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Tufts Center for the Study of Drug Development
TUFTS UNIVERSITY

Impact REPORT

ANALYSIS AND INSIGHT INTO CRITICAL DRUG DEVELOPMENT ISSUES

Amendments reduce number of patients, but at high cost, longer study times

Nearly half of all substantial amendments are deemed avoidable

- 57% of all protocols, across all phases, have at least one substantial global amendment (defined on page 4 in "About this study").
- Phase II protocols have the highest incidence of substantial amendments (77%), averaging 2.2 amendments per protocol.
- The most frequent changes stemming from amendments are associated with modifications and revisions to study volunteer demographics and eligibility criteria.
- Protocols with even one amendment experience a substantially lower actual number of patients screened and enrolled relative to plan, compared to protocols without any amendments.
- Study conduct durations for protocols with at least one substantial amendment take, on average, three months longer.
- The total median direct cost to implement a substantial amendment for Phase II and Phase III protocols is $141,000 and $535,000, respectively.

Unplanned delays, disruptions, and costs associated with protocol amendments have spurred the research-based biopharmaceutical industry to identify new approaches to simplify protocol design, reduce the frequency of amendments, and better inform decision-making. A new Tufts CSDD analysis, results of which are summarized here, builds on an analysis conducted in 2010 and explores the impact of substantial protocol amendments on study conduct performance and cost. The results provide new insights into protocol design decision-making and how to anticipate and better manage amendments.

The incidence and frequency of substantial amendments remain high and their impact on study cycle time and budgets are substantial. Drug sponsors are responding through piloted and broad use of feasibility review committees, common protocol templates, and investigative site and patient feedback panels.

Nearly six out of 10 protocols have at least one substantial global amendment

Protocol amendment prevalence by phase

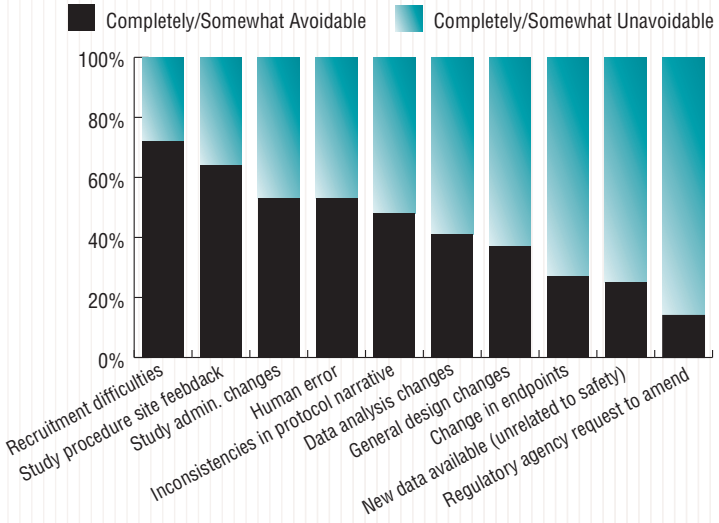
	Share of protocols with at least one substantial amendment	Mean number of amendments for these protocols
Phase I	52%	1.8
Phase II	77%	2.2
Phase III	66%	2.3
Phase IIIB-IV	25%	1.9
All Phases	57%	2.1

Source: Tufts Center for the Study of Drug Development

- Taken in the aggregate, across all phases, 57% of all protocols average 2.1 substantial amendments.
- Phase II protocols have the highest incidence of substantial amendments (77%), averaging 2.2 amendments per protocol.
- Substantial amendments are implemented for two-thirds of later stage and more costly Phase III protocols, with an average of 2.3 amendments per protocol.

45% of all substantial protocol amendments are deemed avoidable

Top 10 Reasons for amending protocols

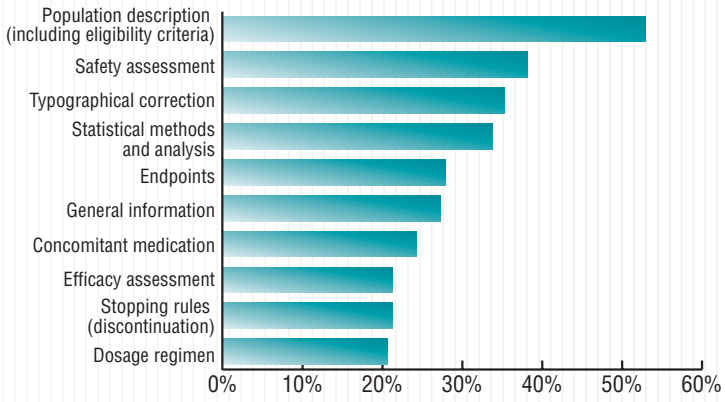


Source: Tufts Center for the Study of Drug Development

- The share of substantial protocol amendments deemed avoidable (45%) has increased since the 2010 Tufts CSDD study, which then found that 33% of amendments were deemed avoidable.
- Among 10 primary reasons for amending protocols, a high percentage of amendments associated with recruitment/retention difficulties and study procedure feasibility were deemed avoidable.
- Only one out of five substantial amendments is requested by a regulatory agency, and the vast majority (86%) of these requests are considered unavoidable.

A substantial protocol amendment triggers many changes

Distribution of changes made to the protocol



Note: the typical amendment resulted in an average of 7 changes to the protocol

Source: Tufts Center for the Study of Drug Development

- The most frequent changes are associated with modifications and revisions to study volunteer demographics and eligibility criteria.
- 38% of changes made as a result of substantial protocol amendments are related to safety assessment activity and 21% are related to efficacy assessments.
- Nearly one out of three changes stemming from a protocol amendment is associated with endpoint modifications.
- 35% of changes result from typographical corrections.

Substantial amendments lead to reduced numbers of patients screened and enrolled

Impact on baseline planning

	Protocols with no amendments	Protocols with at least 1 amendment	P value
Patients screened	-57	-291	0.05
Patients enrolled	+49	-107	0.05
Sites activated	-4.9	-5.3	0.87
Countries where trials conducted	0.10	0.05	0.75

Note: Values are means, actual relative to plan, adjusted for phase and therapeutic area, but not interaction of both

Source: Tufts Center for the Study of Drug Development

- Protocols containing at least one substantial amendment tend to be larger in scope (e.g., more patients, sites, and countries) than those without.
- When implemented, substantial amendments significantly reduce the actual number of patients screened and enrolled relative to the original plan, compared to those protocols without a substantial amendment.
- No significant differences were observed between protocols with and without substantial amendments with regard to the actual number of investigative sites activated and countries relative to baseline plan.

Protocols with at least one substantial amendment have longer study durations

Impact on study timelines

	Mean duration without amendments	Mean duration with amendments
Study initiation	154 days	181 days
Study conduct+	490 days	580 days
Patient enrollment*	352 days	437 days
Study closeout*	140 days	230 days

Note: Values are means, adjusted for phase and therapeutic area, but not interaction of both.
+differences are significant at p<.001.
**differences are significant at p<.0001.*

Source: Tufts Center for the Study of Drug Development

- Adjusting for phase and therapeutic area differences, protocols with at least one substantial amendment have significantly longer cycle times, compared to those protocols without an amendment.
- The most dramatic impact from substantial protocol amendments is observed once enrollment is underway when unplanned delays disrupt study conduct activity.
- On average, protocols with at least one substantial amendment had study conduct durations three months longer than those without an amendment.

Cost to implement a Phase III protocol amendment is triple that of Phase II

Direct cost to implement a substantial amendment

Cost component	Phase II Median $000 (N)	Phase III Median $000 (N)
Added fees to ethical review committees	53 (19)	151 (20)
Change orders to existing vendor contracts	88 (13)	43 (15)
Cost of additional drug supply distributed	2 (11)	0 (14)
New contracts with providers	0 (9)	0 (11)
Increased study grant/ site fees	0 (9)	7 (16)
Miscellaneous	19 (16)	64 (13)

Source: Tufts Center for the Study of Drug Development

- The total median direct cost to implement a substantial amendment for Phase II and Phase III protocols is $141,000 and $535,000, respectively.
- The highest median costs are associated with change orders to existing vendor contracts and additional fees to ethical review committees.
- Incremental fees to investigative sites and the cost of additional drug supply are minimal.

About this study

For this study, only substantial, global protocol amendments were included. These were defined as any change to a protocol on a global level requiring internal approval, followed by approval from the institutional or ethical review board or regulatory authority. Country-specific amendments that affected protocol designs for clinical trials within that region alone were excluded. Between March and July 2015, Tufts CSDD, in collaboration with 15 large and mid-sized pharmaceutical and biotechnology companies and contract research organizations, gathered data on protocols approved between 2010 and 2013. Data were collected and analyzed from 836 Phase I – IIIb/IV protocols that had completed enrollment across all major therapeutic areas and 984 amendments. From this data set Tufts CSDD randomly selected 136 protocols to evaluate study cycle time and performance. Seven participating companies gathered direct cost data to implement an amendment from a sample of 52 protocols actively enrolling study volunteers between January and May 2015. This study was supported in part by an unrestricted grant from Medidata Solutions.

Data collection and analyses were conducted by Stella Stergiopoulos, Senior Project Manager, and Kenneth Getz, MBA, Director of Sponsored Research and Research Associate Professor, both at the Tufts Center for the Study of Drug Development.

Definition of terms

Protocol — A plan detailing the methodology of a clinical study.

Screened patients — Patients who meet the eligibility criteria for participation in a clinical trial.

Enrolled patients — Screened patients who are subsequently randomized to participate in a clinical trial.

Study initiation cycle time — Time from when a protocol is approved to the first patient screened.

Study conduct cycle time — Time from the date a protocol is approved to the date the last patient completed a study (Last Patient, Last Visit).

Study enrollment cycle time — Time from the date the first patient entered a study (First Patient, First Visit) to the last patient who completed the last visit.

Study closeout cycle time — Time from Last Patient, Last Visit to data lock.

About the Tufts Center for the Study of Drug Development

The Tufts Center for the Study of Drug Development at Tufts University provides strategic information to help drug developers, regulators, and policy makers improve the quality and efficiency of pharmaceutical development, review, and utilization. Tufts CSDD conducts a wide range of in-depth analyses on pharmaceutical issues and hosts symposia, workshops, and public forums.

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