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Are Phase 3 Clinical Trials Really Becoming More Complex?

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Abstract

Background: This study uses the data from many of the mandatory fields in ClinicalTrials.gov to examine changes, possibly leading to more complexity in the design and execution of commercially sponsored phase 3 clinical trials. *Methods:* In this analysis we compare baseline year 2008 data, when a broad number of the protocol/study design and execution variables became mandatory, with the data from the last full year of results, 2013. *Results:* There has been relatively little change in the protocol and study design over the years covered in this study. The most pronounced change is associated with single-patient duration: there is a significant increase in the period of time a patient is treated in the study protocol. The study also highlights an important methodological issue: many of the claims in print about complexity have yet been substantiated through the use of peer-reviewed data or in settings where others can interrogate the results. *Conclusions:* In general, there is limited evidence for significant increases in the study and protocol design and execution of phase 3 clinical trials sponsored by pharmaceutical companies.

Keywords

clinical trials, Clinicaltrials.gov, study design, phase 3, study complexity

Introduction

Professional and popular literature has for some time highlighted the declining productivity of new drug research in the branded pharmaceutical industry. The picture is daunting: substantial increases in research and development (R&D) spending, no appreciable growth in the number of approved new chemical entities (NCEs),[1] and more limited market potential for many of the new drugs that have been approved. In response, pharmaceutical companies have taken a number of steps, including mergers and acquisitions,[2] reorganizations, downsizing, increased outsourcing, and the greater use of purchasing power frequently available to larger institutions.[3] Much of these costs savings have been directed to greater R&D spending in an industry that already spends more than any other on R&D as a percentage of sales.[4]

Since the clinical research portion of pharmaceutical R&D constitutes the longest part of the entire new drug R&D process, representing the largest single current expenditure,[5] any significant improvement in R&D productivity may well have to include major changes in processes such as the design and execution of clinical trials. A number of significant pharmaceutical companies have even joined together in a nonprofit organization, TransCelerate BioPharma, to identify and solve common clinical development challenges. Companies taking part in the consortium agree to share financial and other resources, including personnel. The participating companies identified improved clinical trial execution as an initial area of focus.

Throughout these challenges and opportunities, there has been a growing perception that clinical studies have become more complex and difficult to complete in a timely and cost-effective fashion. These complexity attributes include, among others, the number of sites and countries involved, patients enrolled, inclusion/exclusion criteria used, medical procedures incorporated in the study protocols, and endpoints measured. However, few of these claims have been substantiated through

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the use of peer-reviewed data in venues accessible to third-party analyses. The assertions have also sometimes been anecdotal or based upon the same nonaccessible data.

So one may ask, ''Are phase 3 commercial clinical trials really becoming more complex in their design and execution?'' We think the evidence is actually mixed, and it depends on how complexity is measured.

This study did not examine the actual length of time required to complete clinical trials. Similarly, we do not discuss the clinical results of these studies. Although the results of completed clinical trials have more recently become mandatory fields in ClinicalTrials.gov, the amount of study outcome data are still too limited to be useful in broadly based research about overall drug development trends. Both clinical outcome and study completion times will be addressed in subsequent research.

Commercially led phase 3 clinical trials were the focal point of this study. The design and execution of commercially and non–commercially funded clinical trials may be substantially different. To minimize any possible confounding affects due to the source of funding and leadership, the research team will conduct a separate analysis of non–commercially led trials, specifically comparing the profiles for the two types of studies.

The Challenge of Clinical Trial Complexity

The increasing complexity and work burden of conducting clinical trials has received attention in a range of places, from peer-reviewed papers to industry professional publications to popular news outlets. An Institute of Medicine report even concluded that the randomized controlled trial (RCT) may be unsustainable because of the time and expense involved. RCTs have to meet a broader, often more demanding, set of scientific and commercial goals.[6] The costs and time involved with RCT may become prohibitive.

Possible increasing complexity in the design and execution of clinical trials will only serve to increase costs and lengthen times. Three areas illustrate these concerns: study location, sample size, and protocol complexity.

Pharmaceutical companies since the 1990s have been looking for additional countries outside of North America and Western Europe from where the organizations can draw patients for global clinical trials. Pharmaceutical companies chose the location of clinical sites for their studies for a number of reasons. The primary reason to work with a particular site for a study is that site's ability to enroll relevant patients and treat those patients according to the dictates of the study protocol. Additional reasons though, for instance a medical presence in a potentially interesting market, may also play a role in influencing which particular countries will be used.

Pharmaceutical companies and contract research organizations (CROs) in the 1990s began to locate sites in many Eastern European countries which had formerly been within the Soviet Union's sphere of influence. More recently these organizations have expanded their geographic scope to locate clinical sites throughout Asia and the Asian subcontinent. It has been argued that that these sites represent attractive and cost-effective venues, which have the ability to enroll and treat patients according to the study protocol in a timely fashion. These sites may often have highly trained medical professionals, large number of medically naïve patients, and lower costs than those found in North America and Western Europe.[7-9] Just as importantly, in some cases these new countries may represent commercially attractive markets. China is a case in point. The popular press has even become intrigued by this increased use of additional geographies because of their combined commercial and medical attractiveness.[10,11]

Companies in all industries invest in developing and marketing new products to gain advantages over the competition. Research across multiple industries has long established that product innovation and quality are important elements in a company's financial success.[12] Pharmaceutical companies though face a particularly pressing, and constant, need to innovate because of the distinctive role played by patent life. When a branded drug's patent expires, sales can plummet rapidly as generic competitors enter the field. For this reason, pharmaceutical companies must continually come up with new products to replace lost sales from their older drugs going off patent. To make this an even harder task, these new products have to represent demonstrable medical and financial value over drugs that have lost patent protection.

Some industry observers have averred that it has become increasingly difficult for pharmaceutical companies to secure regulatory approval for the new drugs. Additionally, it is also challenging to ensure market acceptance of these products because of the commercial need to establish statistically significant differences between the study compound and the nonactive comparator, whether the comparator is a placebo or the standard of care. As a potential way to deal with this commercial test, pharmaceutical companies have increased patient numbers in clinical trials to establish statistically significant differences between the patients in the active and nonactive arms of clinical trials.[13] Studies must also show a disproportionate increase in effectiveness over the standard of care to justify increased economic costs over the current treatment. Today, many times a study must support or show both clinical and economic value. All other things being equal, larger sample sizes can more easily deliver statistically significant differences. It has been asserted that clinical trials are enrolling more patients to reach more easily those statistical thresholds.[14]

The literature is also replete with arguments about the increasing complexity of study and protocol design. A case in point is the number of inclusion/exclusion criteria used in protocols. Observers assert the number of criteria is growing. This proliferation may either be due to more finely targeted patient populations or simply be the result of poorly chosen, even unnecessary, inclusion/exclusion criteria, sometimes simply reproduced from earlier clinical studies. Careless study design may have brought about avoidable inclusion/exclusion amendments. Similarly, the number of procedures in the protocol continues to increase for many of the same appropriate and inappropriate reasons.[15-17]

Publications such as the 2010 Institute of Medicine Report call for major changes in the ways RCTs are designed and conducted. Industry leaders lament the increasing complexity of protocol/study design and execution. The data in ClinicalTrials.gov provide empirical benchmarks of actual protocol/study design and execution, which are open to review and interrogation because the data are public.

Methodology

The ClinicalTrials.gov Database

In 2007, the United States government issued regulations surrounding clinical trials being conducted within the US and others clinical trials operating under the auspices of the US Food and Drug Administration (FDA). The desire for greater transparency substantially underpinned the creation, and subsequent expansion, of ClinicalTrials.gov. People with a particular medical problem should have more information about relevant clinical trials to improve their likelihood of taking part in these trials.[18-20] Potential study subjects would know which clinical trials were being conducted and where they could go to enroll and participate in the studies. ClinicalTrials.gov would also help ensure that the medical community would be more aware of both unsuccessful and successful clinical studies.[21,22] ClinicalTrials.gov would make the entire clinical trial topography more open to interested individuals, groups, and organizations.

In recent years, there has been an increase in the number of publications drawing upon ClinicalTrials.gov data. The existing research, largely academic in origin, can be categorized in 4 broad categories:

1. Correlation between trial registration in ClinicalTrials.gov and publication in biomedical journals[22–25]
2. Understanding the taxonomy of ClinicalTrials.gov registry[26]
3. Characterizing the medical trends and trial attributes in ClinicalTrials.gov[20,27-32]
4. Assessing the registration completeness of trials in ClinicalTrilas.gov[24-26,31,32,34,35]

Data completeness and accuracy are important considerations in the use on any dataset. Consequently, we previously analyzed data completeness and quality for the ClinicalTrial.gov specific variables reported in this study.[33] We concluded that for these mandated variables, which we have labeled one of 3 types (ie, study identification, study protocol and design, and study execution), the dataset constitutes a potentially very valuable research resource. With the exception of site identification detail, the data are currently complete enough to undertake potentially useful research. Missing data in each variable never exceeded 3%. Even with the site level identification variables, missing data were less than 10%. These missing data were concentrated in several companies, which have in more recent years begun to enter much more complete data about site detail. However, we suspect that open text fields such as inclusion/exclusion criteria or endpoints may be the most problematical for completeness. Although companies almost always enter fairly extensive information, we have no way of knowing if the fields are complete. For example, companies may just stop entering criteria after a self-determined number. However, we deemed this situation unlikely since the criteria counts followed a near-perfect negative binomial distribution.

The research team, in order to review the ClinicalTrials.gov database, built an XML parser that compiled an SQL database with all the current information contained within ClinicalTrials.gov website. Inconsistent coding was a large obstacle in reviewing the data. The verbatim field "single patient duration" was automatically recoded into numeric days using a SQL program. Outcomes with "single patient duration" that contained vague language such as "throughout hospital stay" and outcomes with "single patient duration" that was blank were classified as "uncodable." The verbatim field "conditions" was coded into MedDRA 16.1. We then performed a systematic review of all phase 3 studies led by industry sponsors that had been received as of February 25, 2014 as defined by the "first received date" field.

The variables used for this study can be found in the Appendix. The complete, analyzable dataset used for the analyses can be found in the online Supplementary Material for this article.

Statistics

We performed 2 types of statistical analyses; one to detect differences over time, and one to understand statistically significant differences between the therapeutic categories. We first analyzed the trends over time by study start year. For every binary categorical outcome variable we utilized logistic regression to model the outcome variable as a function of year to determine if there had been a changing trend over the past 6 years. An example of such a categorical binary variable is whether a placebo arm was present or not in a particular study. For each

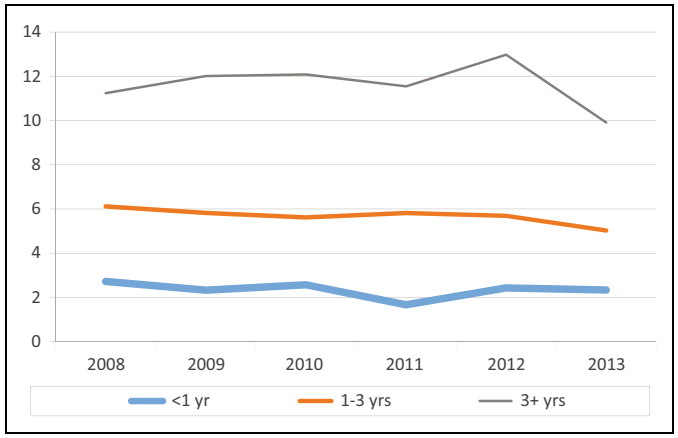

Figure 1. Average number of countries per study by duration.

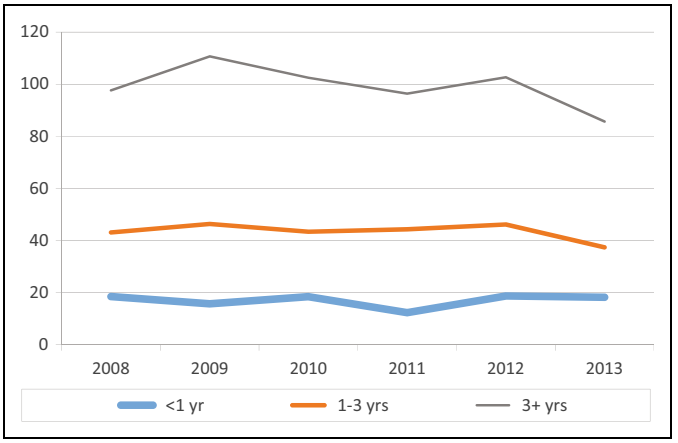

Figure 2. Average number of sites per study by duration per year.

binary design variable, we then controlled for therapeutic area with an interactive term between therapeutic area and year to determine if there were any specific therapeutic areas that deviated from the patterns observed in the rest of the data. For the metric outcome variables we utilized linear regression to model the variables as a function of year to determine if there was a trend over the past 6 years. An example of such an outcome variable was number of study arms. As with the categorical data, we then controlled for therapeutic area through the use of an interactive term.

For some study execution variables, we had to account for the bias that exists due to the planned length (first patient first visit to last patient last visit) of the study. For example, incomplete studies have not yet enrolled all their sites so we would expect to observe a decrease in the number of enrolled sites simply as a measurement artifact due to the function of time. We did not account for this by eliminating incomplete studies because we would be removing longer studies in later years. This would also eliminate a large number of studies and introduce another, unnecessary, bias. We therefore stratified the studies into 3 groups based on study duration, and analyzed the groups: less than 1 year, 1 to 2 years, and 3 or more years. This methodological issue affected 2 key variables: number of countries and number of sites.

A complete listing of all the logistic and least squares regressions equations can be found in the Supplementary Material. Each listing shows the full model with all the variables initially entered into the stepwise analyses. In addition each final model is shown.

Results

Study Execution Variables

Number of Countries and Sites per Study

There was no statistically significant change in the number of countries per study (Figure 1). In addition, we saw no statistically significant change in the number of sites per study (Figure 2). In each stratum however, we observed a demonstrable fall off in countries and sites for studies which have not completed site initiation. We would expect to see this from the measurement bias associated with studies that have long expected completion times or that require additional time to establish sites in more countries. The number of unique phase 3 studies shown in the figures varied only slightly each year; starting with n = 792 in 2008, the respective number of observations for each subsequent year through 2013 are 776, 812, 855, 851, and 793. Since missing data never exceeded 3% of any of variables, there were no meaningful differences from the number of observations by year for each subsequent graph.

Study and Protocol Design Variables

Number of Patients Enrolled per Study

The average number of patients enrolled per study did not change, although there was a mild but statistically significant increase within one therapeutic area, metabolism and nutrition disorders, and a decrease in another therapeutic area, vascular disorders (Figure 3). This metabolism and nutrition disorders change occurred chiefly between 2012 and 2013, and the vascular disorders throughout 2008 to 2013. No other therapeutic area showed any statistically significant or analytically meaningful change. Throughout the figures, we only show the results for individual therapeutic areas if a therapeutic area's results are statistically significantly different from the total dataset. Although the other, nonreported therapeutic changes are not significant, the full equations are available in the Supplementary Material.

Number of Inclusion/Exclusion Criteria per Study

There was a statistically significant increase in the number of inclusion/exclusion criteria (Figure 4). Every year was associated with a 0.41 increase in criteria counts. Although the increase was not large, the mere size of the database helps make even mild changes statistically significant. Two therapeutic areas,

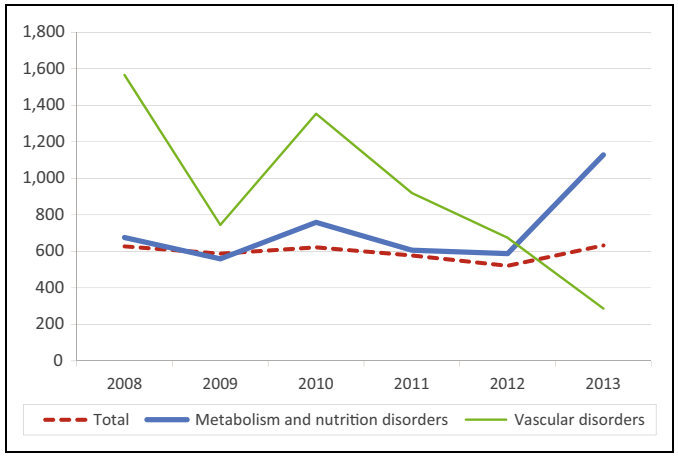

Figure 3. Average patient enrollment per study by year.

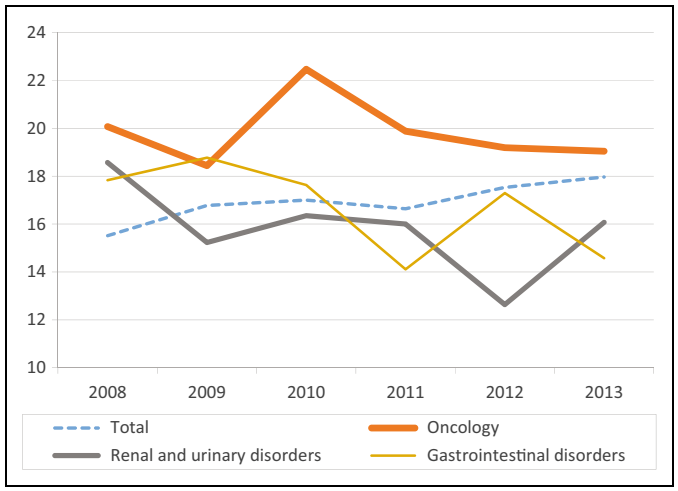

Figure 4. Average number of inclusion/exclusion criteria per study by year.

renal and urinary disorders as well as gastrointestinal disorders, statistically significantly differed from the overall sample by evidencing a slight decreasing trend in the total number of criteria.

Number of Arms per Study

Overall there was a very small however statistically significant decrease in the number of arms per study (Figure 5). Only therapeutic areas respiratory, thoracic and mediastinal disorders, and psychiatric disorders showed a statistically significantly greater decrease. The therapeutic areas general disorders and administration site conditions, along with blood and lymphatic system disorders, showed the only significant increase.

Percentage of Placebo-Controlled Studies

The number of studies with at least one placebo arm per study decreased (Figure 6). There were no significant differences across the individual therapeutic areas.

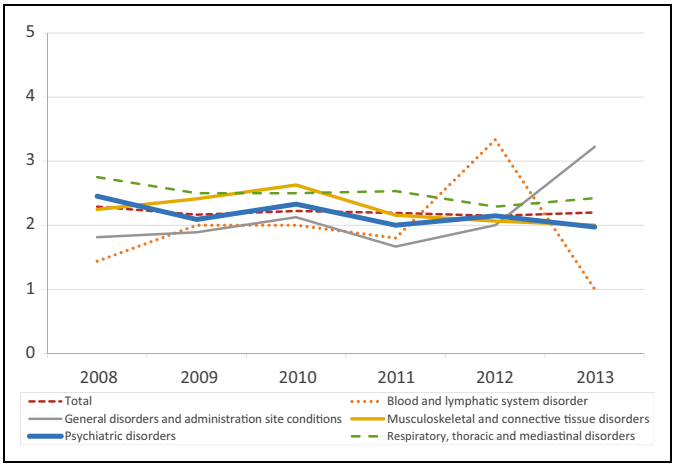

Figure 5. Number of arms per study by year.

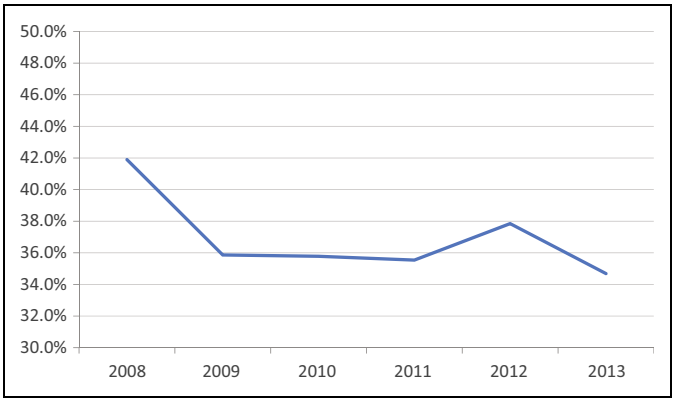

Figure 6. Percentage of studies with at least one placebo arm by year.

Percentage of Cross-Over Design per Study

The number of studies with cross-over design per study decreased significantly by 52% between 2008 and 2013 (Figure 7). There were no significant differences across the individual therapeutic areas.

Single-Patient Duration per Study

There was a 30% increase in the length of single-patient duration, or how long a patient must be treated to comply with the study protocol (Figure 8). Within nervous system disorders and infection and infestations there was no increase. Across all the other therapeutic areas however, there was an increase, with the trend particularly pronounced in oncology. The single-patient duration in oncology studies increased 41% from 638 days in 2008 to 899 days in 2013.

Number of Endpoints per Study

We also examined the number of endpoints per study to see if there was a trend. Unfortunately, "secondary endpoint" is not a mandatory field, so these data were very incomplete. There was

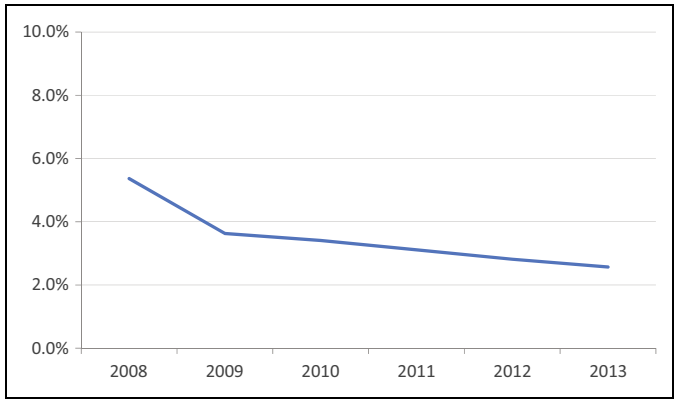

Figure 7. Percentage of studies with cross-over design by year.

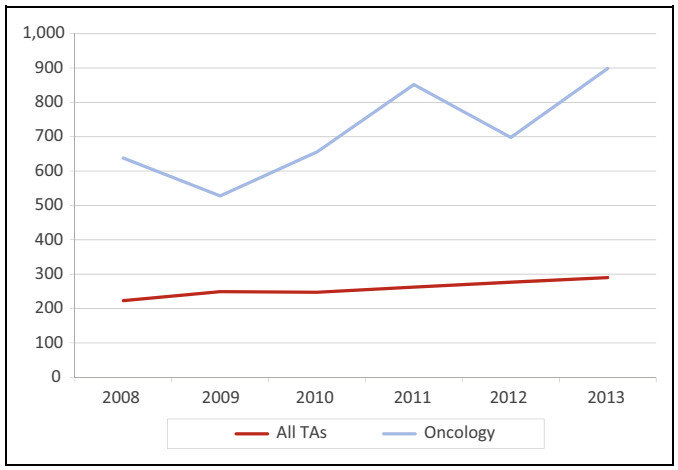

Figure 8. Single-patient duration (in days) by year.

usually only one primary endpoint in a study, sometimes a second primary endpoint, and infrequently more than two. In any event the average number of endpoints in phase 3 studies did not increase in the time period studied.

Discussion and Implications

Since 2007 the United States has required all commercial and noncommercial organizations conducting clinical trials under FDA auspices to submit certain required information to an existing database, ClinicalTrials.gov. Over time new voluntary variables were introduced, and many of these eventually became mandatory. This pattern will most likely continue. The current database now represents an important source of information about the clinical trials landscape for both commercial and noncommercial organizations.

This study used the data from many of the mandatory fields in ClinicalTrials.gov to examine changes in the design and execution of commercially sponsored phase 3 clinical trials. Phase 2 studies will be examined in a separate study. In this analysis we compared baseline data in year 2008, when a broad number of the protocol/study design and execution variables became mandatory, with the data from the last full year of data, 2013. At a time when many industry observers and participants are calling for major changes in the conduct of pharmaceutical R&D, a review of commercially led phase 3 clinical trial activity in ClinicalTrials.gov showed a great deal of continuity from 2008 to 2013 in the design and execution of clinical trial protocols or studies, with 2 important exceptions.

Specifically, there was no statistically significant change in the number of countries per study. We saw no statistically significant change in the number of sites either. The average number of patients enrolled per study did not change, although there were differences in a couple of therapeutic areas. There was a small but statistically significant increase in the number of inclusion/exclusion criteria. There was also a very small yet statistically significant decrease in the number of arms per study, with more significant changes isolated in several specific therapeutic areas. Additionally, the number of studies with at least one placebo arm decreased, while the number of studies with cross-over design decreased significantly. Lastly and most clearly, there was a significant increase in the length of single-patient duration, that is, the period of time a patient is treated in the study protocol.

There may be an increase in procedural complexity due to the introduction of additional unique procedures, and/or as a function of more patient visits. A larger number of visits, with the same set of procedures at each visit, would in itself increase procedural complexity. The data in ClinicalTrials.gov indicate that patients are in the studies for longer periods of time; we could reasonably hypothesize that the number of patient visits could be also increasing. Unfortunately, the number of patient visits was not a variable in this database. If there was an increase in the total number of procedures it would be important to know if this were due to an increase in the number of unique procedures or an increase in the number of visits, or both. The answer could go a long way in determining whether the solution is a more direct management and design one, that is, the elimination of nonessential procedures, or an issue more profoundly scientific in nature, growing out of longer more complex patient treatment consistent with current medical practice and research.

The general issue of growing protocol and study complexity in the industry and other literature highlights an important methodological issue. The published studies asserting growing procedure and inclusion/exclusion complexity have chiefly rested on data that cannot be interrogated by others, a frequently used standard requirement for peer-reviewed scientific research. When these results are reported with proprietary data sets, it is especially difficult to query or replicate the findings.

The first substantive question has to be, why so little change? Given the hurdles facing new drug development

efforts for pharmaceutical companies and the growing calls for transformation, one might have expected to see more substantial changes. Perhaps the time frame of this analysis was simply too short. With more time, major changes may take place in the design and execution of phase 3 clinical trials. However, it would seem that any first rumblings of these changes cannot yet be detected in any major way in the ClinicalTrials.gov database.

Even the design and execution complexity spoken about by many was not broadly supported by the data. The number of sites and countries per study were not larger, even as pharmaceutical companies look to new markets. Protocols did not require more patients. They did not have more study arms. They did have appreciably more inclusion/exclusion criteria.

The reduction in the number of studies with placebo arms may be due to more extensive proof of absolute efficacy that many companies are pursuing in phase 2. As well, the European preference is for active rather than placebo controls.

The decrease in the use of cross-over studies in phase 3 is not surprising. The assumptions required for a cross-over design are rarely met in practice except for general anesthetic agents. There are few other indications that lend themselves to the practicality of the design.

We have seen one particularly noteworthy difference, the length of time a patient must be in a study to complete the treatment as prescribed in the study protocol. There may be a number of plausible medical and scientific reasons for the increase. For instance, given the pressure to develop drugs that can compete with existing branded and generic drugs from both financial and medical value perspectives, studies may be looking to make more comprehensive efficacy and/or cost-effectiveness claims. Additionally, the longer time spent in clinical trials by patients may reflect changing medical treatment outside of the clinical research setting. An alternative argument may be that the growing procedural complexity in protocol designs has led to longer patient durations. The increased number of procedures has required study patients to remain in the study for longer periods. Rather than major changes in science and medicine prompting longer patient durations, protocol design complexity may be the explanation. The greater lengthened patient duration in oncology studies might give pause to the explanatory power of this alternative explanation. Is longer patient duration in oncology studies primarily due to more procedures or, instead, new medical approaches?

Limitations

There has been growing attention devoted to the use adaptive clinical trials from phases 1 to 3 from both scientific and commercial perspectives.[34-36] The design and execution of clinical trials using this approach may be more wide spread than we were able to find in our analysis of the database. There is no variable that specifically indicates the use of an adaptive design. We searched for the words *adapt*, *adaptive*, and *Bayesian* across the all commercially led phase 1 to 3 studies registered in ClinicalTrials.gov. In particular we looked in the following verbatim fields: brief title, brief summary, primary outcomes, and secondary outcomes. We came up with only 83 studies containing 1 or more of these words. With so few observations we could not identify any differences over time. It may very well be that there is growing use of adaptive clinical trials that we are unable to detect. For example we knew of several studies from published literature that were adaptive in design. We then located the studies in the database but found no keywords in the verbatim fields.

This study concentrates on the clinical trials conducted by the pharmaceutical industry as a whole, identifying statistically significant differences when present in one or more therapeutic areas. We did find some differences by individual therapeutic areas for the specific variables. However, we did not find that any single therapeutic area consistently differed from the others across a design and execution variables. Since pharmaceutical companies and researchers often focus their efforts in particular therapeutic areas, a series of therapeutic specific analyses may be useful.

We could not directly address one issue, possible increased protocol complexity as measured by the number of procedures in the protocol treatment regimen, that is, the procedures to be performed at each patient visit. Neither the number of visits nor procedures called for in the protocol were identified in the database.

Conclusions

We used the data from many of the mandatory fields in Clinical Trials.gov to examine changes in the design and execution of commercially sponsored phase 3 clinical trials. This study compared a baseline year, 2008, when many protocol/study design and execution variables became mandatory, with the data from the last full year of data, 2013. At a time when many industry observers and participants are calling for major changes in the conduct of pharmaceutical R&D, a review of commercially led phase 3 clinical trial study/protocol design and study execution data in ClinicalTrials.gov revealed little change from 2008 to 2013. The most important exception was the number of days a patient spends in a phase 3 study.

The issue of complexity may be one of definition. Study and protocol complexity has been used in many contexts, and measured in at least as many ways. By most of the definitions there has been little change. By other definitions there has been some, to substantial, amounts of change.

Many of the individual variables analyzed in this study invite further study. A case in point is the question of the countries in which studies and sites are located. The ClinicalTrials.gov data

indicate that the numbers of countries and size have not increased. The distribution of these studies and site by country may be substantially changing. We are examining this question in another study. The use of publically available data from ClinicalTrials.gov will hopefully help move much of the discussion about study design and execution. Anecdotes and findings based on proprietary data may indeed prove correct in many cases. We cannot establish the full value of these findings though until the data are open to public scrutiny. The conclusions in this article can be challenged by the data in ClinicalTrials.gov and from other open data sources.

Appendix: Study Registry Variables

Study Identification Variables	Relevant Database Field Names
First received date[a]	[firstreceived_date]
Last updated date	[lastchanged_date]
Verification date	[verification_date]
Brief title[a]	[brief_title][b]
Brief summary	[brief_summary][b]
NCT number[a]	[NCT_Number]
Responsible party	[responsible_party][b]
Study sponsor[a]	[lead_sponsor], [agency][b], [agency_class]
Study Execution Variables	
Start date[a]	[start_date]
Primary completion date	[primary_completion_date]
Recruitment status[a]	[overall_status]
Site information[a]	[facility], [name][b], [city], [state], [ZIP], [country]
County location[a]	[country]
Study and Protocol Design Variables	
Study phase	[phase]
Primary outcome measures[a]	[measure][b], [time_frame][b], [safety_issue], [description][b]
Secondary outcome measures[a]	[measure][b], [time_frame][b], [safety_issue], [description][b]
Study type[a]	[study_type]
Enrollment[a]	[enrollment]
Study design[a]	[allocation], [endpoint classification], [intervention model], [masking], [primary purpose]
Single-patient Duration	[time_frame][b]
Condition[a]	[condition][b]
Intervention/arms[a]	[arm_group_label][b], [arm_group_type], [description][b]
Eligibility criteria[a]	[eligibility_criteria][b]
Gender	[Gender]
Age	[min_age], [max_age]
Accepts healthy volunteers	[healthy]

[a]Data element required by the International Committee of Medical Journal Editors (ICMJE) and the World Health Organization International Clinical Trials Registry Platform (ICTRP).
[b]Verbatim field.

Declaration of Conflicting Interests

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Supplementary Material

Supplementary material for this article is available on the journal's website at http://tirs.sagepub.com/supplemental.

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