CLINICAL TRIALS

Key cost drivers of pharmaceutical clinical trials in the United States

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Abstract

Background: The increasing cost of clinical research has significant implications for public health, as it affects drug companies' willingness to undertake clinical trials, which in turn limits patient access to novel treatments. Thus, gaining a better understanding of the key cost drivers of clinical research in the United States is important.

Purpose: The study which is based on a report prepared by Eastern Research Group, Inc., for the US Department of Health and Human Services, examined different factors, such as therapeutic area, patient recruitment, administrative staff, and clinical procedure expenditures, and their contribution to pharmaceutical clinical trial costs in the United States by clinical trial phase.

Methods: The study used aggregate data from three proprietary databases on clinical trial costs provided by Medidata Solutions. We evaluated per-study costs across therapeutic areas by aggregating detailed (per patient and per site) cost information. We also compared average expenditures on cost drivers with the use of weighted mean and standard deviation statistics.

Results: Therapeutic area was an important determinant of clinical trial costs by phase. The average cost of a Phase 1 study conducted at a US site ranged from US$1.4 million (pain and anesthesia) to US$6.6 million (immunomodulation), including estimated site overhead and monitoring costs of the sponsoring organization. A Phase 2 study cost from US$7.0 million (cardiovascular) to US$19.6 million (hematology), whereas a Phase 3 study cost ranged from US$11.5 million (dermatology) to US$52.9 (pain and anesthesia) on average. Across all study phases and excluding estimated site overhead costs and costs for sponsors to monitor the study, the top three cost drivers of clinical trial expenditures were clinical procedure costs (15%–22% of total), administrative staff costs (11%–29% of total), and site monitoring costs (9%–14% of total).

Limitations: The data were from 2004 through 2012 and were not adjusted for inflation. Additionally, the databases used represented a convenience, that is, non-probability, sample and did not allow for statistically valid estimates of cost drivers. Finally, the data were from trials funded by the global pharmaceutical and biotechnology industry only. Hence, our study findings are limited to that segment.

Conclusion: Therapeutic area being studied as well as number and types of clinical procedures involved were the key drivers of direct costs in Phase 1 through Phase 3 studies. Research shows that strategies exist for reducing the price tag of some of these major direct cost components. Therefore, to increase clinical trial efficiency and reduce costs, gaining a better understanding of the key direct cost drivers is an important step.

Keywords
Clinical trial cost, cost drivers, clinical procedure costs, site retention costs, site monitoring costs, administrative staff costs

Background

One of the major barriers to conducting clinical research in the United States is its high cost. Studies estimate that it now costs somewhere between US$161 million and US$2 billion to bring a new drug to market.[1–3] One particularly well-known and often-cited paper by DiMasi et al.[1] arrives at a total pre-approval cost estimate of US$802 million in 2000

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dollars to develop a single drug (inflated to 2012 dollars, this estimate is US$1.07 billion).[1,4] More recent estimates of drug development costs are around US$1.3 billion to US$1.7 billion.[5]

Although experts debate the accuracy of various cost estimates, there is widespread agreement that clinical trial costs are substantial and rising. According to a 2007 article as cited by Collier,[5] the average cost of developing a drug had risen at a rate 7.4% higher than inflation over the past two decades, mostly due to rising clinical trial costs. Costs also tend to increase as an investigational drug progresses through each phase of the pipeline, and, as the Institute of Medicine notes, Phase 3 clinical trials have become "extraordinarily expensive."[1,2,6]

While the reasons for these high costs are manifold, a few key trends stand out. One contributing factor is the productivity of the drug industry in past years. High levels of investment in research and development have yielded so many drugs that companies are now finding it difficult to develop truly innovative pharmaceuticals. As a result, most new drugs are actually just variations of existing drugs, intended to be only incrementally more effective or safer than those already on the market and so require larger trials to identify small but statistically significant benefit. In addition, there has been a shift in the biopharmaceutical industry toward chronic and degenerative disease research. The growth in the number and proportion of older consumers has resulted in a shift in the leading causes of death from infectious to chronic diseases in the United States[7] creating the potential for secure, steady, and sizeable revenue streams for companies that can capture shares of these markets. However, developing drugs to treat chronic and degenerative diseases requires longer clinical trials to observe relevant outcomes.[1,5] Moreover, clinical trial protocols have become increasingly complex, involving numerous assessments, exploratory endpoints, biomarkers, biopsies, and so on, consequently increasing the administrative burden and overall costs of trials.[8] Another significant trend contributing to higher clinical trial costs is the increased use of health care cost containment strategies, such as cost-effectiveness data requirements, in the United States and other countries. All of these factors contribute to clinical trials with large numbers of patients and long timeframes, which in turn result in greater expenditures on recruitment efforts, data collection, compliance with administrative requirements, and other trial components.

Regulatory barriers also contribute to the high cost of conducting clinical research. Most regulations and accompanying guidelines governing clinical research were written when the clinical research enterprise was smaller in terms of the number of active trials and before multi-center trials became common (in the 1980s and 1990s). Even though these regulations and guidelines were intended to protect the safety and rights of human research participants as well as the scientific validity of trial results, they have not been evaluated formally to determine whether they actually achieve those purposes.[9] Some in fact have had unintended consequences, creating additional obstacles to conducting clinical research. For example, the ethical review process as required under 21 Code of Federal Regulations (CFR) 56 does not clearly define the roles and responsibilities of various oversight bodies and what is expected of investigators.[6] As a result, in recent years, institutional review boards (IRBs) have expanded their responsibilities, undertaking new tasks such as review of investigators' conflicts of interest, protection of patient health information, assessment of trial design, and risk management. Consequently, clinical trials now require more approvals from different people within a single IRB, resulting in additional delays; yet, there are no indications that safety is improved by this practice.[9] Another example is the adoption of inefficient approaches to the conduct and monitoring of clinical trials resulting from the overly rigid interpretation of the International Conference on Harmonization Good Clinical Practice guidelines.[10] To monitor clinical trials, it is a common practice in the pharmaceutical industry to conduct site visits frequently (every 4–8 weeks) and to verify source data during these visits.[11,12] It is estimated that monitoring can account for 15%–30% of total trial costs.[13] Rather than adopting a risk-based approach to monitoring, a conservative interpretation of the regulations and guidelines has resulted in 100% source data verification becoming the industry standard, a particularly costly practice that on average consumes one-third of companies' entire Phase 3 trial budgets.[14,15]

Finally, drug developers also impose a number of barriers upon themselves, adding further unnecessary cost and delay to clinical research. Some of these costs and delays are avoidable as they result from insufficient early planning and/or inefficiencies in company practices (e.g. avoidable protocol amendments, protracted contract negotiations, and internal review), but the majority stems from a desire to avoid failure at all costs.[16] Risk aversion leads companies to take unnecessary steps at various points throughout the clinical trial process, driven primarily by the advice of company legal advisors to ensure regulatory compliance and minimize liability.[9] As a result, studies end up being overpowered because each assumption is made conservatively by company statisticians and others (especially those in larger companies) who are insulated from the cost consequences of their recommendations.

Other barriers include disconnect between clinical research and medical care and increasing competition for qualified investigators and sites due to a shortage of biostatisticians and information specialists.[17]

The increasing cost of clinical research has significant implications for public health as it affects drug

companies' willingness to undertake clinical trials. To slow and/or reverse this upward trend in clinical trial costs requires a radical transformation in the way clinical research studies are designed, conducted, and integrated with clinical practice.

We examined the different factors, such as therapeutic area, IRB approval, patient recruitment, administrative staff, and clinical procedure expenditures, and their contribution to clinical trial costs and their variability in the United States by clinical trial phase (Phases 1 through 3). While other investigators have looked at total clinical trial costs as well as select cost drivers (such as IRB amendments, source data verification costs, and so on), we believe that our study is the first to take a comprehensive look at all of the direct cost components of clinical trials.

Methods

Data

We analyzed aggregate data from three proprietary databases on clinical trial costs available from Medidata Solutions:[18]

- Medidata Grants Manager® (PICAS® database) is a database of negotiated investigator grants including more than 250,000 grants and contracts and 27,000 protocols in over 1400 indications. It provides benchmarked costs typically used for clinical trial budget planning.
- Medidata CRO Contractor® (CROCAS® database) contains thousands of negotiated outsourcing contracts. It includes data from contract research organization (CRO) contracts, detailed across such dimensions as therapeutic area, phase, and geography.

- Medidata Insights® is a clinical analytics solution that provides data on clinical operational performance metrics alongside company and industry benchmarks. It comprises data from more than 7000 studies gathered from over 120 clinical trial sponsors.

Combined, the three databases contain detailed information derived from actual negotiated contracts for studies funded by the global pharmaceutical and biotechnology industry. These data are used by pharmaceutical companies, contract research organizations, and academic researchers to identify prevailing rates for trial planning, budget development, and grant negotiation.[19]

The data files acquired for this study comprised means for a wide range of clinical trial direct cost elements by study phase and therapeutic area, including study-level costs (such as IRB approvals and source data verification costs), patient-level costs (such as recruitment and clinical procedure costs), and site-level costs (such as monitoring and project management; see Table 1). Additionally, the data included numbers of planned patients per site and numbers of sites per study. A complete list of these data elements, along with more detailed descriptions of each field, unit specifications, and sources, as well as information on the characteristics of the datasets, are given in Supplementary Appendix Table 1.

The data covered the period 2004 through 2012 and were disaggregated by study phase (Phases 1, 2, and 3) and Medidata-defined therapeutic areas. The total number of contracts included in the analysis was around 31,000 and the number of contracts by therapeutic area ranged from around 600 to 6500.

The data provided did not include information on trials funded by organizations other than

Table 1. Clinical trial cost components.

Type of cost	Elements
Per-patient	Patient recruitment costs
	Patient retention costs
	Registered nurse and clinical research associate costs
	Physician costs
	Clinical procedure costs
	Central laboratory costs
Per-site	Per-patient costs listed above multiplied by number of planned patients
	Site recruitment costs
	Site retention costs (per month) × number of site management months
	Administrative staff costs (per month) × number of project management months
	Site monitoring costs (per day) × number of site monitoring days
Per-study	Per-site costs listed above multiplied by number of sites
	Data collection, management and analysis costs
	Cost per institutional review board (IRB) approval × number of IRB approvals
	Cost per IRB amendment × number of IRB amendments
	SDV cost (per data field) × number of SDV fields

SDV: source data verification.

pharmaceutical companies and hence represent only a subset of all trials conducted over the 2004–2012 period.

Analysis methods

Based on the cost elements provided, we computed the average total cost per study, x_{jk}, by clinical trial phase, j, and therapeutic area, k, by appropriately aggregating the per-patient, $x_{jk}^{Patient}$, and per-site, x_{jk}^{Site}, related cost elements using equation (1)

$$
\begin{aligned}
x_{jk} = {} & \text{Data collection management and analysis} \\
& + \text{IRB approval}_{jk} \\
& + \text{IRB amendment}_{jk} + \text{source data verification}_{jk} \\
& + \left(x_{jk}^{Site} \times \text{number of sites per study}_{jjk} \right) \\
& + \text{site overhead} + \text{all other} \quad (1)
\end{aligned}
$$

where IRB approval costs are the product of the number of IRB approvals and cost per IRB approval, IRB amendment costs are the product of the number of IRB amendments and cost per IRB amendment, source data verification costs are the product of the number of source data verification fields per study and cost of source data verification per field, site overhead costs were estimated at 25% of per-study costs, and all other costs, which include costs for sponsors to run the study and other costs not captured elsewhere, were estimated as 30% of the sum of per-study costs and the 25% site overhead, and

$$
\begin{aligned}
x_{jk}^{Site} = {} & \text{site recruitment}_{jk} + \text{site retention}_{jk} \\
& + \text{administration staff}_{jk} \\
& + \text{site monitoring}_{jk} \\
& + \left(x_{jk}^{Patient} \times \text{number of planned patients per site}_{jk} \right) \\
& \quad (2)
\end{aligned}
$$

where site retention costs are the product of number of site management months and site retention costs per month, administrative staff costs are the product of the number of project management months and administrative staff costs per month, and site monitoring costs are the product of the number of site monitoring days and per-day site monitoring costs, and

$$
\begin{aligned}
x_{jk}^{Patient} = {} & \text{patient recruitment} + \text{patient retention} \\
& + \text{registered nurse and clinical research associate} \\
& + \text{physician} \\
& + \text{clinical procedure} + \text{central laboratory} \quad (3)
\end{aligned}
$$

It should be noted that site overhead is not always applied to all costs in a negotiated clinical investigator contract by the clinical site. In some cases, the site may negotiate overhead only on certain portions of the contract such as clinical procedures. Thus, 25% of total direct per-study costs may be an overestimate of actual overhead costs per study.

To examine key direct cost drivers by clinical trial phase across the different therapeutic areas, we weighted the data by the number of contracts available by therapeutic area. More specifically, for each cost component, i, and clinical trial phase, j, we computed a weighted mean, $\bar{x}_{ij}$, and its weighted standard deviation, S_{ij}, where the weights are the total number of contracts (i.e. sum of investigator and contractor contracts contributing to the PICAS and CROCAS datasets)

$$
\bar{x}_{ij} = \frac{\sum_{k=1}^{N_j} w_{jk} x_{ijk}}{\sum_{k=1}^{N_j} w_{jk}} \quad (4)
$$

$$
S_{ij} = \frac{\sqrt{\sum_{k=1}^{N_j} w_{jk} \left(x_{ijk} - \bar{x}_{ij} \right)^2}}{\sqrt{\frac{(N'_j - 1) \sum_{k=1}^{N_j} w_{jk}}{N'_j}}} \quad (5)
$$

where w_{jk} is the total number of contracts available for the phase and therapeutic area, k, combination; x_{ijk} is the reported mean for cost component i, clinical trial phase j, and therapeutic area k; $\bar{x}_{ij}$ is the simple average of cost component i for that phase j across all therapeutic areas; N_j is the number of therapeutic areas that are associated with the phase in question; and N'_J is the number of non-zero weights.[20]

To compare variability across the different direct cost components for a given clinical trial phase, we also computed the relative standard deviation, RSD_{ij} as

$$
RSD_{ij} = \frac{S_{ij}}{\bar{x}_{ij}} \times 100 \quad (6)
$$

where $\bar{x}_{ij}$ is the weighted mean and S_{ij} is the weighted standard deviation for cost component i and study phase j, as defined previously. The use of RSD allowed for meaningful comparisons of precision across cost elements.[21]

Results

Figure 1 presents the average per-study costs for each of the therapeutic areas by clinical trial phase. Immunomodulation per-study costs (US$6.6 million) were the highest in Phase 1 with costs of studies in ophthalmology (US$5.3 million) and respiratory system (US$5.2 million) ranking second and third, respectively. In Phase 2, hematology trial costs (US$19.6 million) ranked first, followed by pain and anesthesia (US$17.0 million) and immunomodulation (US$16.0 million) trials. The most costly Phase 3 studies were in pain and anesthesia (US$52.9 million) with studies in the ophthalmology (US$30.7 million) and
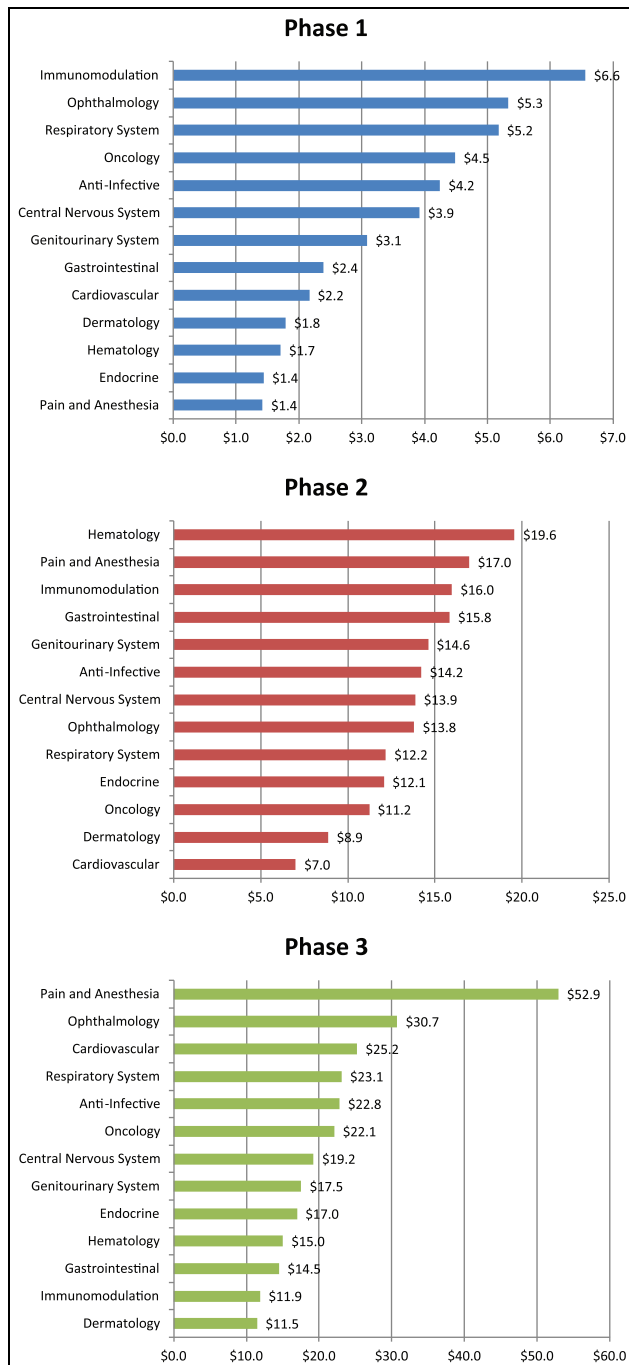
Phase 1

Therapeutic Area	Cost
Immunomodulation	$6.6
Ophthalmology	$5.3
Respiratory System	$5.2
Oncology	$4.5
Anti-Infective	$4.2
Central Nervous System	$3.9
Genitourinary System	$3.1
Gastrointestinal	$2.4
Cardiovascular	$2.2
Dermatology	$1.8
Hematology	$1.7
Endocrine	$1.4
Pain and Anesthesia	$1.4

Phase 2

Therapeutic Area	Cost
Hematology	$19.6
Pain and Anesthesia	$17.0
Immunomodulation	$16.0
Gastrointestinal	$15.8
Genitourinary System	$14.6
Anti-Infective	$14.2
Central Nervous System	$13.9
Ophthalmology	$13.8
Respiratory System	$12.2
Endocrine	$12.1
Oncology	$11.2
Dermatology	$8.9
Cardiovascular	$7.0

Phase 3

Therapeutic Area	Cost
Pain and Anesthesia	$52.9
Ophthalmology	$30.7
Cardiovascular	$25.2
Respiratory System	$23.1
Anti-Infective	$22.8
Oncology	$22.1
Central Nervous System	$19.2
Genitourinary System	$17.5
Endocrine	$17.0
Hematology	$15.0
Gastrointestinal	$14.5
Immunomodulation	$11.9
Dermatology	$11.5

Figure 1. Costs by therapeutic area (in US$ million).

Figure 2. Costs by therapeutic area and phase (in US$ million).

pain and anesthesia (US$71.3 million) followed by ophthalmology (US$49.8 million) and anti-infective (US$41.2 million) trials (Figure 2). Trials in dermatology, endocrinology, and gastroenterology had the lowest overall costs.

Table 2 presents weighted average costs and weighted standard deviations per study by cost component and by clinical trial phase across all therapeutic areas. Excluding the estimated all other and site overhead cost components, in Phase 1, clinical procedure costs (US$476,000)—which included costs of medical procedures (e.g. physical exams and electrocardiograms), medical questionnaires, and clinical assessments but excluded other direct peripheral costs, such as physician fees, salaries, facility charges, study set-up costs, advertising expenses, patient recruitment costs, pharmacy fees, and document storage costs—were the highest, accounting for 22.3% of total. These were followed by source data verification costs (US$326,000; 15.3% of total) and central laboratory costs (US$252,000; 11.8% of total). In Phase 2, expenditures that contributed the most to overall direct costs in descending order included clinical procedure costs (US$1.5 million; 19.4% of total), administrative staff costs (US$1.3 million; 17.7% of total), site retention costs (US$1.1 million; 14.8% of total), site monitoring costs (US$1.1 million; 14.3% of total)—which included site visit costs for collecting and checking case report forms, source data verification, and other charges for the review and maintenance of regulatory binders, drug accountability, and query resolution—central laboratory costs (US$805,000; 10.6% of total), and registered nurse and clinical research associate costs (US$441,000; 5.8% of total). Even though they were still sizeable and higher in absolute terms than those in Phase 1, source data verification costs constituted only 5.3% of total per-study Phase 2 costs. Similar to Phase 2, clinical procedure costs (US$2.3 million; 19.8% of total),

cardiovascular areas (US$25.2 million) ranking second and third, respectively. As expected, study costs were highly dependent on the *total number of planned patients* (= *number of planned patients per site* × *number of sites per study*) which were variable by therapeutic area and clinical trial phase: 11 (hematology) to 170 (ophthalmology) for Phase 1, 148 (oncology) to 389 (gastrointestinal) for Phase 2, and 216 (hematology) to 1431 (pain and anesthesia) for Phase 3.

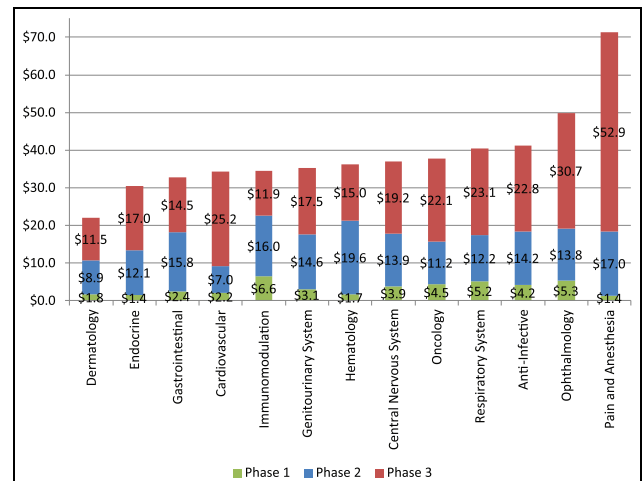Overall, the therapeutic area with the highest combined average per-study costs across all phases was

Table 2. Clinical trial costs, by cost component and phase.[a,b]

Cost component	Phase 1		Phase 2		Phase 3	
	US$	Percentage of subtotal	US$	Percentage of subtotal	US$	Percentage of subtotal
Per-patient costs						
Patient recruitment costs	US$37,050 (US$21,666)	1.74	US$161,140 (US$102,066)	2.12	US$308,672 (US$174,702)	2.71
Patient retention costs	US$6145 (US$4745)	0.29	US$15,439 (US$6970)	0.20	US$24,727 (US$15,868)	0.22
Registered nurse and clinical research associate costs	US$178,237 (US$90,473)	8.36	US$441,053 (US$140,390)	5.80	US$939,540 (US$614,943)	8.25
Physician costs	US$109,681 (US$57,626)	5.15	US$381,968 (US$117,217)	5.03	US$805,508 (US$499,426)	7.08
Clinical procedure costs	US$475,667 (US$371,586)	22.32	US$1,476,368 (US$633,448)	19.43	US$2,252,208 (US$1,033,618)	19.79
Central laboratory costs[c]	US$252,163 (US$203,342)	11.83	US$804,821 (US$313,577)	10.59	US$849,180 (US$600,134)	7.46
Per-site costs						
Site recruitment costs	US$51,904 (US$32,814)	2.44	US$233,729 (US$83,799)	3.08	US$395,182 (US$195,983)	3.47
Site retention costs	US$193,615 (US$79,974)	9.09	US$1,127,005 (US$544,068)	14.83	US$1,305,361 (US$1,382,296)	11.47
Administrative staff costs	US$237,869 (US$128,547)	11.16	US$1,347,390 (US$427,859)	17.73	US$2,321,628 (US$1,910,047)	20.40
Site monitoring costs	US$198,896 (US$128,142)	9.33	US$1,083,186 (US$392,798)	14.25	US$1,624,874 (US$717,034)	14.28
Per-study costs						
Data management costs	US$50,331 (US$8467)	2.36	US$59,934 (US$21,060)	0.79	US$39,047 (US$19,416)	0.34
Cost per IRB approvals	US$11,962 (US$6305)	0.56	US$60,188 (US$16,092)	0.79	US$114,118 (US$46,404)	1.00
Cost of IRB amendments	US$1094 (US$255)	0.05	US$1698 (US$447)	0.02	US$1919 (US$277)	0.02
Source data verification costs	US$326,437 (US$65,659)	15.32	US$406,038 (US$80,573)	5.34	US$400,173 (US$66,429)	3.52
Subtotal (in US$ million)[d]	US$2.13 (US$ 0.86)	100	US$7.60 (US$1.46)	100	US$11.38 (US$4.93)	100
Site overhead[e]	US$528,685 (US$235,862)	NA	US$1,741,811 (US$302,049)	NA	US$2,541,313 (US$1,091,082)	NA
All other costs[e]	US$1,139,887 (US$468,077)	NA	US$4,003,615 (US$752,108)	NA	US$5,967,193 (US$2,577,692)	NA
Total (in US$ million)	US$3.80 (US$1.56)	NA	US$13.35 (US$2.51)	NA	US$19.89 (US$8.59)	NA

NA: not applicable.

Note that the reported numbers represent weighted average costs and standard deviations.

[a]The numbers in parentheses represent weighted standard deviations.

[b]The cost for each phase assumes that a single trial is conducted.

[c]Phase 1 study sites tend to have in-house or local laboratories rather than central laboratories.

[d]Percentages may not add up to 100% due to rounding.

[e]Extrapolations are based on those cost components for which estimates were available from Medidata.

administrative staff costs (US$2.3 million; 20.4% of total), site retention costs (US$1.3 million; 11.5% of total), site monitoring costs (US$1.6 million; 14.3% of total), central laboratory costs (US$849,000; 7.5% of total), and registered nurse and clinical research associate costs (US$940,000; 8.3% of total) contributed the most to overall per-study Phase 3 costs.

Figure 3 presents the RSD of each cost component by trial phase. Patient retention, site recruitment, and central laboratory costs consistently had the highest RSDs across all phases. In contrast, source data verification, IRB approval, and IRB amendment costs had the lowest RSDs across all phases. In Phase 1, central laboratory costs (81% RSD), clinical procedure costs (78% RSD), and patient retention costs (77% RSD) had the most variation among all cost components. Central laboratory costs ranged from a low of US$33,000 (hematology) to a high of US$765,000 (immunomodulation). Similarly, the range for clinical procedure costs across therapeutic areas was also quite wide, US$22,000 (hematology) to US$1.5 million (ophthalmology). Patient retention costs ranged from US$1300 (dermatology) to US$21,000 (ophthalmology). In Phase 2, the degree of variability for the majority of the cost components across therapeutic areas was significantly lower than Phase 1 levels. Patient recruitment costs (63% RSD), site retention costs (48% RSD), patient retention costs (45% RSD), and clinical procedure costs (43% RSD) had the largest variation in Phase 2. Patient recruitment costs ranged from US$71,000 (ophthalmology) to US$435,000 (pain and anesthesia). The range for site retention costs was US$352,000 (cardiovascular) to US$2.65 million (hematology). Patient retention costs also had a relatively wide range of US$7000 (oncology) to US$29,000 (genitourinary system). In Phase 3, site retention costs (106% RSD), administrative staff costs (82% RSD), and central laboratory costs (71% RSD) showed the most variation. Site retention costs ranged from US$342,000 (cardiovascular) to a high of US$6.82 million (pain and anesthesia), administrative staff costs from US$542,000 (dermatology) to US$9.02 million (pain and anesthesia), and central laboratory costs from US$94,000 (respiratory system) to US$3.31 million (anti-infective).

Discussion

Our analysis shows that therapeutic area has been an important determinant of clinical trial per-study costs overall. Costs for trials of immunomodulation, hematology, and pain and anesthesia ranked the highest in Phases 1, 2, and 3, respectively. Additional key drivers of overall direct per-study costs across all clinical trial phases included clinical procedure, administrative staff, and site monitoring costs, excluding estimated site
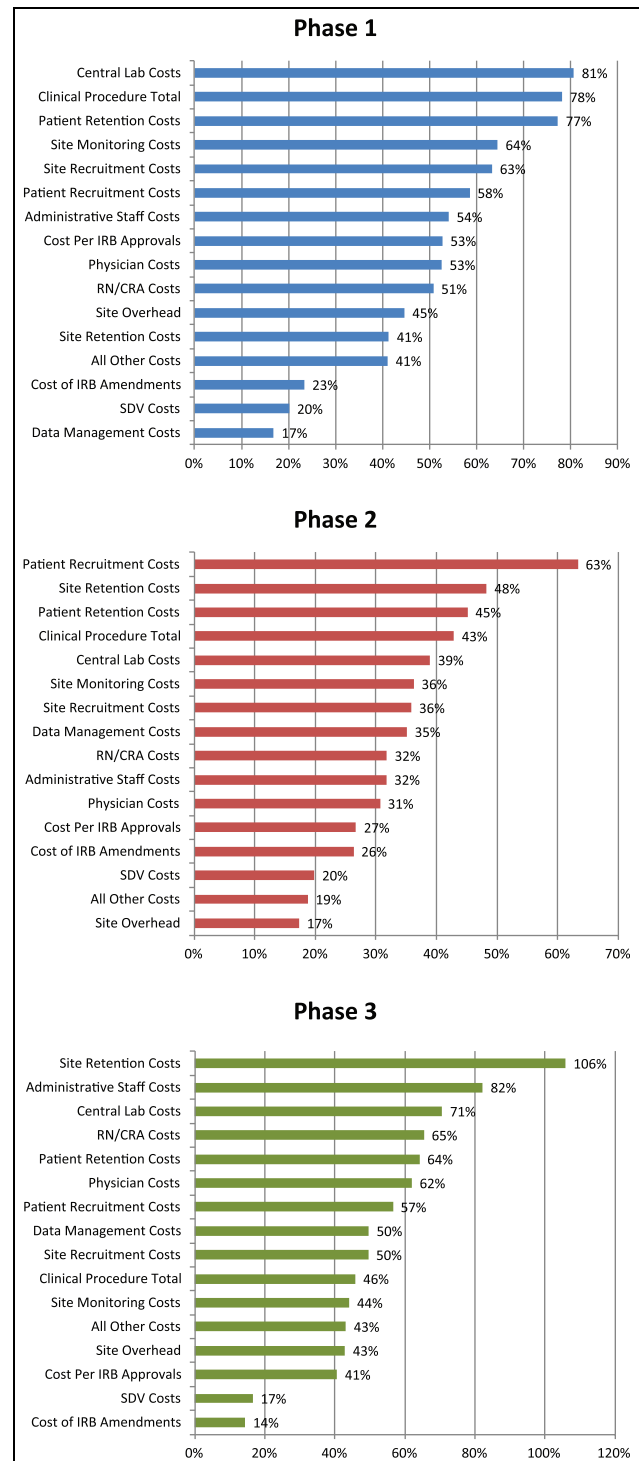

Figure 3. Relative standard deviation (RSD) of cost components, by phase.

overhead costs and costs for sponsors to monitor the study. Recent studies have demonstrated that strategies exist for reducing the price tag of some of these major direct cost components.

Clinical procedure costs accounted for approximately 20% of overall direct per-study costs across Phases 1 through 3 (see Table 2). These costs were

highly variable in Phase 1 (78% RSD) and remained relatively variable in Phases 2 and 3 even though their degree of variability was significantly smaller (from 78% RSD in Phase 1, 43% RSD in Phase 2, and 46% RSD in Phase 3). As the number of clinical procedures conducted increases so does trial monitoring and other related costs (e.g. storage of samples),[6] perhaps unnecessarily if the data collected are not relevant to the specific study.

The reasons for collecting extra data are many and varied. Researchers tend to be overly inclusive, as they are scientifically minded individuals who want to be able to answer the main question and test other theories, as well. Some of the extra data are needed when the clinical value of some endpoints is uncertain. Moreover, while some data are collected in part to satisfy payers and providers (e.g. quality of life measurements and other patient-centric measurements), some data are collected based on patient care experience without careful consideration of whether these measurements are necessary.[22] Some argue that collection of extra data is unavoidable due to the uncertain nature of the process. Others point out that the data being collected are not actually superfluous because there is always need for the data on file, not because the data are required for the US Food and Drug Administration new drug application, but because they are supportive and reasonable to collect.[17]

According to some industry experts, the percentage of data collected that ultimately goes unused varies by trial and may range from 15% to 30%, adding US$20–US$35 million in direct drug development costs for the average drug.[23] Given the size of clinical procedure costs for each study, elimination of non-core and non-essential procedures could result in substantial savings. That said, the cost of collecting data that ultimately goes unused must be carefully weighed against the cost of not collecting data that subsequently turn out to be needed. Collecting additional data later may be more costly, may result in significant delays in trial completion, or be impossible.

Studies have shown that it is possible to reduce clinical procedure costs by simplifying clinical trial protocols and planning carefully to avoid costly protocol amendments, whenever possible.[17] A number of pharmaceutical and biotechnology companies have established internal governance committees to improve and streamline protocol designs in recent years; early results have been encouraging.[24] Companies with such internal governance committees report decreased study complexity which has led to reductions both in the number of clinical procedures and in the number of endpoints per study.[25]

Administrative staff costs accounted for around 11%–20% of overall study costs across Phases 1 through 3 (Table 2). These costs were variable relative to the other cost drivers in Phase 1 (54% RSD). While the degree of variability in administrative staff costs was lower in Phase 2 (32% RSD), it was significantly higher (82% RSD) in Phase 3 (Figure 3). The relatively large contribution of administrative staff costs to overall study costs was somewhat surprising; time spent by administrative staff reportedly accounts for around 23%, with time spent by physicians, registered nurses, and clinical research associates constituting the remaining 77%.[26]

Site monitoring accounted for between 9% and 14% of overall study costs for Phases 1 through 3 (Table 2). While site monitoring costs were relatively variable in Phases 1 and 3 compared to the other cost drivers, they were more stable in Phase 2 (36% RSD in Phase 2 compared to 64% and 44% RSD in Phases 1 and 3, respectively). Site monitoring costs can be reduced by making wider use of mobile technologies, centrally available data to evaluate site performance, electronic data capture, and other efficiency-improving options.[27] Furthermore, adoption of these practices likely would affect many aspects of clinical trials, not only site monitoring timelines and costs but also site management and project management as well as data collection, management, and analysis costs.[27,28]

Continuous collaboration among regulatory bodies, industry, researchers, and academia may help to improve the clinical research enterprise. For example, the Clinical Trials Transformation Initiative, a public–private partnership between the US Food and Drug Administration and Duke University, has made important strides in identifying best practices for investigator training in Good Clinical Practice, communications and contractual relationships between member institutions and a central IRB, and periodic evaluations of safety information during drug development programs, among others.[16,29]

Limitations

Our study had a number of limitations related to the nature of the data used and methods employed for the analysis. First, the data on mean costs by cost element, clinical trial phase, and therapeutic area were from 2004 through 2012 and had not been adjusted for inflation by Medidata prior to aggregation. As the data on costs represented averages across this time range, we were unable to adjust the data for inflation. Prices have gone up approximately 22% over that time period,[4] thus present costs likely are considerably higher. Second, rather than deriving average costs from disaggregated data at the study level, we used aggregate means reported at the clinical trial phase and therapeutic area levels to compute overall per-study and per-cost component averages. This choice may have resulted in over- or under-estimation of various cost elements. Third, while the PICAS, CROCAS, and Medidata

Insights datasets are an important resource for clinical research, they are likely neither comprehensive nor representative of a random sample of all US clinical trials. For example, an examination of the number of investigator and contractor contracts contributing to the PICAS and CROCAS datasets by therapeutic area and clinical trial phase for the 2004–2012 period showed that some of the therapeutic areas (e.g. oncology across all clinical trial phases, central nervous system, and endocrine in Phase 3 studies) may be over-represented, whereas others (e.g. cardiovascular in Phase 1, hematology in Phase 2, and ophthalmology in Phase 3) may be under-represented. To the extent that the cost elements associated with such therapeutic areas are widely different from others, the relative rankings of cost elements may be skewed as we used the number of studies as weights in deriving weighted cost means and variances across therapeutic areas. Fourth, the Medidata datasets did not contain any information on clinical supply costs such as costs of comparator drugs and/or co-therapies or costs of shipping these supplies to study sites. Reportedly, these costs could be significant and are highly variable from one trial to another.[30] Depending on their magnitude, exclusion of these costs from the analysis could have resulted in under-estimation of total per-study costs.

Finally, the data used in the analysis were from trials funded by the global pharmaceutical and biotechnology industry. Hence, study findings may not be generalizable to those trials funded by governments, academic institutions, and other organizations.

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