

Measuring the Incidence, Causes, and Repercussions of Protocol Amendments

Kenneth A. Getz, MBA
Senior Research Fellow,
Tufts CSDD

Rachael Zuckerman, MPH
Senior Research Analyst,
Tufts CSDD

Anne B. Cropp, PharmD
Executive Director,
Global R&D, Pfizer

Anna L. Hindle, MSc
Director, Medical Writing,
Biogen Idec

Randy Krauss, PhD
Associate Director,
Metrics, Analysis and
Performance, Genzyme

Kenneth I. Kaitin, PhD
Director, Tufts CSDD

Drug development companies frequently amend finalized clinical trial protocols. Yet the incidence, causes, and impact of protocol amendments have never been quantified. Tufts Center for the Study of Drug Development (Tufts CSDD) conducted a study, in collaboration with 17 large and mid-sized pharmaceutical and biotechnology companies, examining more than 3,400 clinical trial protocols across development phases and therapeutic areas. Data on protocol characteristics, the number of amendments, the nature and incidence of changes per amendment, the causes of amendments, and the time and cost to implement

amendments were among those analyzed. Tufts CSDD found that more than 40% of protocols were amended prior to the first subject/first visit, and one third of amendments were avoidable. Each amended protocol had an average of 2.3 amendments resulting in 4 months of incremental time to implement. Protocol amendments translate into significant unplanned expense and delays for research sponsors and unexpected burden for investigative sites. These findings underscore the substantial impact of protocol amendments on drug development efficiency and present an opportunity to realize substantial cycle time and cost savings.

Key Words

Protocol amendments;
Protocol design; Protocol
complexity; Protocol
design changes

Correspondence Address

Kenneth A. Getz,
Senior Research Fellow,
Tufts Center for the Study
of Drug Development,
Tufts University,
75 Kneeland Street,
Suite 1100,
Boston, MA 02111
(email: kenneth.getz@tufts.edu).

INTRODUCTION

Amendments made to finalized clinical trial protocols are commonplace, but they are widely viewed as a nuisance, resulting in study delays and additional costs (1). Clinical trial protocols that have undergone a rigorous internal review and approval process are often changed for a variety of reasons, including revisions to subject eligibility criteria; requests for modification from regulatory agencies, institutional review boards (IRBs), or ethical review boards (ERBs); the addition of new countries due to poor recruitment; the availability of new safety information; the introduction of new standards of care for a given illness; or typographical errors and clarifications in procedural descriptions.

Clinical research professionals perceive protocol amendments as a major problem, but it is perhaps more accurate to view amendments as solutions to underlying problems. These include the growing pressure to collect more data during clinical trials, increasing difficulty in recruiting study volunteers, and intensifying pressures that sponsors face in initiating and completing clinical trials within ambitious time frames (2).

Despite the widespread practice of amending

protocols, very little is known about the incidence and cause of amendments, and their economic and operating impact. Wise and Drury (3) found that 45% of 100 general, practice-based multicenter research protocols submitted to the ethics committee of the Royal College of General Practitioners were amended. The authors noted that on average, each of the amended protocols had 1.5 changed items. Study volunteer compensation, incomplete informed consent forms, new safety requirements for pregnant volunteers, and inadequate and imprecise scientific content were major reasons cited for amending the protocols.

A study conducted by Losch and Neuhauser (4) showed that protocol amendments related to study volunteer eligibility criteria have a significant impact on statistical methods analyses. The authors demonstrated that protocol amendments change the population sampling and diminish the power of statistical tests performed.

A 2008 study conducted by the Tufts Center for the Study of Drug Development (Tufts CSDD) found a positive association between protocol complexity and the incidence of amendments (2). Less complex protocols—those containing fewer procedures and eligibil-

**Samsung v.
Regeneron**

IPR2023-00442

U.S. Pat. 10,130,681

Exhibit 2371

ity criteria—averaged two amendments; more complex protocols, in contrast, averaged 3.2 amendments (5).

As a follow-up to that study, and in response to the dearth of quantitative data on the incidence, causes, and impact of protocol amendments, Tufts CSDD convened a group of pharmaceutical and biotechnology companies to share protocol amendment data. The results of this study highlight the substantial impact of protocol amendments on drug sponsors and clinical sites, offer ways to better anticipate and plan for protocol amendments, and suggest opportunities to reduce, and even prevent, the use of certain protocol amendments in the future.

METHODS

Seventeen midsized and large pharmaceutical and biotechnology companies participated in this study: Amgen, Astellas, AstraZeneca, Biogen Idec, Cephalon, Forest, Genentech, Genzyme, Lilly, Merck, Millennium, Otuska, Pfizer, Roche, Schering-Plough, Sepracor, and Takeda. Representatives from these companies worked collaboratively with Tufts CSDD to develop the data collection instrument, and then engaged their staff to complete the data collection instrument.

In January and February 2010, each participating company submitted its data on protocols approved internally between January 2006 and December 2008. Protocols approved within the most recent 12 months were excluded from the study to allow enough time for protocols to accumulate amendments. Data from 3,410 protocols were submitted across a wide and representative range of therapeutic areas, providing detailed data on 3,596 amendments containing 19,345 total protocol modifications.

For this study, amendments were defined as any change to a protocol requiring internal approval followed by approval from the IRB, ERB, or regulatory authority. Only implemented amendments—that is, amendments approved both internally and by the ethics committee—were counted and analyzed in this study.

Tufts CSDD staff analyzed both protocol de-

sign characteristics and protocol amendment descriptive and impact measures. With respect to protocol design characteristics, data on the number of amendments, indication (therapeutic area and disease), molecule type, study phase, treatment duration, planned and actual study size (number of subjects, number of sites, and regions where the study was conducted), level of outsourcing (whether various study components were conducted in house, partially outsourced, or fully outsourced), and cycle time milestones (protocol finalized by sponsor; first patient, first dose; last patient, last visit; and final database lock) were collected and analyzed.

Measures on amendment incidence and impact included the total number of amendments, total changes made per amendment, and classification of each change based on which part of the protocol it affected (see Figure 1). In total, 6,855 changes were categorized. Additionally, companies provided data on key cycle time metrics related to implementing each amendment (eg, date problem first identified; date work on amendment began; date revised protocol received internal approval; date revised protocol was submitted to, and approved by, first IRB; date first patient resubmitted under revised protocol; date study halted; and date study began again); external sources used in writing the amendment and in supporting problem resolution; study volunteers enrolled (before and after amendment implementation); patient recruitment rates (before and after amendment implementation); and the cost to implement each amendment including internal resources required to prepare and execute resolution.

In assessing the reasons why amendments were written, companies were asked to subjectively categorize each protocol amendment cause. Classification categories were developed by the participating companies (see Figure 2) based on their collective internal assessments of causes. In total, companies categorized the causes for 2,768 amendments. Next the company representatives mutually agreed on rating those cause categories in terms of whether each was “completely avoidable,” “somewhat avoid-

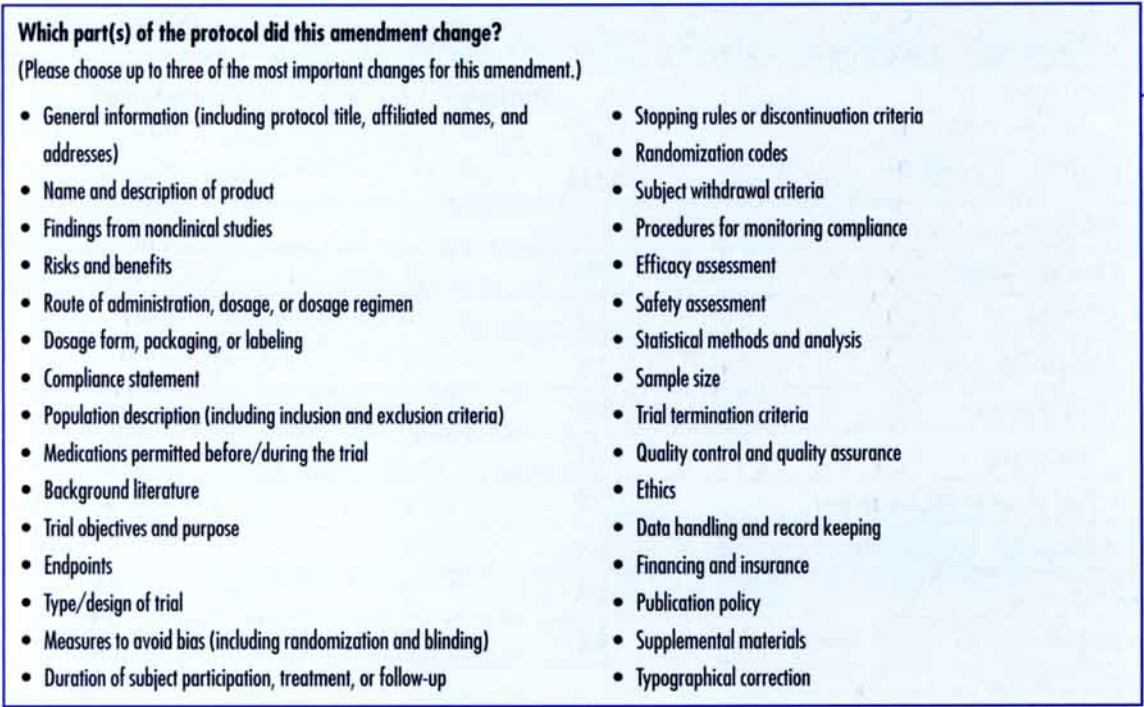


FIGURE 1

List of areas that the amendment changed in the protocol.

able,” “somewhat unavoidable,” or “completely unavoidable.”

Tufts CSDD conducted all data analyses using SAS 9.2 (Cary, NC). Descriptive statistics as well as correlational analyses (ie, Spearman’s rho) were performed. Analyses examining the causes of amendments used only the primary or top-ranked cause; that is, companies were asked to rank order the top three causes of each amendment, but analyses only used the cause ranked most important. Mean values were compared for each measure by trial phase, therapeutic area, and whether the protocol was in progress or completed, with the last defined by the date when the final database was locked.

RESULTS

Tufts CSDD collected data from 3,410 protocols. Those that specified study phase were distributed as follows: 1,640 (54%) were phase 1 studies; 560 (18%) were phase 2 studies; 397 (13%) were phase 3 studies; and 466 (15%) were phase 3b/4 studies. In addition, data from 3,596 amendments were analyzed. For those protocols that specified study phase, 41% of amendments were associated with phase 1

study protocols, 47% with phase 2 and 3 study protocols, and the remainder with phase 4 study protocols. Companies were able to provide data for almost all protocols in the study time frame, with an additional 145 protocols and 1,149 amendments identified that met the inclusion criteria but were not submitted. Characteristics of the sample data analyzed are presented in Table 1.

Protocol data submitted are also representa-

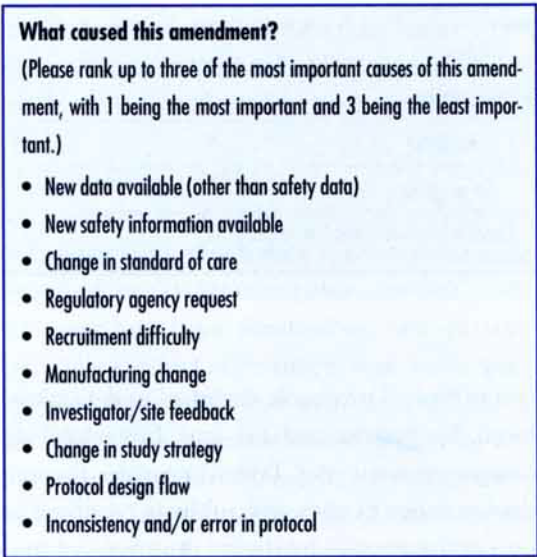


FIGURE 2

List of amendment causes.

TABLE 1

Characteristics of Submitted Data				
	Protocols		Amendments	
	n	%	n	%
Total	3,410		3,596	
Study phase				
1 Healthy volunteers	1,060	31	710	20
Patients	333	10	507	14
Unspecified	247	7	242	7
2 Proof of concept	103	3	199	6
Dose ranging	51	1	117	3
Proof of concept and dose ranging	2	0	3	0
Unspecified	404	12	577	16
3	395	12	756	21
3b/4	466	14	441	12
Therapeutic area				
Central nervous system/neuropsychological	744	22	807	22
Oncology	580	17	848	24
Endocrinology/metabolism	487	14	624	17
Cardiovascular	393	12	247	7
Anti-infective	255	7	220	6
Respiratory	174	5	102	3
Pain/anesthesia	171	5	145	4
Immunomodulation/anti-inflammatory	165	5	203	6
Genitourinary system	121	4	111	3
Gastrointestinal	94	3	71	2
Hematology	43	1	73	2
Other	109	3	114	3
Study status				
Complete ^a	1,315	39	1,266	35
In progress	468	14	812	23

^aComplete is defined as past final database lock.

tive of typical protocols designed and administered by pharmaceutical and biotechnology companies each year. Table 2 provides the median number of sites and subjects recruited as well as the average treatment duration per protocol by clinical research phase.

AMENDMENTS AND CHANGE PER AMENDMENT PREVALENCE

More than half of the protocols required one or more amendments; 56.6% of protocols (n = 1,979) and 58.8% of completed protocols (n = 772) had at least one amendment. Com-

pleted protocols across all phases had an average of 2.3 amendments, though later-stage phase 2 and 3 protocols averaged 2.7 and 3.5 amendments respectively. Each amendment required an average of 6.9 changes to the protocol. Therapeutic areas that had the highest incidence of amendments and changes per amendment include cardiovascular and gastrointestinal protocols. Protocols for respiratory studies had a higher average number of amendments compared to the average across all therapeutic areas; endocrine, hematology, and immunomodulation studies had a higher than average incidence of changes per amendment. Pain study protocols had the lowest incidence of amendments and changes per amendment on average. A breakdown of the average number of amendments and changes per amendment by study phase and therapeutic area are presented in Tables 3 and 4.

Older protocols—those that were approved and implemented in 2006 and 2007—had a significantly higher prevalence of amendments than did protocols that were more recently approved and implemented ($P < 0.001$). Protocols with longer treatment durations also had a significantly higher incidence of amendments. Removing outliers for both variables, Tufts CSDD compared clinical time (defined as time from first dose to last patient, last visit) to the number of amendments per protocol using Spearman's rho correlational analysis. This correlation was statistically significant ($P < 0.001$). Larger protocol scope as defined by the number of investigative sites administering a given protocol was also significantly correlated ($P < 0.001$) with the number of amendments.

Participating companies were asked to indicate up to three of the most important changes made per amendment. Of the 6,855 protocol amendment changes categorized, 1,108 were modifications made to the description and eligibility criteria of the patient population under investigation, 847 noted adjustments made in the number and types of safety assessment procedures performed as one of the three most important changes, and a relatively high number, 715 changes, were alterations and edits made to

Protocol Characteristics and Scope

TABLE 2

Phase	Subjects per Protocol	Number of Sites	Treatment Duration (Days)
Phase 1	36	1	30
Phase 2	120	26	98
Phase 3	446	65	182
Phase 3b/4	258	35	91
All values are medians.			

•

Mean Number of Amendments and Changes per Amendment by Phase

TABLE 3

	Number of Amendments ^a	Protocol Changes per Amendment
Phase 1	1.9	5.6
Phase 2	2.7	6.8
Phase 3	3.5	8.5
Phase 3b/4	2.6	8.3
All phases	2.3	6.9
^a Includes only completed protocols (past final database lock) with at least one amendment.		

general information contained in the protocol (eg, protocol title and study staff contact information). A complete list of change categories and their distribution is shown in Table 5. Differences in the distribution of changes by phase and by therapeutic area were not observed.

AMENDMENT TIMING

For completed studies, 43% ($n = 533$) of amendments for which data were available were signed off by the sponsor before the first study volunteer had been enrolled (ie, first patient, first dose). This occurrence was most pronounced in phase 1 where more than half (52%, $n = 309$) of amendments occurred prior to beginning patient enrollment. In later-stage clinical trials, a smaller percentage of amendments occurred prior to study volunteer enrollment. In phases 2, 3, and 3b/4 studies, 37% ($n = 101$),

TABLE 4

Mean Number of Amendments, Changes per Amendment, and Changes per Protocol by Therapeutic Area			
	Number of Amendments ^a	Protocol Changes per Amendment	Total Changes per Protocol
Anti-infective	2.5	4.4	8.6
Cardiovascular	2.6	10.1	18.8
Central nervous system/neuropsychological	2.2	6.8	16.9
Endocrinology/metabolism	2.2	8.0	19.1
Gastrointestinal	3.9	7.2	16.6
Genitourinary system	2.6	5.0	10.9
Hematology	2.1	9.5	14.6
Immunomodulation/anti-inflammatory	2.4	8.3	16.4
Oncology	2.3	6.7	15.9
Pain/anesthesia	1.8	3.6	6.8
Respiratory	2.9	4.2	7.4
Other	1.9	6.8	18.1
All therapeutic areas	2.3	6.9	15.3

^aIncludes only completed protocols (past final database lock) with at least one amendment.

30% (n = 56), and 38% (n = 67) of amendments, respectively, occurred before first patient, first dose.

AMENDMENT CAUSES

Companies categorized the causes of 2,795 amendments. The most commonly cited cause was the availability of new safety information (19.5%), followed closely by requests from regulatory agencies to amend the study (18.6%), and changes in the study strategy (18.4%). Protocol design flaws and difficulties recruiting study volunteers were also top-cited causes at 11.3% and 9% of categorized amendments, respectively. Table 6 provides the incidence of all 10 primary causes of amendments.

Two thirds (66%) of amendments had causes considered unavoidable, including amendments that were the result of new safety information, new regulatory requests, changes in the standard of care, or study objectives. Of all categorized amendments, one third were in categories considered partially or completely avoidable. Undetected design flaws, inconsistencies or errors in the protocol, and difficulties re-

cruiting study volunteers were rated as amendment causes that sponsors could have better anticipated and avoided. Table 7 presents a grouping of all causes by how easily they are avoidable and preventable.

Some discrimination was observed in the average number of changes made per amendment by cause category. Amendments that were the result of adjustments to the study strategy and objectives prompted an average of 10 changes. Inconsistencies and errors contained within the protocol triggered an average of 9.4 changes per amendment. Table 6 contains the mean number of changes by cause of amendment. Of those causes that facilitated the highest number of changes per amendment, two—new safety information available and regulatory agency request to amend—were considered completely unavoidable.

AMENDMENT IMPLEMENTATION CYCLE TIME AND COST

The majority of companies were unable to provide amendment implementation cycle time and cost data and therefore these results must

TABLE 5

Distribution of Changes Made		
Change Category	n	Percentage of All Changes Selected
Population description (including inclusion and exclusion criteria)	1,108	16
Safety assessment	847	12
General information (including protocol title, affiliated names, and addresses)	715	10
Type/design of trial	531	8
Route of administration, dosage, or dosage regimen	506	7
Typographical correction	425	6
Efficacy assessment	401	6
Statistical methods and analysis	310	5
Medications permitted before/during the trial	282	4
Trial objectives and purpose	258	4
Ethics	230	3
Sample size	210	3
Duration of subject participation, treatment, or follow-up	203	3
Stopping rules or discontinuation criteria	171	2
Dosage form, packaging, or labeling	138	2
Endpoints	99	1
Risks and benefits	80	1
Background literature	57	1
Data handling and record keeping	47	1
Measures to avoid bias (including randomization and blinding)	45	1
Findings from nonclinical studies	35	1
Supplemental materials	35	1
Subject withdrawal criteria	34	0
Procedures for monitoring compliance	29	0
Trial termination criteria	18	0
Name and description of product	12	0
Compliance statement	11	0
Quality control and quality assurance	9	0
Randomization codes	6	0
Publication policy	2	0
Financing and insurance	1	0

Companies could choose up to three changes for each amendment.

TABLE 6

Distribution of Primary Amendment Causes			
Cause	n	Percentage	Mean Number of Protocol Changes
New safety information available	539	19.5	7.9
Regulatory agency request to amend	515	18.6	7.2
Change in study strategy	510	18.4	10
Protocol design flaw	313	11.3	5.7
Recruitment difficulty	249	9.0	4.8
Inconsistency and/or error in protocol	242	8.7	9.1
New data available	196	7.1	8.8
Investigator/site feedback	124	4.5	9.4
Change in standard of care	52	1.9	6.2
Manufacturing change	28	1.0	7.9

be viewed with caution. Based on data from approximately 59 amendments, the median total cycle time from when the protocol problem was identified to when the amendment was fully implemented—defined as first patient resubmitted under the revised protocol—was 65 days. Nearly half (46%) of this time was devoted to determining what changes needed to be made to the protocol. It took an additional 4 weeks (on average 28 days or 43% of the total cycle time) to obtain approval from senior management and the IRB before the first patient could be resubmitted under the revised protocol.

Cost data were provided for only 20 amendments. Among this small sample, the average cost to implement a single protocol amendment was \$453,932. This figure does not include in-

ternal resources utilized to amend the protocol, costs, or fees associated with protocol language translation, and costs associated with resubmission to the local authority. The largest areas of amendment-associated costs were increases in investigative site fees (58% of total costs) and contract change orders with existing third party provider agreements (24%). Table 8 provides a breakdown of cost elements captured that are associated with the implementation of the 20 amendments.

DISCUSSION

The incidence of protocol amendments is high. Nearly 60% of protocols examined required at least one amendment, with the typical protocol having an average of 2.3 amendments. Based on the cycle time data gathered in this study, the results suggest that pharmaceutical and biotechnology companies are spending an additional 4 months to accommodate these 2.3 amendments. Multiply this by the number of global protocols executed per year for any given pharmaceutical company, and the cumulative unplanned delays incurred for R&D programs are staggering. At a minimum, the results of this study offer insights and refinements on project planning and budgeting expectations.

Variability in the average number of amendments and changes per amendment was observed across research phases and therapeutic areas, suggesting opportunities to minimize the number of amendments and reduce the amount of disruption each amendment causes. Initiatives should target those areas with the highest average number of amendments and changes per amendment, specifically phase 3 protocols, and protocols in cardiovascular and gastrointestinal studies.

Larger studies and those involving longer treatment durations are significantly, positively correlated with more amendments. These studies tend to be more demanding (eg, large numbers of study volunteers being recruited at more investigative sites globally) and their protocols tend to be more complex (eg, higher numbers of procedures and eligibility criteria). Protocols in

Avoidable and Unavoidable Amendments**TABLE 7**

Avoidability	n	Percentage	Cause Categories
Completely avoidable	555	20	Protocol design flaw Inconsistency and/or error in the protocol
Somewhat avoidable	373	13	Recruitment difficulty Investigator/site feedback
Somewhat unavoidable	758	27	New data available (other than safety data) Change in strategy/objective Change in standard of care
Completely unavoidable	1,082	39	New safety information available Regulatory agency request to amend Manufacturing change

As a group and based on judgment, participating companies rated these cause categories in terms of whether each was completely avoidable, somewhat avoidable, somewhat unavoidable, and completely unavoidable.

these larger studies may be touched and managed by more investigative site personnel, and they may have more time in the clinical research setting to identify and modify problem areas.

Participating companies in this study note, anecdotally, that larger-scope and longer-duration studies, such as those in phase 3, encourage clinical research scientists to design more ambitious protocols, which may ultimately result in a larger number of protocol amendments. In these large-scale studies, the marginal cost of collecting additional data seems trivial in comparison with the overall study budget, and the data gathered may prove useful in deriving new insights (the "nice to have" additional data versus key data required to answer a scientific question) and in addressing future regulatory agency inquiries. But the high cost and long cycle time of amendment implementation shown in this study, combined with the incremental costs associated with higher protocol complexity and execution burden (2), suggests that the perception of trivial costs may be grossly inaccurate. Indeed, clinical research scientists need to be aware of the potential costs associated with a protocol amendment when making the decision to amend a protocol.

The most common causes of protocol amendments found in this study were regulatory agen-

cy requests, new safety information about the study drug (safety or dose related), evolving standards of care, competitive pressures, inconsistencies in the protocol design and execution process, and patient recruitment difficulties. These causes reflect the myriad considerations that clinical teams weigh to manage clinical research performance. Some of these causes also reflect judgments made, and risks taken, by clinical research management to meet tight deadlines and budget requirements. Faced with time pressures, project teams often must move forward at risk, while pending announcements

Distribution of Direct Costs to Implement an Amendment**TABLE 8**

Item	n	Cost
Contract change orders to existing contracts	20	\$109,523
New contracts with providers	9	\$69,444
IRB fees	19	\$4,384
Increase study grants/site fees	16	\$265,281
Additional drug supply	10	\$5,300
Total^a		\$453,932

^aDoes not include oversight, language translation, or other costs.

of new standards of care and regulatory decisions loom.

Clinical research scientists typically amend a protocol to make clarifications and enhancements to that protocol. The changes made at the time of an amendment are consistent. The largest numbers of changes are design modifications and adjustments to sampling, clinical endpoint measurements, and evaluation. One in four changes is associated with efforts to improve patient recruitment and retention rates. In the current study, 425 (6%) of amendments cited typographical errors and inconsistencies in the protocol narrative as one of the top three changes made to the protocol—changes that in many cases could have been addressed prior to protocol approval.

Our study findings strongly suggest that a large proportion of amendments can be avoided and prevented. Forty-three percent of amendments were written before the first volunteer was even enrolled in the study. Additionally, one third of cited amendment causes were deemed somewhat or completely avoidable.

The average cost per amendment measured in this study, \$453,932, is substantial but should be viewed with caution as it is based on a very small sample size ($n = 20$). Also, the figure is a conservative estimate as it only measures certain direct costs. The figure is missing the estimated direct costs of internal and investigative site resources involved in implementing an amendment, as well as protocol language translation costs, and those costs associated with re-submission to local authorities. No indirect costs—such as those associated with development and commercialization delays—have been measured. The cost data gathered in this study are also limited in that our aggregate estimate combines all submitted cost estimates, although the types of amendments included may not be directly comparable.

It is important to note that many amendments are necessary to optimize study results and ensure patient safety and ethical treatment. According to the 2001/20/EC Directive, amendments are considered substantial and necessary when a change to the approved protocol will

have significant impact on the safety or mental well-being of a clinical trial participant, the scientific quality and value of the trial, or both (6). The ultimate decision to implement a protocol amendment, however, rests with the research sponsor. As such, clinical research scientists may opt to implement protocol amendments as a conservative practice, the result of which is an unplanned impact on the clinical research study budget.

In the highly volatile and challenging economic environment in which pharmaceutical and biotechnology companies currently operate, the substantial cost and time savings realized from a reduction in avoidable amendments could be reallocated to R&D projects and mission-critical infrastructure. Moreover, the 2-month development time savings associated with the elimination of each avoidable amendment is notable, as is the substantial, incremental revenue that would result from faster product commercialization.

Many pharmaceutical and biotechnology companies have already recognized the potential economic and speed advantages that would result from reductions in the incidence of protocol amendments. Sponsor companies have established internal teams and task forces to understand the root cause of protocol amendments and to identify improvement opportunities. Some companies are focusing energy on revising protocol authoring templates to clarify and remove areas of redundancy to minimize errors and inconsistencies and to provide more instructional text for protocol authors. Companies are also evaluating and refining protocol development, feasibility, and approval processes to isolate potential amendment causes before they occur.

New approaches being pursued reflect a commitment on the part of pharmaceutical and biotechnology companies to invest more time upfront prior to protocol finalization. The rush to enroll the first patient in a study is increasingly being viewed by sponsors as a recipe for mistakes in protocol design, poor project planning, and hasty decision making.

The results of our study quantify the inci-

dence of amendments and the associated impact resulting from the amendment implementation process. In addition, this study captures the primary causes of amendments, when they occur, and the cycle time and costs associated with their resolution. There are numerous areas for subsequent research, including a more robust evaluation of the relationship between protocol complexity and amendment incidence; a robust quantification of the economics of implementing protocol amendments; an assessment of the impact of various external forces (eg, commercialization and competitive pressures) on protocol amendment frequency; and the success and failure of newly implemented sponsor practices on reducing the need to amend protocols.

The magnitude of this problem and insights into areas where protocol amendments can be avoided and prevented represents a major opportunity for pharmaceutical and biotechnology companies to improve cycle times and reduce development costs to deliver safe treatments to patients faster and more efficiently.

Acknowledgments—The authors wish to thank the 17 companies that participated in this study and contributed their valuable time and data.

REFERENCES

1. Getz K. The heavy burden of protocol design. *Appl Clin Trials*. 2008;17(5):38–40.
2. Getz K, Wenger J, Campo R, Seguire E, Kaitin K. Assessing the impact of protocol design change on clinical trial performance. *Am J Ther*. 2008;15:449–456.
3. Wise P, Drury M. Pharmaceutical trials in general practice: the first 100 protocols. *Br Med J*. 1996;313:1245–1248.
4. Losch C, Neuhauser M. The statistical analysis of a clinical trial when a protocol amendment changed the inclusion criteria. *BMC Med Res Meth*. 2008;8(16):1–9.
5. Getz K. The downstream impact of protocol design complexity. *Drug Devel Touch Brief*. 2009;93–95.
6. European Commission communication. *Off J Eur Union*. 2010;c 82(March 30):1–19.

Randy Krauss has disclosed that he is a stock shareholder of Genzyme Abbott, Johnson & Johnson, and Novartis. Anne B. Cropp has disclosed that she is a stock shareholder of Pfizer, Inc. Anna L. Hindle has disclosed that she is a stock shareholder of Biogen Idec. Kenneth A. Getz, Rachael Zuckerman, and Kenneth I. Kaitin report no relevant relationships to disclose.