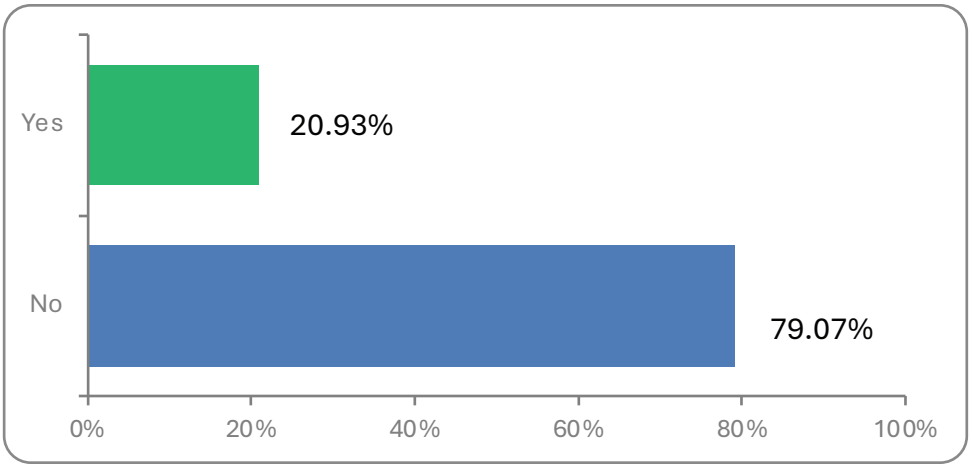


Figure 5. Sites that have specific points where updates are no longer made

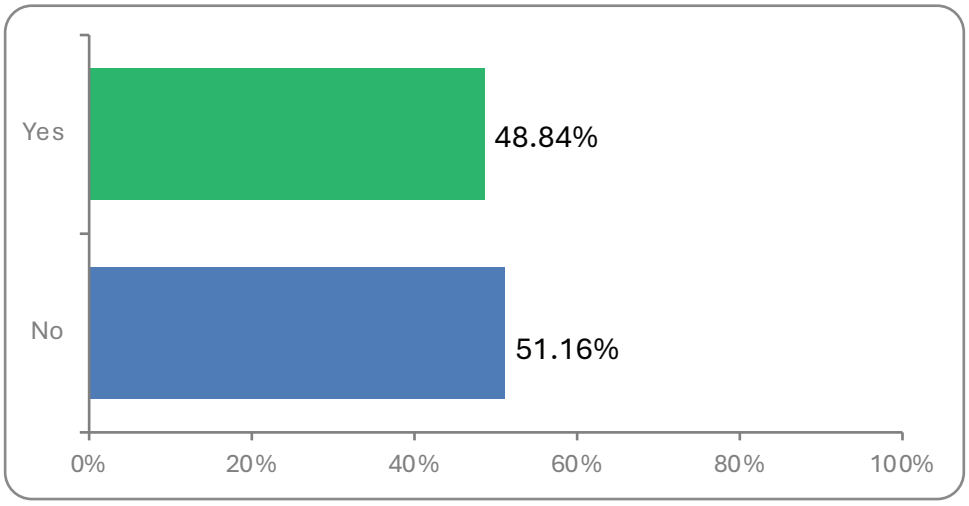


Figure 6. Impact on trial start-up timeline when an amendment is received

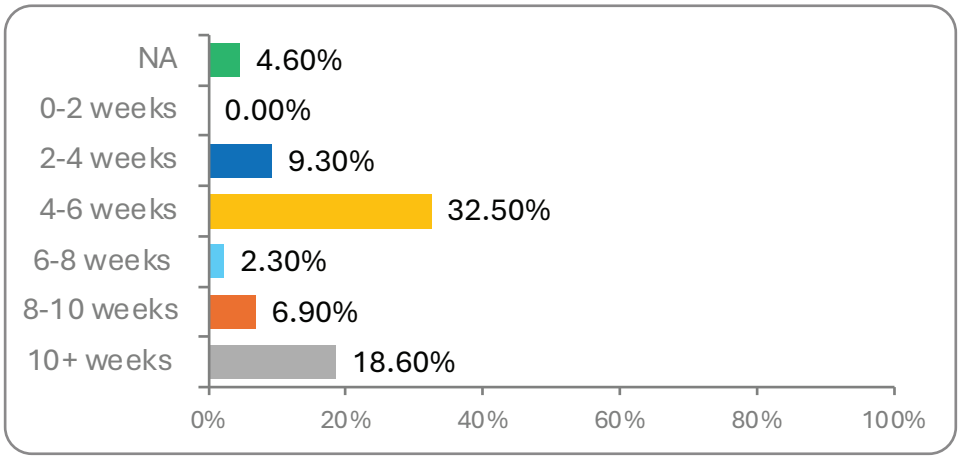
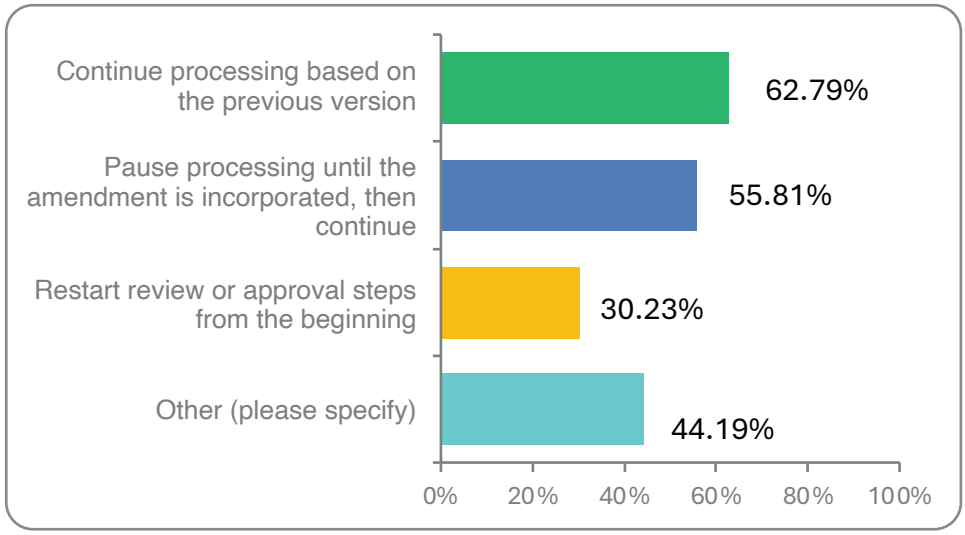


Figure 7. Options on trial start-up activities when an amendment is received



RECOMMENDATIONS

Based on survey findings, working group discussions, and input from external stakeholders, the following recommendations are proposed, in alignment with the guiding principles described above.

Notably, our review identified limited evidence of proactive alignment or expectation-setting prior to trial activation. Attempts to establish rules of engagement after activation starts were consistently viewed as impractical and ineffective.

Accordingly, we recommend developing and adopting the following standardized framework of expectations— "rules of engagement"— defining how sponsors, CROs, and sites coordinate during the pre-activation phase.

(1) Define amendment submission readiness

Establish clear criteria for amendment submission readiness, particularly for the timely receipt of revised protocols, lab manuals, budgets and other documentation provided by the sponsor/CRO, with an understanding that sites will not initiate work until receipt of all affected documents. Sites should not be expected to start amendment work until the sponsor/CRO provides, at minimum, a complete and internally consistent set of revised materials, including (as applicable): (a) amendment submission package coversheet listing all new and revised documents with version dates and, where applicable, noting version date of superseded version; (b) protocol with tracked and clean versions; (c) revised Country Informed Consent Form (ICF) template and, as applicable, any other participant-facing materials impacted; (d) revised Investigator's Brochure or safety letter when relevant; (e) revised pharmacy/drug handling updates; (f) revised lab manual/specimen handling updates; (g) revised Electronic Data Capture (EDC)/Electronic Clinical Outcome Assessment (eCOA) [or other system] completion/use instructions and expected go-live date for post-production changes; and (h) revised budget grid/payment terms and amended contract/work order. When a document is not impacted, the sponsor/CRO should explicitly indicate "no change" in the amendment submission package coversheet to prevent unnecessary reconciliation work.

(2) Establish standardized amendment definitions and taxonomy

Clear, shared definitions of amendment types and Protocol Clarification Letters (PCLs) are required to determine downstream actions and to delineate when the most current amendment must be implemented prior to activation versus when activation may proceed (see Recommendation 4). This taxonomy extends beyond traditional "administrative" (minor) and "substantive" (major) categories to more precisely define operational impact and required follow-up action, including distinctions between formal protocol amendments and PCLs that clarify intent without altering core protocol requirements.

Level	Definition (impact)	Illustrative examples	Enrollment/activation rule (with controls)
L1. Informational/ clerical	No operational, safety, financial, or compliance impact. No participant-facing impact.	Typos; formatting; administrative contact updates; clarifying language that does not change meaning	May activate and enroll without amendment approval. Submit amendment after open to accrual. Controls: document in site file; submit to IRB per local practice (may be batched) after open to accrual.
L2. Operational/ Financial	No safety or compliance impact; no material participant-facing impact. Has operational and/or financial impact.	Revised lab shipping address; added site workflow step; clarified visit windows without changing required procedures; budget line-item clarification	May activate and enroll without amendment approval if operational changes can be made quickly and there is no risk of incorrect third-party payer billing. Controls: proceed with updating operational and budget/agreement changes in parallel with ongoing review of previous protocol version. Submit amendment to IRB after open to accrual.
L3. Safety/ Compliance	Includes safety, privacy or compliance impact, but does not require immediate cessation of all start-up work. May also have operational and financial impact.	New/updated risk language requiring ICF revision; added prohibited concomitant medication; new safety monitoring requirement	May activate but cannot consent or enroll without amendment approval. Controls: decision documented; version control enforced; no participant-facing activity under outdated ICF. Submit amendment after IRB approval of prior protocol version.
L4. Significant/ Substantial	Includes material impact to participant experience, eligibility, treatment, primary assessments or safety oversight. Trial package is already submitted to IRB (amendment occurs while under review). May also include operational and financial impact. Trial is at the IRB.	Eligibility criteria change; added cohort with different dosing; substantial schedule of assessments change; new invasive procedure	Must obtain amendment approval before patient enrollment begins. Study activation tasks (SIV, etc.) may be finalized under prior protocol version per Sponsor and Site Discretion Controls: sponsor/CRO issues clear superseded-document list; trial is already at the IRB - proceed with initial IRB approval. Proceed with updating operational and budget/agreement changes in parallel with ongoing IRB review of previous protocol version. Submit amendment to IRB after initial approval obtained.
L5. Critical	Includes critical safety or compliance impact before initial IRB submission has occurred; proceeding under a prior version would reasonably increase risk or create consent invalidity. May also include operational and financial impact.	Dose/route change; major risk project update; new stopping rules; primary endpoint change; major contraindication change	Must obtain amendment approval before activation and enrollment. Control: trial is not at the IRB yet - incorporate amendment and proceed with the approval process. Proceed with updating operational and budget/ agreement changes in parallel with IRB review of current protocol version.

The levels above are intended to provide a shared, operationally actionable taxonomy for sponsors, CROs, sites, and IRBs. Examples are illustrative; final level assignment should be based on the actual impact of the amendment on subject protection, consent, eligibility, safety oversight, data integrity, and site operations.

GOVERNANCE AND CONTROLS FOR RISK-BASED ACTIVATION UNDER A PRIOR PROTOCOL VERSION

- **Decision authority and alignment:** The sponsor and CRO should assign an initial impact level (L1–L5) in the amendment cover memo, including rationale. Sites may request reclassification based on local operational realities. Final determination of IRB submission requirements rests with the reviewing IRB/ERB, in accordance with local regulations and institutional policies.

- **Required documentation and audit trail:** When a site proceeds with any start-up step while an amendment is pending, the site and sponsor/CRO should maintain a contemporaneous decision record (e.g., dated email memo or activation note) that captures: version(s) in effect, the assigned level, what activities are permitted, what activities are prohibited, and the trigger for moving to the amended version.

- **Version control and superseded materials list:** Sponsor/CRO should provide a clear listing of "superseded documents" with effective dates. Sites should ensure only the currently approved ICF/protocol are available for use and that outdated versions are archived to prevent inadvertent use.

- **Consent and participant-facing guardrails:** No participant should be consented using an ICF that is missing newly identified material risks, eligibility changes, or procedures that would apply to that participant. If an amendment impacts consent content, enrollment should not occur until the IRB-approved ICF aligned to the applicable protocol is in place (consistent with L3–L5 rules above).

- **Exception handling:** Any deviation from the level-based rules should be treated as an exception requiring documented sponsor/CRO concurrence and, when relevant, IRB acknowledgment or approval.

(3) Establish defined turnaround times and communication protocols

Sites and sponsors/CROs should commit to clearly defined timelines for key internal steps and implement structured mechanisms for proactive communication when delays or challenges arise, including transparency regarding mitigation efforts. Both sites and CROs/sponsors need to designate a single point of contact to facilitate status updates and communication.

- **Acknowledgment of receipt:** Site confirms receipt of complete package (or identifies missing items) within 2 business days of receiving the amendment package from sponsor/CRO.

- **Site feasibility of implementation:** Site provides initial assessment of expected implementation timeline and key blockers within 5 business days after acknowledgment of receipt.

- **Clarification turnaround:** Sponsor/CRO responds to site questions that block IRB submission or operational build within 5 business days (or provides an interim response and estimated time of arrival for complete response).

- **Escalation triggers:** Escalate when Service Level Agreement (SLA) timelines are exceeded or amendment is reissued in multiple waves without an updated consolidated package.

The table below outlines roles and responsibilities for key steps to operationalize rules of engagement. It uses a commonly adopted taxonomy, the RACI (Responsible, Accountable, Consulted, Informed) framework. See glossary for a description of RACI framework designations.

Activity	Sponsor/CRO	Site	IRB/ERB
Prepare amendment readiness package (complete document set and cover memo)	A/R	C	I
Assign initial L1–L5 level; distribute amendment package	A/R	I	C
Determine L1-L5 level	I	C	A/R
Confirm site implementation plan, version control, and readiness to open to accrual	I	R/A	C
Review and approve amendment submission (per IRB processes)	I	C	R/A

(4) Ensure reimbursement for amendment-related work

CROs/sponsors will establish an understanding that sites will invoice for and receive reimbursement for time and effort associated with processing pre-activation amendments across all the groups involved within the site. This is in addition to start-up costs invoiced by the site.

5) Enable activation under a prior protocol version when appropriate

In alignment with local or central IRBs, sites should be permitted to activate trials under a previously approved protocol version when subsequent amendments are not safety critical. This approach allows study start-up activities, including screening and patient enrollment, to proceed while amendments are under review. Rigid requirements to fully implement all amendments prior to activation were consistently identified as a major source of delay, even when the nature of the amendment does not necessitate suspension of forward progress.

CONCLUSION

Implementation of these standardized expectations, supported by a shared glossary, a level-based taxonomy (L1-L5), and defined governance controls for risk-based activation, will support more timely clinical trial activations. In addition, these expectations will reduce avoidable reworking and encourage bundling of amendments through clearer submission readiness requirements. Perhaps even more significantly, following the aforementioned guiding principles will foster further collaboration across the stakeholder groups that are all critical to successfully activate and conduct clinical trials.

The call to action is for sites, CROs, sponsors, and IRBs to join those represented in this group to help finalize details around operationalizing expectations 1-5 above, using them, and then sharing details about their impact with the oncology clinical trials community.

GLOSSARY OF KEY TERMS

- **Activation:** The point at which a site is authorized to begin study activities per sponsor/site requirements (also known as "site green-light" or "open to accrual") and may begin participant-facing activities (i.e., screening, consenting, enrollment). Activation is distinct from IRB approval and from first subject screening/consent.

- **Pre-activation amendment:** A protocol amendment issued after initial study start-up materials have been provided to sites but before the site becomes open to accrual.

- **Prior protocol version:** The most recent protocol version that has been approved by the relevant IRB(s) and adopted at the site at the time a subsequent amendment is issued.

- **Amendment submission readiness:** The condition in which the sponsor/CRO has provided a complete amendment package (all documents needed for IRB submission and site implementation), enabling sites to begin work without avoidable rework.

- **RACI:** A commonly used framework to define roles and responsibilities across or within an organization. Responsible (R): individuals or teams who actually perform the task, Accountable (A): the individual ultimately accountable for the completion of the task, Consulted (C): the individuals or groups that are consulted before a decision or task is completed, and Informed (I): those who are kept up-to-date on the progress of the task or decision.

- **Risk-based activation:** A controlled approach that allows certain start-up steps to proceed while an amendment is under review, based on defined impact levels and subject protection guardrails.

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