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Assessing the Impact of Protocol Design Changes on Clinical Trial Performance

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Although it is widely acknowledged that protocol design plays a crucial role in the success of clinical research studies, how protocols have changed over time and the impact of these changes on clinical trial performance have never been quantified. To measure protocol design trends, the Tufts Center for the Study of Drug Development analyzed data on 10,038 unique phase 1–4 protocols conducted between 1999 and 2005. Tufts Center for the Study of Drug Development analyzed study conduct performance data on 57 individual phase 2 and 3 protocols administered at US-based investigative sites. The results of this study indicate that the number of unique procedures and the frequency of procedures per protocol have increased at the annual rate of 6.5% and 8.7%, respectively, during the time period measured. Investigative site work burden to administer each protocol increased at an even faster rate of 10.5% between 1999 and 2005. Additionally, during this time period, study conduct performance—that is, cycle time and patient recruitment and retention rates—worsened; and the number of protocol amendments, observed serious adverse events, and length of case report forms increased substantially. Implications of these results for simplifying protocol designs and minimizing negative effects on study conduct performance are discussed.

Keywords: clinical study design, clinical research protocols, protocol design, clinical trial cycle time, patient recruitment and retention, drug development

INTRODUCTION

It is widely held that protocol design plays a critical role in the successful administration and completion of clinical research studies.[1,2] Clinical research professionals have long noted anecdotally that protocol design not only affects the scientific value of a clinical research study but also influences many operational factors that impact how well the study is conducted. The key operating areas believed to be most impacted by poor protocol design include the ability of investigative site personnel to secure ethical approval and timely study initiation; the ability of the clinical investigator and study coordinator to follow protocol design instructions; the ability of site personnel to screen, enroll, and retain study volunteers; and the ability of project managers to control clinical study costs.

Several trends have been reported in the literature that support these perceptions and document changes in protocol design over time. According to Wampler[3], for example, the number of procedures performed per protocol and per patient has been rising steadily since the 1990s. The mean number of procedures performed on each study volunteer has increased 11% annually since the year 2000.[4] Kahn et al[5] have noted that the rising complexity and associated costs of study protocols have made it more difficult for investigative sites to complete clinical studies on time and within budget. A 2004 study found that more than 90% of all clinical trials failed to complete volunteer enrollment within the initial study time frame, resulting in an

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average delay of 6 weeks.[6] Furthermore, published Food and Drug Administration investigator site inspection results reveal that failure to follow protocol design requirements is among the most commonly cited area of Good Clinical Practice noncompliance.[7]

Interviews of clinical research managers in biotechnology and pharmaceutical companies, conducted by the Tufts Center for the Study of Drug Development (Tufts CSDD), indicate that sponsor companies actively modify and amend research protocols to address delays due to poor design while clinical studies are underway—a practice that is both highly disruptive and costly.[8] According to Tufts CSDD, biopharmaceutical companies report making an average of 3 amendments to phase 1 protocols and 7 amendments to phase 2 and 3 protocols, with the cost to implement each amendment ranging from $250,000 to $450,000.

Although the Tufts CSDD interviews shed some light on the impact of protocol design on study conduct and its economics, the findings are limited. To date, the full extent of protocol design trends and the direct impact of protocol design on study conduct performance have not been assessed. Similarly, changes in volunteer eligibility criteria and types of procedures administered over time have not been quantified. To address these issues, Tufts CSDD conducted primary and secondary data analyses to understand how protocol designs (eg, eligibility criteria, procedure frequency, and type) have changed over time and the direct impact of these changes on clinical trial performance (eg, time lines, investigative site workload, and patient recruitment and retention effectiveness).

It is well documented that the long time lines, high cost, and substantial risks that occur during the clinical phase of drug development pose formidable challenges for sponsors vying to bring new pharmaceutical and biopharmaceutical products to market. Protocol design improvement is a critical area of focus today for drug sponsors and clinical investigators looking to eliminate drug development inefficiencies.

METHODOLOGY

Measuring protocol design changes

Retrospective data analyses were conducted on 10,038 protocols drawn from proprietary Pharmaceutical Investigators Cost Assessment Service (PICAS) database of Fast Track Systems, Inc. This database contains detailed protocol and investigator grant information from over 75 pharmaceutical and biotechnology companies covering all therapeutic areas and geographies representative of the current state of drug development activity.[9]

For this analysis, protocols were selected if they had received institutional review board (IRB) approval between 1999 and 2005. In addition to the study design information already captured within PICAS, Tufts CSDD coded eligibility criteria and procedural criteria for each protocol. All coding was verified by 3 independent raters, with an intercoder reliability of 90%. The following eligibility classifications were established and coded:

1. Demographics: general characteristics of study participants (eg, age, race, gender, and family composition);
2. Lifestyle choices not associated with the study: participant behaviors that are independent of requirements for the study (eg, smoking status, medications, sexual behaviors, and nutrition);
3. Lifestyle choices associated with the study: participant behaviors that will occur or change as a result of study enrollment (eg, willingness to take medication, necessary changes in sexual behavior, and smoking cessation during course of trial);
4. Pre-existing medical conditions: physical and psychological conditions and histories previously diagnosed in participants (eg, previous surgeries, family medical history, and disease history);
5. Medical procedures associated with the study: procedures and tests performed during the course of the study or as a threshold requirement for study participation (eg, tests for specific glucose levels and willingness to undergo protocol-based procedure);
6. Disease stage and progression: characteristics of diseases at various stages in their development (eg, tumor size, white blood cell count, and cancer progression);
7. Administrative requirements and general guidelines associated with study participation (eg, signing of informed consent and proper transportation).

The following protocol procedural categories were established and coded for this study:

1. Laboratory tests: laboratory tests, panels, and cultures for vitamin levels, infectious and bacterial agents, and toxins;
2. Blood work: laboratory tests and assays examining hematology and coagulation, such as blood counts, bone marrow compositions, and prothrombin/thromboplastin times;
3. Questionnaires and subjective assessments: self-administered or physician-administered questionnaires, rating scales, and assessments for psychological and medical conditions;

4. Office consultations and examinations: full evaluation and management procedures for both medical and psychological conditions, both new patient and follow-up examinations;
5. X-rays and imaging: preventative and diagnostic procedures, including ultrasounds, CAT scans, x-rays, and magnetic resonance imagings of internal organs;
6. Heart activity assessments: electrocardiograms (EKGs), stress tests, and electrocardiographic monitoring for both diagnostic and preventative purposes.

Quantifying impact on study conduct performance

To assess the impact of design change on the work burden of investigative sites to administer protocols, Tufts CSDD adapted the relative value unit (RVU) methodology pioneered by Medicare. Created in 1992, Medicare's RVU scale was established to determine payment levels for physicians' relative costs instead of prevailing charges for medical services. The RVUs are based on the estimated value of physician time and expertise to administer medical procedures.[10]

Using Medicare's methodology, Tufts CSDD created Work Effort Units (WEUs) for clinical trial procedures conducted to support each protocol. Clinical trial procedures that were comparable to common medical procedures were assigned Medicare's RVU values. For those procedures that were not already assigned a Medicare RVU, a panel of 10 physicians at the Tufts University School of Medicine was convened to estimate the time spent per procedure. The panel was also asked to pair clinical trial procedures with similar procedures already assigned RVU values by Medicare. WEUs values were established for each protocol procedure based on the panel's average assessed value or the average comparable RVU value selected. Tufts CSDD assigned a WEU to each procedure for all 10,038 protocols in the Fast Track Systems database. "Investigative Site Work Burden" is the product of WEUs per procedure and the frequency of procedures that were conducted over the course of the protocol.

In addition, questionnaires were administered to a randomly selected, convenience sample of senior staffers at pharmaceutical and biotechnology companies chosen from Fast Track's proprietary database. Companies were eligible for selection if they had provided protocol information on studies conducted during the time period 1999–2006 and if institutional memory of each protocol was still available. To control for the wide variability in the duration of clinical trials targeting acute versus chronic illnesses and for the cycle time variations between clinical trials conducted in developing countries versus those conducted in the United States and Western Europe, Tufts CSDD limited its analysis to only phase 2 and 3 protocols investigating chronic illnesses and conducted in the United States.

The questionnaire was designed to assess various aspects of study conduct performance (ie, cycle time, patient enrollment rates, IRB review rates, average number of amendments per protocol, average length of case report forms, and the average number of queries per form). In all, 14 biopharmaceutical companies completed and submitted questionnaires. Of these, 5 were able to provide complete and detailed questionnaire responses on 57 unique protocols: 28 protocols were conducted during 1999–2002 and 29 were conducted during 2003–2006.

Using the 57 unique protocols provided by participating companies, Tufts CSDD coded the inclusion and exclusion criteria using its 7 eligibility categories.

RESULTS

Measuring protocol design changes

Unique procedures per protocol

Between 1999 and 2005, the annual growth rate in the number of unique procedures per protocol across all therapeutic areas was 6.5%. Phase 4 postapproval studies showed the highest annual growth rate [9.1% (n = 1788)]—in unique procedures per protocol between 1999 and 2005 (Table 1). The median number of unique procedures per protocol was highest in phase 1 studies. Across all therapeutic areas and phases in 2005, the median number of unique procedures conducted per protocol was 35.

During 1999–2005, protocols for studies in ophthalmology, pain management, and gastrointestinal indications saw the highest annual growth rates in the median number of unique procedures across all phases (Table 2).

Procedural frequency per protocol

Procedural frequency measures the number of times that a given procedure is conducted during the duration of the study to support a given protocol. For example, if blood work is conducted 3 times during the course of a study, then it would receive a procedural frequency count of 3.

Phase 1 clinical trials tend to have the highest overall level of procedural frequency. In 2005, a total of 217 procedures per protocol (n = 51) were conducted in phase 1 (Table 1). Each of the 40 unique procedures, therefore, was conducted an average of 5.4 times over

Table 1. Key protocol design characteristics and trends.

	All phases	Phase 1	Phase 2	Phase 3	Phase 4
Unique procedures per protocol					
Median number in 2005	35	40	35	33	32
Annual growth rate (1999–2005)	6.5%	6.1%	5.8%	5.5%	9.1%
Total procedures per protocol*					
Median number in 2005	158	217	195	132	99
Annual growth rate (1999–2005)	8.7%	9.5%	12.1%	6.1%	11.0%
Work burden per protocol†					
Median WEUs in 2005	37.1	50.6	46.5	31.9	24.2
Annual growth rate (1999–2005)	10.5%	14.0%	12.5%	7.9%	10.8%

*Defined as the number of unique procedures multiplied by their frequency during the duration of the protocol.
†Defined as the product of WEUs per unique procedure multiplied by their frequency.

the course of the trial. Unique procedures were conducted an average of 6.5, 4.0, and 3.1 times, for phases 2, 3, and 4 trials, respectively. Across all therapeutic areas and phases, 158.3 procedures were conducted in 2005—an average of 4.5 per unique procedure—during the course of a clinical trial. By therapeutic area, studies focusing on pharmacokinetics, hematology, and gastrointestinal diseases had the highest procedural frequencies.

The annual growth rate in procedural frequency during 1999–2005, across all phases and therapeutic areas, was 8.7%. Annual growth in procedural frequency during the same period was highest for protocols in phase 2 (12.1%) and lowest for protocols in phase 3 (6.1%) (Table 1). By therapeutic area, gastrointestinal indications, pain management, and ophthalmology saw the highest annual growth rates in procedural frequency per protocol in the 1999–2005 period.

Types of procedures per protocol

Figure 1 shows the distribution of procedures conducted per protocol during 1999 and 2005. In 2005, laboratory tests and blood work were the most common types of procedures conducted per protocol, accounting for 50% of all procedures per protocol for studies across all development phases and therapeutic

Table 2. Protocol design characteristics and trends by therapeutic area.

	Unique procedures		Total procedures*		Work burden†	
	Median number All phases (2005)	Annual growth (%) 1999–2005	Median number All phases (2005)	Annual growth (%) 1999–2005	Median WEUs All phases (2005)	Annual growth (%) 1999–2005
Anti-infectives (N = 801)	28	0.6	124	0.2	30	2.5
Cardiovascular (N = 782)	31	6.7	128	14.1	19	2.5
CNS (N = 1459)	39	5.7	122	4.8	39	4.2
Dermatology (N = 224)	15	−6.9	63	−1.0	15	−0.7
Devices and diagnostics (N = 32)	23	9.3	33	9.4	11	3.8
Endocrinology (N = 850)	37	8.0	128	4.8	25	5.6
Gastrointestinal indications (N = 236)	40	11.3	227	30.5	45	25.1
Obstetrics/gynecology (N = 536)	24	0.7	53	−3.8	17	2.3
Hematology (N = 190)	35	8.9	230	13.8	31	13.9
Immunology (N = 752)	49	10.4	193	12.0	36	13.2
Ophthalmology (N = 91)	51	36.2	181	21.2	52	11.3
Oncology (N = 1450)	34	7.1	208	11.2	52	9.6
Pain/anesthesia (N = 1332)	33	12.8	162	22.5	34	18.7
Pharmacologics (N = 203)	49	7.4	258	11.7	51	13.7
All therapeutic areas (N = 10,038)	35	6.5	158	8.7	37	10.5

*Defined as the number of unique procedures multiplied by their frequency during the duration of the protocol.
†Defined as the product of WEUs per unique procedure multiplied by their frequency.

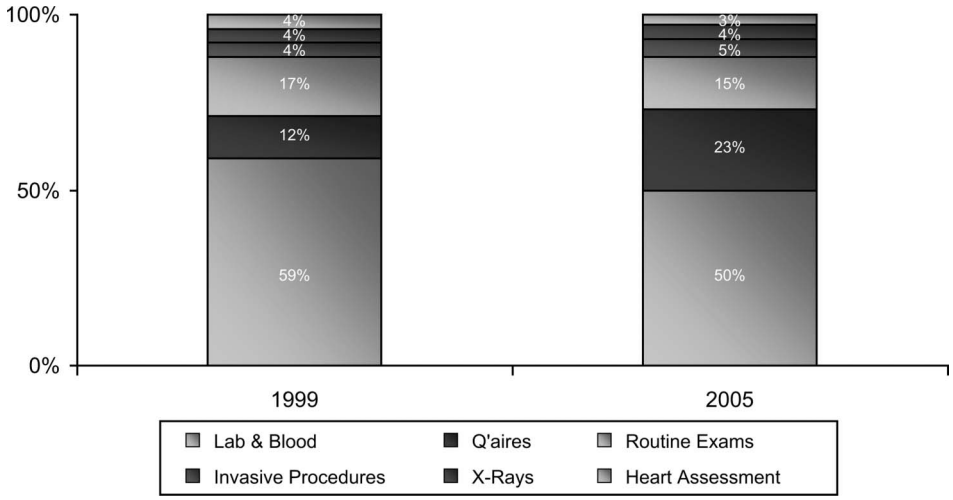

FIGURE 1. Distribution of procedures per protocol (All phases 1999–2005).

areas. Questionnaires and subjective study volunteer assessments (eg, Quality of Life Questionnaires and Physician's Global Assessment Scales) were the second most common procedures per protocol, accounting for 23.3% of the total.

Table 3 shows change in the distribution of procedure type per protocol by development phase during 1999–2005. As a proportion of all procedure types, the administration of questionnaires and subjective study volunteer assessments showed the greatest growth across all phases of development but most notably in phase 3 and 4 clinical studies. Laboratory tests and blood work and office consultations and examinations saw the largest relative declines as a proportion of all procedures performed per protocol.

Eligibility criteria per protocol

Figure 2 compares protocol eligibility criteria during 1999–2002 and 2003–2006. In the later period, protocols averaged a modest increase in the number of exclusion criteria. The average number of inclusion criteria, however, jumped nearly 3 times from the earlier period (10) to the later period (26).

In both periods, the most common inclusion criteria were Medical Procedures Associated with the Study (eg, medical testing results requirements or the willingness on the part of the patient to undergo testing during the clinical trial) and Pre-existing Medical Conditions. Medical Procedures Associated with the Study accounted for 33% of procedures during 1999–2002 and 31% during 2003–2006. Pre-existing Medical Conditions accounted for 18% in the earlier and 23% in the later period. Logistics and general study requirements were the least common inclusion criteria, accounting for 9% and 10% of all inclusion criteria in the earlier and later time periods, respectively.

The average number and type of exclusion criteria used per protocol were similar for the 2 time periods, with a few exceptions. From 1999–2002 to 2003–2006,

Table 3. Distribution of procedures per protocol by phase.

		Laboratory tests and blood work (%)	Consultation and routine examination (%)	Questionnaires and subjective assessments (%)	Invasive procedures (%)	Heart activity assessments (%)	X-rays and imaging (%)
Phase 1	1999	69.8	17.2	3.3	2.7	5.1	1.9
	2005	60.4	18.0	11.2	4.6	4.1	1.7
Phase 2	1999	55.5	16.0	13.5	5.8	4.3	5.0
	2005	53.0	14.4	17.9	4.9	3.2	6.6
Phase 3	1999	54.0	16.1	17.2	4.5	3.5	4.7
	2005	42.6	13.8	32.2	4.0	2.7	4.8
Phase 4	1999	51.8	20.0	15.2	5.9	3.0	4.1
	2005	41.5	15.9	34.5	4.7	2.2	1.2

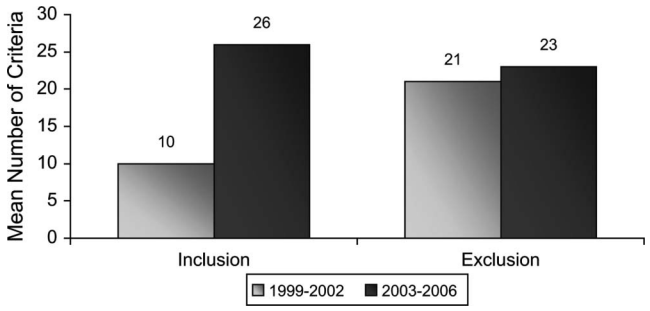

FIGURE 2. Protocol eligibility criteria.

the proportion of exclusion criteria related to Lifestyle Habits and Choices Associated with the Study increased from 5% of the total to 10%. Although it represents a small percentage of the total, demographic criteria also grew sharply, quadrupling from 1% of all exclusion criteria to 4%. The most common exclusion criteria in both time periods were Pre-existing Medical Conditions, which accounted for 52% of all exclusion criteria during 1999–2002 and 43% during 2003–2006.

Quantifying impact on study conduct performance

Impact on investigative site workload

In 2005, the median investigative site work burden across all phases to administer all procedures required per protocol was 37.1 WEUs (Table 1). Ophthalmology, oncology, and pharmacokinetics protocols had the highest investigative site work burden in 2005 (Table 2).

During 1999–2005, investigative site work burden increased annually by 10.5%. The largest annual growth—33%—in work burden occurred between 2003 and 2005. Annual growth in investigative site work burden was highest in phase 1. During 1999–2005, investigative site work burden increased by 14% (n = 1900) to administer phase 1 protocols. Additionally, during 1999–2005, investigative site work burden increased the most in gastrointestinal, pain and anesthesia, and hematology studies. Dermatology was the only therapeutic area to become less burdensome over the 6-year time period, with a change in work burden of −0.7% (n = 224).

Impact on study conduct performance

The design characteristics and performance results for 57 unique protocols were aggregated into 2 cohorts and analyzed. Results are presented in Table 4. Group 1 contained 28 protocols conducted during 1999–2002; group 2 contained 29 protocols conducted during 2003–2006. Changes in design characteristics between protocol cohorts were consistent with and mirrored the changes observed in the larger database of 10,038 protocols. The average number and frequency of unique procedures per protocol increased substantially. Investigative site work burden increased dramatically.

Table 4. Impact on study conduct performance.

	1999–2002	2003–2006
Per protocol		
Unique procedures (median)	33.5	44
Total procedures (median)*	89.8	150.5
Work burden (median)†	21.7	37.8
Select study cycle times metrics		
Days from protocol ready to first patient/first visit (median)	115	129
Days from protocol ready to last patient/last visit (median)	413	714
Days from protocol ready to data lock (median)	460	780
Select patient recruitment and retention metrics		
Percent screened who were randomized	75%	59%
Percent randomized who completed study	69%	48%
Other metrics		
Case report form pages (median)	55	180

*Defined as the number of unique procedures multiplied by their frequency during the duration of the protocol.
†Defined as the product of WEUs per unique procedure multiplied by their frequency.

A notable increase was observed in all cycle time metrics for protocols conducted during 2003–2006, with one exception, the time from submission of the protocol to receipt of the IRB decision decreased from 45 days during 1999–2002 to 22 days during 2003–2006. No differences were found in the average number of additional progress reports submitted to the IRB for protocols conducted in the 1999–2002 and the 2003–2006 cohorts. An average of one additional progress report was submitted in each time period.

The median number of days from protocol readiness to first patient/first visit rose 12%. The median cycle time from protocol readiness to drug availability increased 19%. Median broad cycle time from protocol readiness to last patient/last visit increased 73% from the earlier to the later cohorts, and median elapsed time from protocol readiness to data lock increased 70%. Finally, the average overall duration of clinical trials increased 74%.

The average number of protocol amendments increased modestly between 1999 and 2006: from 2

during 1999–2002 to 3 during 2003–2006. However, the average length of the case report form increased 227%, from 55 pages per protocol to 180 pages per protocol, for the 2 cohorts.

Measures of patient enrollment performance changed notably across the 2 protocol cohorts. Enrollment rates for volunteers who met the rising number of protocol eligibility criteria dropped from 75% during 1999–2002 to 59% during 2003–2006. Retention rates for study volunteers dropped from 69% to 48% for the 2 comparison time periods.

Patient enrollment cycle times increased for protocols conducted during the later time period. Median cycle time from first patient/first visit to last patient/first visit increased 53%, and median cycle time from first patient/first visit to last patient/last visit increased 65%.

Finally, the median number of adverse events reported in the 2 cohorts jumped dramatically, from 667 in the 1999–2003 cohort to 1481 in the 2003–2006 cohort, an increase of 122%. There was also a 12-fold increase in the median number of serious adverse events reported (2 per protocol during 1999–2002 vs 25 per protocol during 2003–2006). These sharp increases may be due, in large part, to changes in the way that adverse events are defined and counted.

DISCUSSION

The results presented in this study clearly illustrate that the number of unique procedures and the procedural frequency per protocol have increased notably during the past 7 years, with wide variation across therapeutic areas. Whereas the number of exclusion criteria has not changed since 1999, the average number of inclusion criteria per protocol has increased substantially. Moreover, protocols have increasingly required the use of questionnaires and subjective study volunteer assessments and heart assessments, x-ray and imaging procedures, and invasive procedures. Procedural frequency per protocol is substantially higher in phases 1 and 2. This finding is consistent with recent Tufts CSDD studies that have documented growing sponsor reliance on early-phase clinical studies to determine whether to commit to larger and more costly phase 3 studies.[11]

Investigative site work burden to administer each protocol has increased notably during the past 7 years and these increases vary widely by therapeutic area. The results further suggest that it is the combination of changes in the number, frequency, and type of unique procedures per protocol that is driving higher levels of investigative site work burden. Growth in investigative site work burden is, therefore, a function of both growing complexity of protocol design and rising administrative demands to execute these procedures.

Study conduct performance seems to have been adversely impacted by changes in protocol design during the past 7 years. When comparing study conduct performance for those protocols conducted in 1999–2002 with those in 2003–2006, the latter protocols had longer cycle times to enroll patients and collect study data, poorer patient randomization and completion rates, higher numbers of protocol amendments and observed adverse and serious adverse events, and more lengthy informed consent and case report forms.

Numerous factors may be behind the growing number of unique procedures and inclusion criteria in the more recent protocols. For example, during the past 10 years, a large and growing proportion of investigational treatments in drug development programs are targeting chronic illnesses that are more difficult to treat and require longer and more elaborate methods to measure safety and efficacy end points. Protocols for the study of investigational biologics typically require longer cycle times, more stringent eligibility requirements, and more elaborate methods—including diagnostic assessments of biomarkers to evaluate safety and efficacy. As the composition of the drug development pipeline continues to focus on more chronic and complex illnesses and biologics-based therapies, protocol designs are expected to become even more demanding and challenging.

A number of clinical research professionals within pharmaceutical and biotechnology companies have suggested that regulatory agency requirements may also be major drivers of protocol design complexity. Pharmaceutical and biotechnology companies design more ambitious protocols to gather additional clinical data that they anticipate will be required by the regulatory agency. Some have argued, however, that not all of the data required by the protocol are scientifically necessary. Eligibility criteria and the number and types of procedures per protocol are rising steadily, as evidenced by the results of this study. Sponsor companies may need to do a better job of challenging whether these design elements are critical to the desired project end points.

In the current drug development environment, regulatory agencies are particularly sensitive to sponsor companies gathering additional safety data. As such, new protocols can be expected to contain a growing number of procedures designed to satisfy agency sensitivities. This suggests that phase 1 and 2 studies may continue to see more rapid relative growth in the number and frequency of procedures.

It is important to note that the sample size in this initial analysis of protocol design impact on study conduct performance is relatively small (n = 57). As such, these results should be interpreted with some caution. The current analysis is based on a convenience sample of highly difficult to obtain metrics. Study conduct metrics gathered per protocol are typically not routinely compiled by pharmaceutical and biotechnology companies or captured in an accessible manner. If feasible, a larger sample of protocols will be used in future studies. In addition, subsequent analyses are planned to evaluate protocol design approaches that most contribute to improvements in study conduct performance and to understand the impact of design changes on a global basis.

Although causality has not been determined, the results do suggest that as protocol designs have become more ambitious and demanding, study conduct has become less efficient and effective. These results challenge the notion that improvements in study conduct performance can be achieved through aggressive investigative site management. Opportunities to achieve higher levels of study conduct performance also lie with improvements in protocol design.

Given intense pressure on sponsor companies to accelerate development cycle times and lower drug development costs, the results of this study speak to the necessity of simplifying protocol designs to ease investigative site work burden and, ultimately, to improve study conduct efficiency. Protocols in therapeutic areas that have seen the highest growth in the number of procedures, eligibility requirements, and work burden may be good initial candidates for determining whether simplification is practical and, indeed, possible.

The results also highlight the importance of up front planning to anticipate how protocol design variations will impact investigative site work burden. Protocols for studies in specific therapeutic areas, such as gastrointestinal indications and pain management, have become particularly demanding. These may be good areas initially to incorporate additional planning activity.

Investigative sites have long held that sponsors are demanding more from them for less relative compensation, resulting in lower study staff motivation to conduct clinical trials. This claim may be legitimate. The results of this study show that investigative site work burden to administer protocols has been increasing by 10.5% annually since 1999. During this same period, compensation per procedure to investigative sites has been declining 3% annually.[12] A review of clinical study grant amounts per protocol and the work burden required to administer that protocol may assist sponsor companies in determining more motivating study compensation levels.

The results of this study provide compelling insights into the role that protocol design change plays in study conduct performance and work burden. In the current drug development environment, improved protocol designs may hold the key to achieving higher levels of efficiency and effectiveness for the research-based pharmaceutical and biopharmaceutical industry.

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