Protocol Amendments in Practice

Site Start-Up Perspectives on Handling the Burden, Operationalizing the Volume, and Driving Solutions

Sept. 2, 2026

Agenda

1. Research Summary: Cross-Industry Amendment Findings and Landscape
2. Panel Discussion: Protocol Amendments
3. Q&A
4. Closing Remarks

Session Participants

Panelists

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Research Summary: Cross-Industry Amendment Findings and Landscape

Amendment Landscape and Frequency

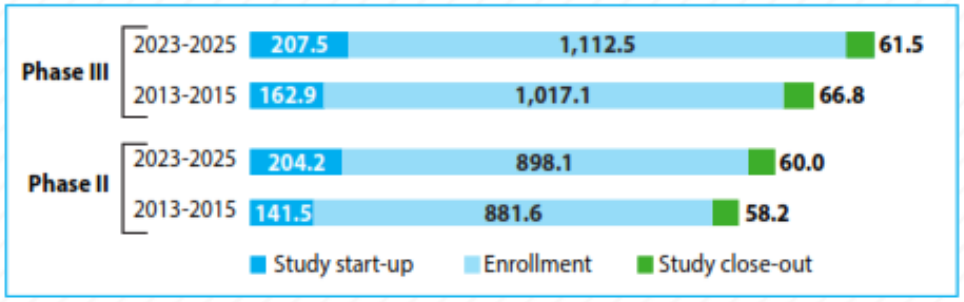
Mean number of deviations and substantial amendments per protocol by phase

	Phase II		Phase III	
	2013-2015	2023-2025	2013-2015	2023-2025
Deviations	75.3	141.8	118.5	296.3
Substantial amendments	2.2	3.1	2.3	3.4

Source: Tufts Center for the Study of Drug Development

- The typical Phase III protocol with a primary completion date during 2023-2025 had an average of 296.3 deviations and 3.4 substantial amendments, up 150% and 48%, respectively, during the past decade.
- Phase II protocols in the 2023-2025 sample had an average of 141.8 deviations and 3.1 substantial amendments, up 88% and 41%, respectively, compared to the earlier time period.
- Previous CSDD studies found that the typical amendment for a Phase III protocol adds three months of unplanned time and nearly $1 million in unbudgeted direct costs to implement.

Duration in days by key clinical trial time periods



Source: Tufts Center for the Study of Drug Development

- During the past decade, study start-up durations—from protocol approval to first patient, first visit (FPFV)—saw the highest increases, of 44% in Phase II and 27% in Phase III clinical trials.

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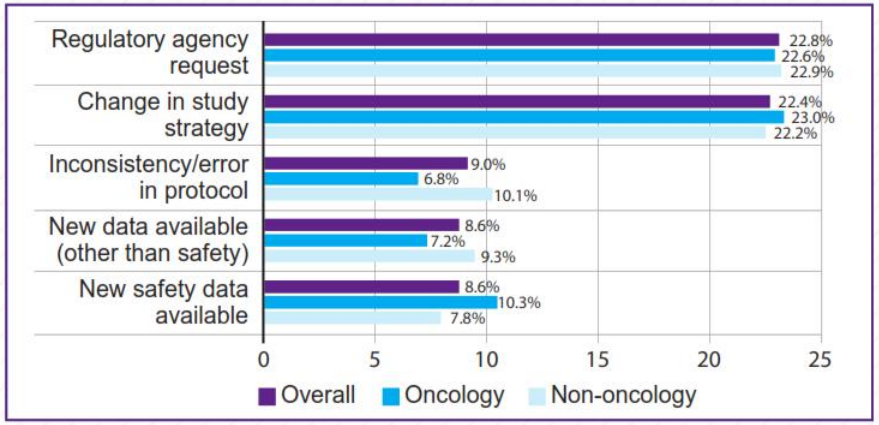
Amendment Landscape and Frequency

Prevalence and average number of amendments per protocol

Phase*	Total protocols evaluated	Number of protocols with amendments	Prevalence of amendments	Mean† number of amendments per protocol and CoV
Overall	952	691	76.8%	3.3 (0.74)
Phase I	342	229	67.0%	3.1 (0.74)
Phase II	238	212	89.1%	3.3 (0.71)
Phase III	272	224	82.4%	3.5 (0.76)
Phase IV	48	26	54.2%	2.4 (0.59)

Note: * Sigificiant difference in prevalence by clinical phase ($p < .001$, Chi Square)
† When at least one amendment has been implemented
CoV = Coefficient of variation
Source: Tufts Center for the Study of Drug Development

Causes reported for implementing an amendment



Note: Significant difference in freququency of primary causes between oncology and non-oncology protocols ($p < .0001$, Chi Square)
* Getz K, Zuckerman R, Cropp A, *et al.* Measuring the incidence, causes, and repercussions of protocol amendments. *Drug Inf Journal*, 2011;45(3):265–275.
Source: Tufts Center for the Study of Drug Development

- More than 75% of clinical trial protocols require at least one substantial amendment, with the highest prevalence (89%) observed in Phase II.
- Regulatory agency requests are the most common reason for implementing protocol amendments.
- Study assessments and study designs are the areas most commonly modified, which impacts coverage analysis, budget, and therefore contracts.
- Protocol amendments represent the largest cause of unplanned delays and unbudgeted costs in a clinical trial.
- For those cases where amendments are required, clinical teams implement an average of 3.3 amendments per protocol, with the highest mean number observed in Phase III protocols.

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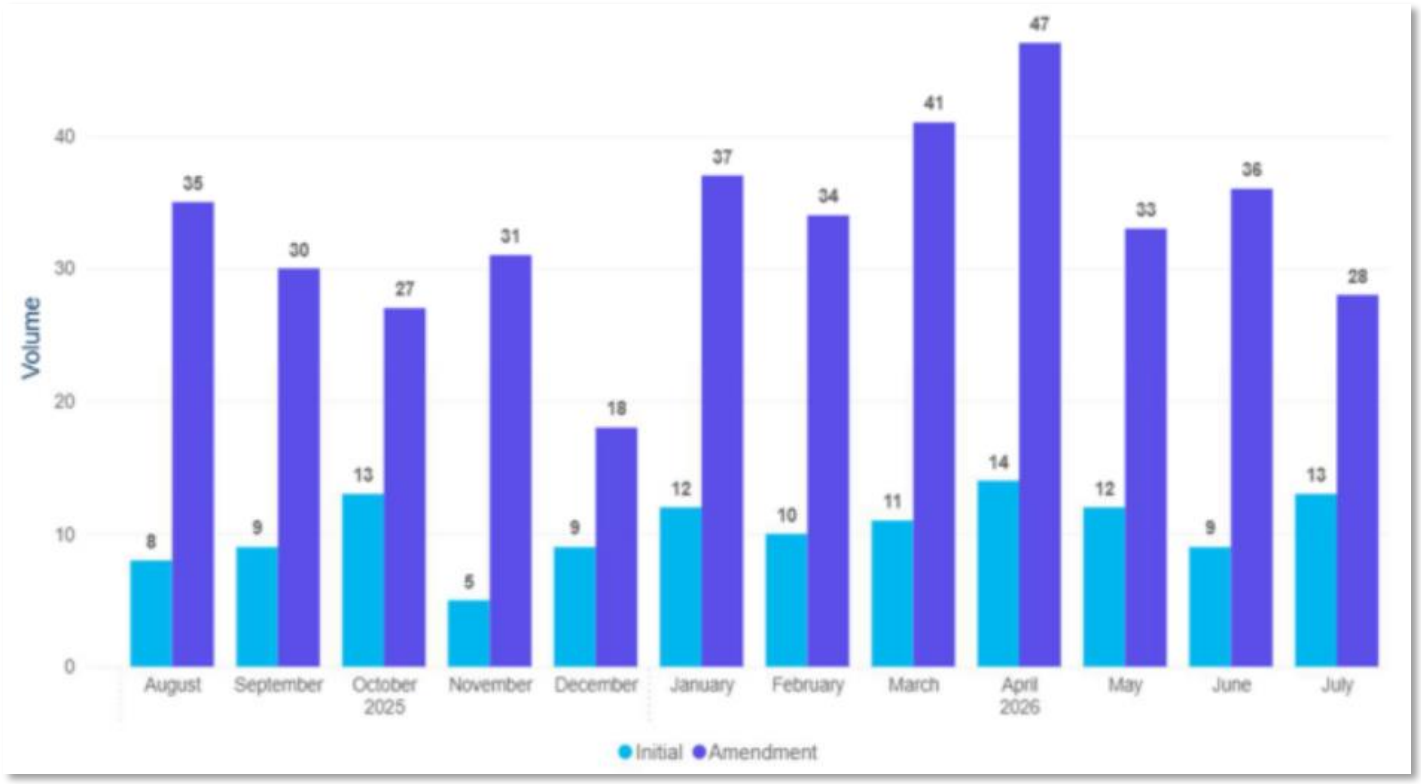
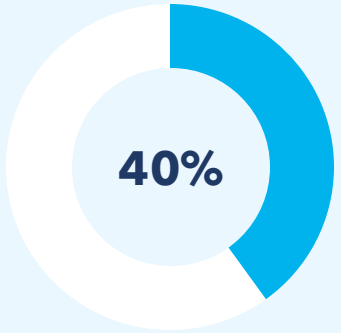
Real-Life Example of a Sites Amendment Volumes



Amendment efforts outpace initial study efforts—causing bottlenecks, resourcing constraints, a need for prioritization, and a constant backlog to manage.

Pre-Activation Amendment Impacts by Numbers



of sites allocating dedicated resources to manage amendment implementation

3-5 or 6-10

pre-activation amendments per month

3-5 amendments: 46.51%
6-10 amendments: 30.23%

4-6

weeks of delay in start-up

20%

of sites reporting delays of 10 weeks or greater in start-up

Association of American Cancer Institutes: Accelerating Clinical Trial Activation: A Collaborative Framework for Managing Pre-Activation Protocol Amendments

Site Pre-Activation Amendment Struggles

1. Site start-up times are a core internal metric for sites and in cases for NCI designated cancer centers these timelines play into designation status (90 calendar day target), Phase 1 trials often with expedited targets of 45-60 calendar days

2. Amendments happening pre-activation can greatly delay these start-up timelines and delay time to first participant enrolled

3. Some sites refuse to process pre-activation amendments until initial protocol activation occurs unless there is an urgent need for safety of participants

4. Early awareness of protocol amendments could reduce the time sites spend on efforts when an amendment is coming. It is a common clue to sites a protocol amendment may be coming when a Sponsor/CRO goes silent during negotiations

5. Re-work causes strain on site resources and may include non-compensated efforts leaving sites the ones footing the bill

Real-World Example 1

Central IRB Approval as First Amendment Signal

1

Site gets notified that a protocol amendment has been approved by the central IRB.

+

2

No necessary site amendment processes have been initiated, and no updated budget template has been provided to the Site.

=

RESULT

Even though IRB approval is received, the protocol amendment requires site amendment efforts prior to implementation. Because no amendment documents or budget template were provided by the CRO/Sponsor in advance, delays are caused and require site follow-up.

IMPACTS:

- Delays implementation of amendments as prevents the ability for concurrent site amendment steps to occur while IRB review occurs
- Requires sites project managing the collection of the required documents to complete internal amendment steps (e.g., budget template)
- Does not signal Sponsor/CRO alignment to prioritize the amendment processing

Real-World Example 2

Incomplete information/amendment package

1

Site gets notification from the Sponsor/CRO that an amendment to the protocol is available with an updated protocol.

+

2

Not all information/documents necessary to initiate site protocol amendment steps are provided

=

RESULT

Even thought protocol amendment was proactively communicated, due to an incomplete package of information/documents for the site to process the amendment delays are caused and requirement of site follow-up

IMPACTS:

Delays implementation of amendment

Requires sites project managing the collection of the required documents to complete internal amendment steps (e.g., budget template)

Real-World Example 3

Proactive Communication, Complete Package, Enabled Efficiencies

1

Sponsor/CRO proactively communicates a protocol amendment and provides a complete set of information/documents to enable site processing

+

2

Site quickly determines amendment impacts and initiates necessary activities to implement amendment

=

RESULT

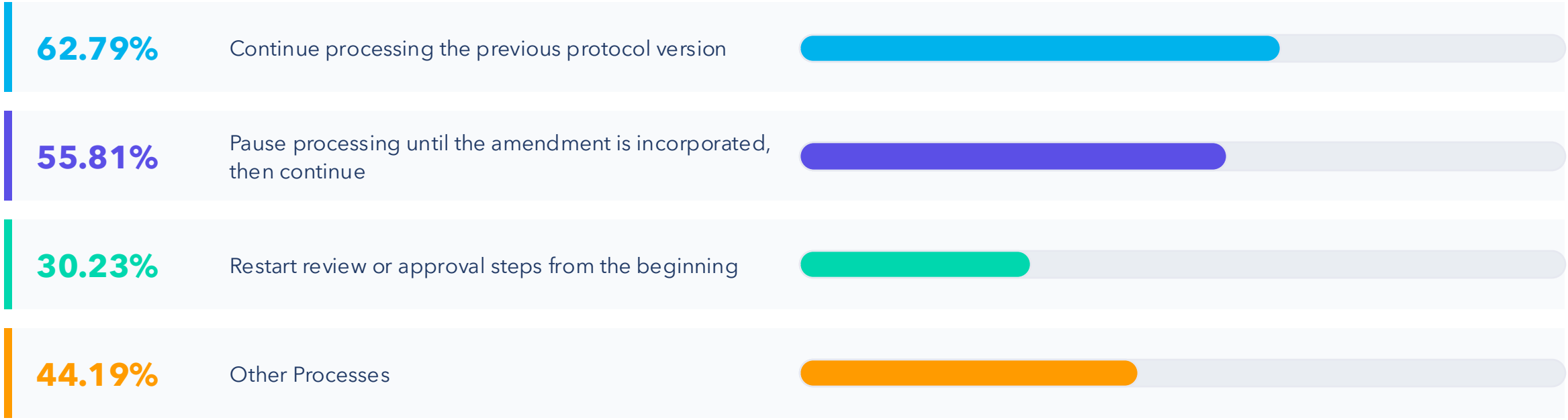
Priority is aligned; site processing can occur promptly eliminating "white-space" and allowing for concurrent amendment activities across Sponsor/CRO, Site, and IRB.

IMPACTS:

- Expedites implementation of amendment
- Reduces burden on all stakeholders, especially Sites
- Reduces waste that materializes into lost revenue by Sites

What are Sites Doing

The Options on Trial Start-up Activities When an Amendment is Received Pre-Activation



The recent Association of American Cancer Institutes (AACI) paper "Accelerating Clinical Trial Activation: A Collaborative Framework for Managing Pre-Activation Protocol Amendments" provides a great taxonomy on actions related to enrollment/activation rules for differing levels of protocol amendment categories (e.g., clerical, safety related, critical)

Association of American Cancer Institutes: Accelerating Clinical Trial Activation: A Collaborative Framework for Managing Pre-Activation Protocol Amendments

Panel Discussion

DISCUSSION

1 When a protocol amendment arrives, what is the first operational signal that tells you whether implementation will be smooth or painful?

2 What information must be included in the initial amendment packet to enable your teams to act efficiently without rework?

DISCUSSION

Q

What sponsor/CRO behaviors materially change the site experience?

DISCUSSION

Q

When and how do you escalate an amendment both internally and/or externally?

DISCUSSION

Q **What internal resources have helped your teams process amendments and maintain clear communication/awareness internally (e.g., CTMS vs. Excel vs. Power BI/Smartsheet)?**

DISCUSSION

Q What has been your experience around implementing amendment fees or penalty clauses to help ensure the cost of the site efforts for amendments are recouped?

Driving Solutions Across Industry

The goal is not to eliminate every amendment; it is to make amendment operations sufficiently predictable that sites can protect participants, ensure compliance, and maintain sustainability.

1. Standardize the packet

- Require actionable amendment impact details early.
- Pair regulatory documents with budget/coverage analysis inputs.

2. Govern the handoffs

- Define owners for regulatory, finance, CA/MCA, contracts, CTMS, and operations.
- Use escalation pathways when the work stalls.

3. Measure the friction

- Track volume, cost impact, timing, and sponsor/indication patterns.
- Use the evidence to improve future feasibility and sponsor partnerships.

1-page impact summary	New cohorts, calendar changes, CPT/billing implications, training and operational impacts.
Budget template with packet	Delivered with the amendment packet when billing / budget is impacted.
Escalation contact worksheet	Named contacts and defined routes for stalled budget, coverage analysis, negotiation, and implementation issues.
Internal policy / procedure	Triage, CA/budget needs, feasibility re-assessment, amendment thresholds, and fees.

Resources

- ACRP Clinical Researcher Article- Navigating Protocol Amendments
- AACI Article- Accelerating Clinical Trial Activation: A Collaborative Framework for Managing Pre-Activation Protocol Amendments
- 2026 WCG MAGI@Home Conference
  - October 19 – 23
  - Tracks for budgets, contracts, billing compliance, operations, and quality/regulatory
- Guide: Improving Protocol Amendment Execution Through Site–Sponsor Alignment
- For Sponsors: Site-Ready Amendment Checklist

AUDIENCE POLL

Would you be interested in speaking with WCG about strategies to reduce study startup and execution delays at your organization?

Select your response in the poll panel.

Q&A

Thank you!

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