

Therapeutic area variability in the collection of data supporting protocol end points and objectives

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More than 22,000 procedures from 116 protocols were classified according to the end points and objectives that they support and their direct costs were determined. The distribution of procedure classifications and costs for four therapeutic areas – oncology, endocrinology, CNS and anti-infectives – were analyzed and substantial variability was observed. Endocrine and anti-infective protocols contained a high relative average number of supplementary, tertiary and exploratory (i.e., 'non-core') end points. Oncology and CNS protocols had the highest relative proportion of procedures supporting 'core' end points and objectives and lower relative proportions of those supporting 'non-core' end points. The relative proportion of direct costs to administer endocrine protocol procedures supporting 'non-core' end points and objectives was significantly higher than that of other therapeutic areas. The results of this study provide important benchmarks by therapeutic area to help clinical teams optimize protocol design.

Keywords: clinical research protocols • clinical trial design • protocol complexity • protocol design • study budgets

One out of every five procedures per protocol collects data that is not associated with a primary, key secondary or GCP–ICH compliance-related protocol end point [1]. This finding, from a recent study conducted by the Tufts Center for the Study of Drug Development (Tufts CSDD; MA, USA) along with its estimate that a total of US\$4–6 billion is spent globally each year to collect extraneous protocol data, highlights a critical need and a compelling opportunity to optimize and simplify study designs.

A large and growing body in the literature indicates that higher levels of protocol complexity are associated with lower levels of clinical research data quality, higher study costs and much longer study durations [2–4]. Higher levels of study design complexity are also associated with longer cycle times, and lower patient recruitment and retention rates [5–8].

A decade of research on protocol design complexity conducted by Tufts CSDD corroborates and adds to this body of knowledge. Our research shows that study designs are extremely demanding both scientifically and operationally, and that they have become significantly more complex since 2000. In 2012, to demonstrate safety and efficacy, a typical Phase III protocol had 170 procedures on average performed on each study volunteer during the course of 11 visits spread out over 230 days. Ten years ago, the typical Phase III protocol had an average of 106 procedures. Study volunteers came from an average of 34 countries and 196 research centers, up from 11 countries and 124 research centers ten years ago. Each volunteer had to meet 50 eligibility criteria on average to participate in the study – up from an average of 31 inclusion and exclusion criteria ten years ago [9].

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Tufts CSDD research has demonstrated that complex protocols are inversely related to recruitment and retention effectiveness [5]. Another Tufts CSDD study found that more complex protocols are associated with a significantly higher number of protocol amendments – a highly disruptive activity causing significant unplanned expense and delays [10].

In June 2013, Tufts CSDD published the results of a study demonstrating that whereas the marginal cost of adding a protocol procedure may be low relative to the overall study budget, in the aggregate, spending on extraneous protocol procedures is substantial. Of the 25,103 individual Phase II and III protocol procedures analyzed, Tufts CSDD found that more than one out of five (22%) supported tertiary and exploratory objectives and end points. The average cost to administer procedures supporting these 'non-core' objectives and end points represented 19% of the entire study budget, or \$1.7 million per Phase III protocol and \$0.3 million or 13% of the average total Phase II study budget [1]. The estimated total cost to the pharmaceutical industry each year to perform procedures supporting 'non-core' objectives and end points for all Phase II and III protocols is \$4-6 billion. This estimate is very conservative as it excludes all indirect costs for personnel and infrastructure required to capture, monitor, clean, analyze, manage and store extraneous protocol data and it does not include any estimate for the unnecessary risk to which patients may be exposed.

During the past 18 months, a number of pharmaceutical and biotechnology companies have acknowledged that their study designs have become too complex and they are looking in earnest for ways to simplify their protocol designs in order to improve drug development efficiency, quality and cost [9]. This paper provides new benchmark data on protocol design practice variability across four therapeutic areas, based on the 2013 study. Tufts CSDD continues to gather data on protocol design characteristics by therapeutic area. The results of these studies will supplement that presented in this paper and will assist pharmaceutical and biotechnology companies in optimizing their protocol designs.

Methods

Between November 2011 and May 2012, Tufts CSDD collected data on protocol design characteristics from 15 mid- and large-sized pharmaceutical and biotechnology companies. Each company inputted data on their protocols using a custom electronic data collection tool designed by Medidata Solutions Worldwide (NY, USA).

Tufts CSDD only analyzed Phase II and III protocols for this study. To minimize atypical protocol designs, pediatric, medical device studies, orphan drug and extension studies were excluded from the sampling frame. Participating companies provided complete data on 116 unique Phase II and III protocols, completed since 2009. Of the total, 31 (27%) protocols were Phase II/III oncology studies; 20 (17%) were Phase II/III endocrine studies; 19 (16%) were Phase II/III CNS studies; and another 19 (16%) were Phase II/III anti-infective studies. Although a wide variety of other therapeutic areas are represented in this study, the total number of protocols targeting disease in any other therapeutic area was not sufficient to support comparisons.

Detailed data on protocol design characteristics – including number of end points; number of investigative sites; number of patients screened and randomized; and number of patient eligibility criteria – were collected.

Each participating company's internal staff reviewed its protocols, assigned procedures and completed the electronic data collection process.

Procedures were classified according to the objective and end point they supported as defined by the clinical study report and the statistical analysis plan. Procedures added as part of the implementation of a protocol amendment were also classified. Four main procedure classifications were developed for use in this study:

- 'Core' procedures are those that supported primary and/or secondary study objectives or primary or key secondary and safety end points;
- 'Required' procedures are those that supported screening requirements and regulatory compliance-related activity including drug dispensing, informed consent form review, adverse event assessment, and study drug return;
- 'Standard' procedures are those that are commonly performed during initial and routine study volunteer visits including medical history, height and weight measurement and concomitant medication review;
- 'Non-core' procedures are those that supported ancillary secondary, tertiary and exploratory end points, and safety and efficacy procedures not associated with a study end point or objective.

All participating companies reviewed and discussed the classification scheme in a training session to promote more consistent coding practices between companies. Medidata's PICAS® database containing economic data from grants and contracts supporting more than 27,000 ethical/institutional review board-approved multispecialty protocols was used to compile the direct cost data to perform protocol procedures. Classified procedures were matched to their corresponding direct administration cost. Direct costs were also calculated for patients who dropped out of each study prematurely. In these instances, the direct cost for all procedures performed through each patient's last visit was aggregated. In all, data on 22,143 procedures from 116 protocols were classified and direct cost data from 16,607 procedures was analyzed. Tufts CSDD conducted all data analyses using SAS 9.3 (Cary, NC) and Microsoft Excel.

Results

Of the 116 protocols analyzed, 68 (59%) were Phase III studies and 48 (41%) were Phase II studies. A summary of the distribution of all procedures and their direct costs by phase and a description of each classification scheme are presented in Table 1. Approximately half of all Phase II and III procedures supported 'core' end points and objectives. Whereas 17.9% of procedures supported 'non-core' Phase II end points, one in four Phase III procedures supported these supplementary, tertiary and exploratory end points.

The design and scope characteristics of the protocols analyzed in this study were generally representative of Tufts CSDD industry benchmarks derived from previous studies [11]. In the overall sample of 116 protocols, each had an average of 184 total procedures conducted and 33 inclusion and exclusion criteria. Oncology protocols had an average of 186 total procedures and 28 eligibility criteria; endocrine study protocols had a total of 174 procedures and an average of 37 inclusion and exclusion criteria; CNS protocols had an average of 210 procedures and 36 study volunteer eligibility criteria; and anti-infective protocols had an average of 182 procedures and 33 inclusion and exclusion criteria.

On average 130 investigative sites participated in each of the 116 total protocols and 437 patients were randomized. For endocrine study protocols, an average of 92 investigative sites participated and 430 patients were randomized. For oncology and CNS protocols, 206 and 40 investigative sites participated and 298 and 331 patients were randomized respectively. On average 72 investigative sites and 471 randomized patients participated in anti-infective protocols.

The total average number of end points per protocol was 13 with one primary end point, five secondary end points and seven (54%) supplementary (e.g., tertiary, exploratory) end points. Endocrine and CNS protocols had the highest relative proportion of supplementary end points (Figure 1).

The distribution of procedures by end point classification and therapeutic area is presented in Figure 2. Whereas half of all procedures supported 'core' end points and objectives overall and for anti-infective studies, a higher proportion of procedures did so for oncology and CNS studies. A third of endocrine study protocols supported 'core' end points and objectives. Endocrine studies also had a higher relative percentage of procedures supporting 'required' and 'standard' end points.

One-third of procedures in endocrine study protocols and 27% of procedures in anti-infective studies supported 'non-core' end points and objectives. Oncology and CNS study protocols had a smaller relative proportion of procedures supporting these supplementary, tertiary and exploratory end points.

The direct cost to administer procedures by end point type varied by therapeutic area. Overall, 48% of the study budget or \$2.9 million on average was spent on the direct cost to administer procedures supporting 'core' end points and objectives. The direct cost to administer procedures supporting 'core' end points for oncology and CNS studies were proportionally higher at 61% of the total study budget and 59% of the study budget respectively. Procedures supporting endocrine and anti-infective study 'core' end points made up onethird and 43% of the total study budget respectively. **Table 2** summarizes the mean and proportion of direct procedure costs by end point classification.

Approximately 18 cents of a total study budget or \$1.1 million on average, across all therapeutic areas,

Table 1. Distribution of procedures and direct cost per procedure by end point classification.									
End point type	Definition	Phase II procedures (%)	Phase III procedures (%)	Phase II procedure cost (%)	Phase III procedure cost (%)				
Core	Supporting primary, key secondary or safety end points	54.4	47.7	55.2	46.7				
Required	Supporting screening and compliance-related requirements	8.0	10.0	16.3	22.7				
Standard	Supporting baseline and routine volunteer visits	19.7	17.6	15.4	12.0				
Non-core	Supporting supplementary, tertiary and exploratory end points	17.9	24.7	13.1	18.6				
All values are percentages of the total per protocol.									
n = 48 Phase II and 68 Phase III protocols.									



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is spent on procedures supporting 'non-core' supplementary, tertiary and exploratory end points. For oncology protocols, \$850,000 on average, or 8% of the total study budget, is spent on procedures supporting 'non-core' end points and objectives. A similarly low proportion of a CNS study budget (9%) is spent on procedures supporting 'non-core' end points. A relatively high proportion of endocrine study protocol procedures (24%) and anti-infective study protocol procedures (30%) are spent on procedures supporting 'non-core' end points. Table 2 also shows the distribution of direct procedure costs to support 'required' and 'standard' end points and objectives. Oncology study protocols have a higher relative proportion of, and average spend associated with, direct procedure costs supporting 'required' or regulatory compliance objectives. Endocrine and CNS study protocols have a higher relative proportion of direct procedure costs supporting 'standard' end points. Anti-infective study protocols have a lower relative proportion of direct costs supporting 'required' end points.



Figure 2. Distribution of procedures by end point classification and therapeutic area.

Therapeutic area variability supporting protocol end points & objectives Review: Clinical Trial Methodology

Table 2. Distribution of direct procedure cost by end point classification and therapeutic area.										
End point Type	Total budget (US\$ millions)	Core (US\$ millions; % of total)	Required (US\$ millions; % of total)	Standard (US\$ millions; % of total)	Non-core (US\$ millions; % of total)					
Overall	6.1	2.9 (47.5)	1.3 (21.3)	0.8 (13.1)	1.1 (18.0)					
Oncology	10.8	6.6 (61.1)	2.7 (25.0)	0.6 (5.6)	0.9 (8.3)					
Endocrinology	2.1	0.7 (33.3)	0.4 (19.1)	0.5 (23.8)	0.5 (23.8)					
CNS	3.2	1.9 (59.4)	0.3 (9.4)	0.7 (21.9)	0.3 (9.4)					
Anti-infective	3.0	1.3 (43.3)	0.4 (13.3)	0.4 (13.3)	0.9 (30.0)					
All values are mean direct costs and percentage of total study budget.										

Discussion

Variability in the distribution of procedures and direct procedure costs was observed across the four therapeutic areas analyzed. Endocrine and anti-infective protocols contained a high relative average number of supplementary, tertiary and exploratory end points. Oncology and CNS protocols had the highest relative proportion of procedures supporting 'core' end points and objectives and the lowest relative proportion of those supporting 'Non-Core' end points. Endocrine protocols had the lowest relative proportion of procedures supporting 'core' end points.

The relative proportion of direct costs to administer endocrine and anti-infective protocol procedures supporting 'non-core' end points and objectives was significantly higher than that observed in oncology and CNS studies. Oncology protocols in this analysis had the highest relative proportion of direct procedure costs associated with regulatory compliance.

Variability by therapeutic area is a function of many factors including the nature of specific disease and the unique challenge of differentiating the safety and efficacy of therapeutic interventions; competing designs in later stage clinical trials targeting similar mechanisms of action; the safety risk associated with select treatments and the higher utilization of assessments required to demonstrate safety; real and anticipated expectations from regulatory agencies; the higher prevalence of biomarker use and diagnostic tests; the growing use of comparator and cotherapies; and the increased focus on stratified patient populations.

Informal interviews with managers in clinical research functions suggest numerous reasons why protocol complexity has increased and why variability by phase and therapeutic area is observed. New scientific knowledge about chronic disease mechanisms and how to measure their progression and economic impact, for example, requires more elaborate and robust ways to demonstrate drug safety, efficacy, outcomes and comparative effectiveness. Crowded classes of investigational therapies and the ongoing movement to develop personalized medicines are pushing research sponsors to collect more data and to target smaller patient subgroups to more effectively differentiate small and large molecule interventions. Research sponsors are increasingly collecting biomarker and genetic data that may be analyzed as part of the study or stored and analyzed at a future date.

Clinical research teams – in particular medical scientists and statisticians – add procedures to gather more contextual data to aid in their interpretation of the findings and to guide development decisions. Context-setting variables provide clinical validation and help explain unusual and unexpected results. Medical writers and protocol authors often permit outdated and unnecessary procedures into new study designs because they are routinely included in legacy protocol authoring templates and operating policies.

Drug developers also routinely add procedures believing that the marginal cost of doing so, relative to the entire clinical study budget, is small when the risk of not doing so is high. Clinical research teams anticipate requests for more data from regulatory agencies, purchasers and payers that could potentially delay regulatory submission, product launch and product adoption. Additional protocol data is also collected as a hedge against the study failing to meet its primary and key secondary objectives. This additional data may prove valuable in *post hoc* analyses that reveal new and useful information about disease etiology and its treatment and new development directions.

The results of this study serve as a preliminary point of comparison for clinical research professionals in pharmaceutical and biotechnology companies to understand their protocol design practices. The authors acknowledge that the protocol characteristics and the distribution of procedures and direct procedure costs by therapeutic area are based on a relatively small sample size. Still, given the labor-intensive nature of this research, the results of this study provide an important first look. Further research is needed to establish more robust benchmarks for the three therapeutic areas examined in this study. In addition, Tufts CSDD plans to gather more data to deepen our understanding of a larger number of therapeutic areas.

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At a minimum, the results of this study highlight the need to evaluate each protocol individually based on the end points and objectives established in the clinical study report and statistical analysis plan. In those instances where procedures do not support 'core', 'required' and 'standard' end points and objectives, comparisons with industry practices may help direct clinical teams in identifying ways to reduce and simplify study designs.

Simplifying and reducing the number of procedures rests with more rigorous feasibility assessment prior to approval and placement of the protocol at the research center. The results of this study provide preliminary benchmarks on study design practices for four therapeutic areas – oncology, endocrinology, CNS and anti-infective – and offer pharmaceutical and biotechnology companies an opportunity to make initial comparisons between industry and internal protocol design practices.

Future perspective

Sponsor companies will increasingly adopt new approaches to test and adjust the feasibility of their study designs to improve drug development performance and efficiency. Adaptive trial designs are also expected to play a growing role in study design optimization by pushing sponsor companies to perform more rigorous upfront planning and simulation prior to reviewing and approving their protocol designs.

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Executive summary

- Protocol designs have become increasingly demanding and complex, both scientifically and operationally.
- Studies in the literature have demonstrated that higher levels of protocol complexity are associated with poorer clinical research data quality, higher study costs and longer study durations.
- A recent study by the Tufts Center for the Study of Drug Development indicates that one out of five procedures per protocol, overall, are 'non-core' in that they collect data that is neither tied to a primary or key secondary end point nor to a procedure associated with regulatory compliance.
- The Tufts Center study results also show wide variability in the prevalence of 'non-core' procedures and their proportional direct costs by therapeutic area indicating opportunities to benchmark and simplify study designs.

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