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Tufts Center for the Study of Drug Development
TUFTS UNIVERSITY

IMPACT REPORT

ANALYSIS & INSIGHT INTO CRITICAL DRUG DEVELOPMENT ISSUES

Rising protocol design complexity is driving rapid growth in clinical trial data volume

Phase III protocols now collect an average of 3.6 million data points

- Phase II and Phase III protocols each have approximately 20 endpoints, with an average of 1.6 primary endpoints.
- Number of endpoints for Phase II and Phase III protocols grew 27% since 2009.
- Phase III trials now collect on average three times more data, compared to 10 years ago.
- The mean number of distinct Phase II and Phase III protocol procedures increased 44% since 2009.
- The mean number of countries and sites where Phase II and Phase III protocols are conducted grew substantially since 2009.
- Adaptive clinical trials typically enroll 45% fewer patients, and go from protocol approval to database lock 86 days faster, compared to traditional protocols.

High and rising protocol design complexity is an expected consequence of the biopharmaceutical community's engaging in more ambitious and customized drug development activities. Growing investment in treatments targeting rare diseases, efforts to stratify participant subgroups using biomarker and genetic data, and increasing demand for structured and unstructured patient data from numerous sources—encompassing both clinical research data and real world evidence—are all contributing factors, and they are likely to continue to drive still more complex clinical trials.

This *Tufts CSDD Impact Report* presents the results of a recently completed study, updating benchmarks on protocol design practice. Given the inverse relationship between complexity and clinical trial performance, new strategies and tactics—many that have been introduced during the coronavirus pandemic—are needed to drive development speed, efficiency, and quality.

Phase II and Phase III protocols each have approximately 20 endpoints with 1.6 primary endpoints

Number of protocol endpoints, eligibility criteria, and procedures for completed trials

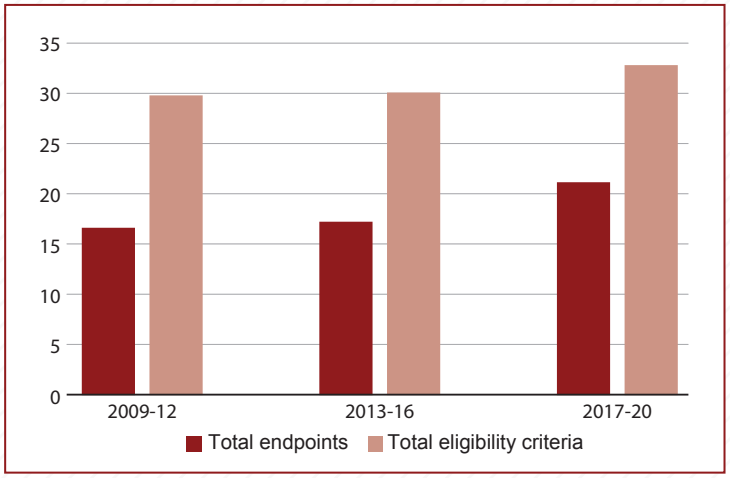
	Phase I	Phase II	Phase III
Number of internal protocol reviews	3.4	4.2	7.2
Total endpoints	16.0	20.7	18.9
Total primary endpoints	2.9	1.6	1.6
Total eligibility criteria	31.2	31.3	30.2
Total procedures performed per patient	174.9	263.2	262.9

Note: All values are means, reflecting protocols conducted during 2013-19.
Source: Tufts Center for the Study of Drug Development

- On average, 263 total procedures are performed in Phase II and Phase III protocols to support a mean of 21 and 19 total endpoints, respectively.
- Protocols have a mean of approximately 31 eligibility criteria, whether for Phase I, II, or III clinical trials.
- Phase III protocols undergo an average of seven internal reviews, including expert advisory and patient and investigative site panel input, prior to finalization.

Mean number of endpoints and eligibility criteria for Phase II and Phase III protocols continue to increase

Trends in endpoints and eligibility criteria for Phase II and Phase III protocols



Note: All values are means.
Source: Tufts Center for the Study of Drug Development

- The total mean number of endpoints per Phase II and Phase III protocols conducted in 2017-20 grew 27% since the 2009-12 period.
- The total mean number of eligibility criteria (inclusion and exclusion criteria combined) increased 10% from the 2009-12 to 2017-20 periods.
- Since 2003, the average number of endpoints per Phase III protocol increased 6% annually.

Phase III trials now collect on average three times more data points than 10 years ago

Sites, participants, and data volume

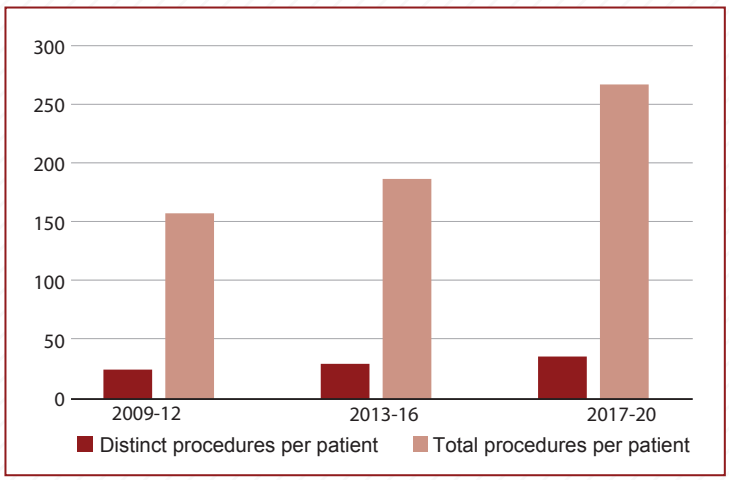
	Phase I	Phase II	Phase III
Total countries	1.8	6.3	14.0
Total sites	6.8	34.3	87.0
Number of planned patient visits	13.9	18.4	21.3
Total data sources	3.8	4.3	4.0
Total data points collected	724,465	2,235,402	3,560,201

Note: All values are means, reflecting protocols conducted during 2013-19.
Source: Tufts Center for the Study of Drug Development

- Currently, the typical Phase I protocol is conducted in an average of seven investigative sites based in two countries.
- Phase II and Phase III protocols—conducted in an average of 34 and 87 investigative sites and 6 and 14 countries, respectively—screen an average of 12 patients, yielding an average six to seven randomized patients per site.
- Approximately 3.6 million data points are collected per Phase III protocol, nearly 60% more than collected by Phase II protocols and 400% more than Phase I protocols.

Mean number of distinct Phase II and Phase III protocol procedures increased 44% since 2009

Trends in number of procedures performed per patient for Phase II and Phase III protocols



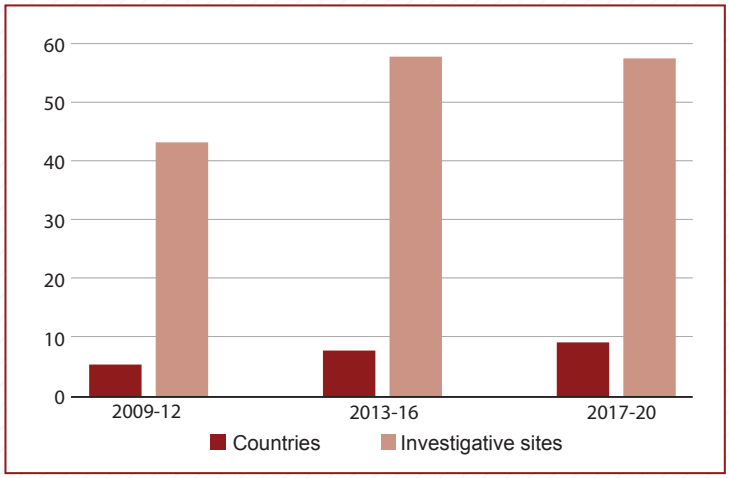
Note: All values are means.

Source: Tufts Center for the Study of Drug Development

- Total Phase II and Phase III procedures per patient performed by site personnel, clinicians, lab and assessment technicians, and by patients themselves increased 69% from 2009-12 to 2017-20.
- Whereas each distinct procedure was conducted an average of six times during protocol execution in the 2009-12 period, each distinct procedure in 2017-20 was conducted, on average, nearly 7.5 times.
- The total average number of procedures supporting Phase III protocols grew 6% per year since 2003.

Growth in global sites conducting Phase II and Phase III protocols grew by 33% since 2009

Trends in Phase II and Phase III global clinical trial placement



Note: All values are means.

Source: Tufts Center for the Study of Drug Development

- The mean number of countries where Phase II and Phase III protocols are placed nearly doubled since 2009.
- The average number of investigative sites conducting Phase II and Phase III protocols increased 33% from 2009-12 to 2017-20.
- Executing Phase II and Phase III protocols across more countries and investigative sites increases operational complexity, e.g., interactions with additional regulatory agencies and health authorities, delivering trial supplies, and monitoring clinical trials in widely dispersed areas.

Master protocol designs entail more patients and take an average of 1.9 years longer vs. traditional trials

Comparison of key elements and metrics by design type for Phase II and Phase III protocols

	Number of Endpoints at Datalock	Eligibility Criteria	Total Procedures Performed	Number of Sites	Number of Patients Randomized	Clinical Trial Duration (Days)
Traditional designs	20.2	31.0	278.9	51.2	456	1,019.4
Adaptive designs	15.7	34.8	316.3	43.5	249	933.4
Master protocols	26.9	34.5	280.2	46.6	501	1,704.8

Notes: All values are means, reflecting protocols conducted during 2013-19. Clinical trial duration is defined as protocol approval to database lock.

Source: Tufts Center for the Study of Drug Development

- Newer master protocol designs, e.g., basket, umbrella, pragmatic protocols, have substantially higher average number of endpoints and randomized patients, compared to traditional or adaptive designs.
- Master protocols take approximately 1.9 years longer to execute than traditional Phase II and Phase III protocol designs.
- Adaptive clinical trials typically enroll 45% fewer patients and go from protocol approval to database lock nearly three months (86 days) faster than trials supporting traditional protocols.

About this study

Data in this report were derived from a working group study conducted between February and November 2020. Eighteen pharmaceutical and biotechnology companies and two major contract research organizations (CROs) participated in the study and submitted data from protocols that were completed, or had achieved database lock, by December 31, 2019. A total of 142 data variables, from 220 protocols (N=60 Phase I; N=85 Phase II; and N=75 Phase III), across multiple therapeutic areas, were analyzed. CSDD drew trend data from past working group studies benchmarking protocol design practice.

This analysis was conducted by Michael Wilkinson MPH, project manager; Zak Smith, MA, senior analyst; and Ken Getz, MBA, principal investigator, professor and director, all of Tufts CSDD.

Definition of terms

Adaptive clinical trial — A clinical trial design that allows for modifications to one or several aspects of the trial based on data obtained from patients during the trial.

Basket clinical trial — A type of clinical trial that evaluates one targeted therapy on multiple diseases or multiple disease subtypes concurrently.

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.

Master protocol — A comprehensive protocol evaluating multiple hypotheses of sub-studies that are conducted concurrently. These sub-studies are commonly conducted on populations based on specific tumor and histologic types, and/or molecular markers. There are three primary master protocols: basket, pragmatic, and umbrella.

Pragmatic clinical trial — A type of clinical trial that focuses on correlation, rather than causation, between treatments and outcomes in real-world health system practice. Also called practical clinical trial.

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

Umbrella clinical trial — A type of clinical trial that evaluates multiple targeted therapies for one disease or several diseases (e.g., that are expected to respond to an investigational drug).

About the Tufts Center for the Study of Drug Development

The Tufts Center for the Study of Drug Development at Tufts University School of Medicine is a multidisciplinary research center dedicated to optimizing drug development performance and efficiency through robust, data-driven assessments, analysis, and insight.

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