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Tufts Center for the Study of Drug Development
TUFTS UNIVERSITY

Impact REPORT

ANALYSIS AND INSIGHT INTO CRITICAL DRUG DEVELOPMENT ISSUES

Protocol design optimization starting to improve study performance

The incidence of non-core data remains high

- One-fifth of Phase II and one-third of Phase III protocol procedures, on average, collect non-core data that are not associated with a primary or key secondary endpoint, regulatory compliance, or standard baseline assessments.
- 80% of all Phase II non-core data and 87% of all Phase III non-core data collected were source data verified by study monitors.
- The majority of surveyed large and mid-size pharmaceutical and biotech companies reported implementing facilitated review processes and mechanisms within the past five years to challenge protocol design feasibility.
- 21% of surveyed companies use simple adaptive trial designs to improve data quality and success rates and cut costs.
- Drug companies are reluctant to use social media to solicit feedback from sites and patients on protocol feasibility, although they recognize the value it can provide.

Drug developers and their partners have long recognized that complex protocol designs negatively impact clinical trial performance. Still, during the past decade it has been difficult for sponsor companies to streamline protocol design given the need to provide robust and comprehensive data in light of increasing scientific complexity, anticipate and address regulatory, health authority, and payer requests, and identify new areas of inquiry and development direction.

Pressure to achieve higher levels of operating efficiency and performance is prompting some drug companies to place greater emphasis on upfront planning and governance to assess and challenge protocol feasibility. Sponsor companies have been implementing a variety of approaches, including establishing facilitated review mechanisms and making greater use of adaptive trial designs. Studies conducted by Tufts CSDD and summarized in this report suggest that these efforts are bearing positive results.

Substantial amount of data collected doesn't support primary and key secondary endpoints

Distribution of Endpoint Type and Procedure Type per Protocol

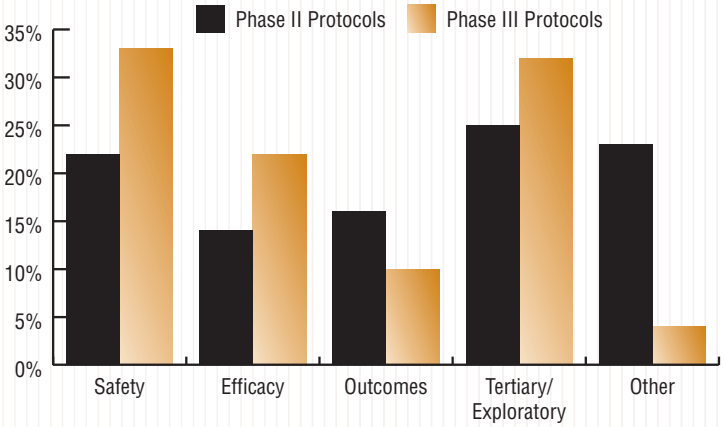
		Phase II Protocols	Phase III Protocols
Endpoints	Primary	14.8%	9.4%
	Key Secondary	38.3%	34.8%
	Tertiary	27.8%	29.7%
	Exploratory	19.1%	26.1%
Procedures	Core	64.9%	58.6%
	Required	4.6%	3.7%
	Standard	9.7%	7.1%
	Non-core	20.7%	30.6%

Source: Tufts Center for the Study of Drug Development

- Primary and key secondary endpoints represented 53% of Phase II protocols and 44% of Phase III protocols.
- 21% of procedures in Phase II protocols and nearly one-third of procedures in Phase III protocols collected data that are non-core, i.e., the data do not support primary or key secondary endpoints, regulatory requirements, or standard baseline assessments.
- Wide variation in the proportion of procedures collecting non-core data was observed across therapeutic areas.

Typically, one-quarter of clinical study budgets is devoted to collecting non-core data

Objectives of Procedures Collecting Non-Core Data



Source: Tufts Center for the Study of Drug Development

- On average, approximately one-quarter of a study budget's direct costs were dedicated to procedures that collect non-core data.
- A large proportion of non-core procedures—particularly in Phase III studies—was associated with safety and efficacy endpoints.
- Less than 20% of procedures that collected non-core data supported outcomes-related endpoints, (e.g., quality of life assessments, reimbursement) and approximately 3% gathered biomarker data.

Most non-core data are source data verified and included in the CSR and submission docs

Assessing Data Usage

	Proportion that appeared in the CSR	Proportion that appeared in the TLF	Proportion that appeared in the Appendix
Data from all procedures (N=5,929)	94.3%	96.6%	56.7%
Non-core data only (N=1,267)	92.4%	95.3%	47.6%

CSR = Clinical Study Report; TLF = Tables, Listings, and Figures

Source: Tufts Center for the Study of Drug Development

- Procedures collecting non-core data were evenly distributed across the entire schedule of assessments.
- 80% of all Phase II non-core data and 87% of all Phase III non-core data collected were source data verified by study monitors.
- Although non-core data do not support primary and key secondary endpoints, sponsor companies reported that nearly all of the non-core data appeared in the clinical study report (92%) and the tables, listings, and figures (95%) in the regulatory submission.

Facilitated reviews appear to be having positive impact on clinical trial performance

Incidence and Impact of Facilitated Review Mechanisms

Modest to Major Improvement Observed in:	Share of Companies
Number of amendments	67.5%
Investigative site work burden	53.3%
Overall study cycle time	44.3%
Speed to last patient last visit	43.6%
Study budgets	42.0%

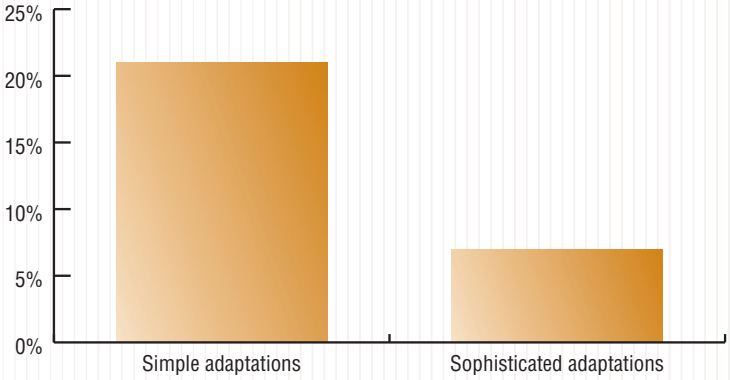
Note: 76% reported having facilitated review processes or mechanisms in place, while 24% reported none in place.

Source: Tufts Center for the Study of Drug Development

- The majority of large and mid-size pharmaceutical and biotechnology companies surveyed reported using facilitated review processes and mechanisms within the past five years to challenge protocol design feasibility.
- Two-thirds of surveyed companies reported observing modest to major reduction in the number of protocol amendments since implementing facilitated reviews.
- Sponsor company experience with cycle time improvements has been mixed following implementation of facilitated review governance and processes.

21% of sponsor companies use adaptive trial designs to improve success rates and cut costs

Share of Total Active Clinical Trials per Company

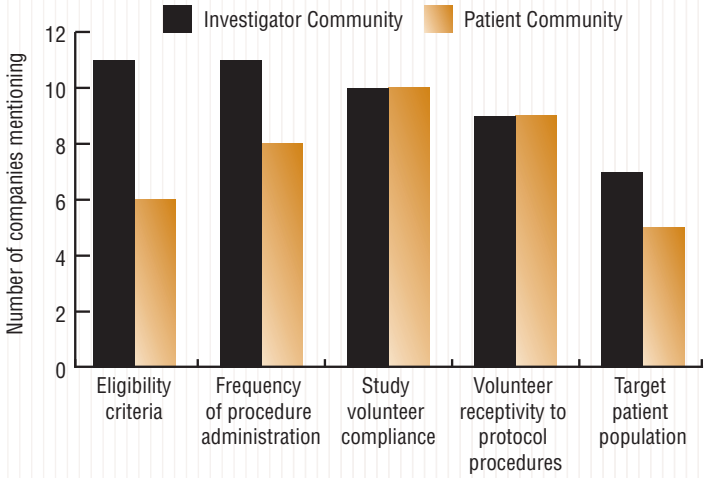


Source: Tufts Center for the Study of Drug Development

- Sponsor companies used simple adaptive trial designs, including early terminations and sample size re-estimations, in 21% of active clinical trials to improve success rates and reduce operating costs.
- For any given pharmaceutical or biotechnology company, less than 10% of active clinical trials used more sophisticated designs, including adaptive dose finding and flexible randomization ratios.
- Interviews with sponsor companies indicate several major barriers to adoption, including concerns about disrupting clinical trial execution, adverse impact on volunteer participation, lack of management and implementation experience, and perceived resistance from regulatory affairs functions.

Sponsors are reluctant to use social media to solicit feedback on protocol design

Protocol Design Areas that Sponsors Said Would Benefit Most from Social Media



Source: Tufts Center for the Study of Drug Development

- No major surveyed company reported using social and digital media communities to solicit protocol design input.
- Sponsor companies expressed strong concerns about using social media to inform clinical trial decisions, given the absence of regulatory agency guidance, and the possibility of introducing research bias and distorting adverse event experience.
- A high percentage of companies, however, perceived value in soliciting feedback on clinical trial convenience and protocol design feasibility via social media from investigative sites and patients if concerns were addressed.

About this review

Data for this review came from multiple studies conducted by Tufts CSDD, including a 2014 evaluation in which eight major pharmaceutical/biotech companies classified 25,287 procedures from 137 recently completed Phase II and III protocols; a 2013 survey of sponsor company experience with facilitated review processes and mechanisms in which 83 industry executives responded; and the results of a 2013 working group study among 20 pharmaceutical and biotechnology companies to assess social and digital media perceptions and usage practices.

The study was conducted by Ken Getz MBA, Associate Professor, and Stella Stergiopoulos BA, Senior Project Manager, both of Tufts CSDD.

Definition of terms

Biomarker — Also called biological marker. A substance, measurement, or indicator of a biological state. Biomarkers may exist before clinical symptoms arise.

Clinical endpoint — Occurrence of a disease or symptom that is a target outcome of a clinical trial.

Clinical trial — A specific type of clinical study in which a medical intervention is tested against a placebo or an active control in human subjects. Clinical study is a broader term that includes other forms of human participatory research, such as pharmacokinetic, epidemiologic, and behavioral studies.

Phase I — Studies typically conducted in healthy volunteers to determine the pharmacokinetic and pharmacologic actions of a drug in human subjects, the side effects associated with increasing doses, and, in some cases, early evidence of efficacy.

Phase II — Studies designed to obtain data on the efficacy of a drug for a particular indication or indications in patients with the disease or condition.

Phase III — Expanded controlled and uncontrolled trials to gain additional data about efficacy and safety, needed to evaluate the benefits and risks of a drug.

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

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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