FROM THE ANALYST'S COUCH

How much do clinical trials cost?

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The cost of bringing new drugs to market and conducting clinical trials is a core concern for pharmaceutical companies, which continue to struggle with rising clinical trial costs year on year owing to more complex clinical development programmes. This complexity is driven by factors that include increased regulatory scrutiny, the growing need to demonstrate not just the safety and efficacy of new drugs but also their value (particularly compared with established treatments for diseases such as diabetes and osteoporosis) and challenges associated with conducting trials in defined patient subpopulations or patients with rare diseases.

Despite a clear need to understand the costs of drug development and the factors responsible, there has been a surprising gap in the data relating to how much it actually costs to conduct clinical trials. Without reliable benchmarks, it is difficult for companies to identify the key pain points in their processes and then chart a path towards improvement. In addition, lack of information makes forecasting and planning budgets more challenging, particularly when embarking on new development paths or running trials in areas in which a company has limited experience.

With the aim of providing companies with a comparative baseline for how much clinical trials cost, KMR Group conducted the landmark Clinical Trial Cost Study in 2016. This assessment provided reliable cross-industry cost data to senior management at major biopharma companies, so that they could evaluate their operational efficiency and make more accurate financial projections, as well as more effectively evaluate the cost burden of licensing and asset acquisition. Here, we present some of the key findings of this analysis.

Analysis

Data were collected directly from 7 major companies (all of which are in the top 20 biopharma companies ranked by revenue in 2016) on 726 interventional studies conducted in patients from 2010 to 2015 (see Supplementary information S1 (box) for details). A standardized approach was used to assign clinical development spending — including personnel, outsourcing and expenses — to individual trials through the use of time reporting systems and directly allocated spending. This inclusive method alleviates the challenges associated with the more traditional comparative analysis that has historically been available. For example, most of the cost data to date are limited to external investment, which not only misses a large portion of the actual cost (for example, company employees), but is further confounded when use of outsourcing varies by study (that is, studies that outsource more will seem more expensive, all other factors being equal).

This detailed data collection process enabled total trial costs to be broken down by key cost areas within each trial: personnel, outsourcing, grant/contract and other expenses. FIG. 1 shows the proportions of each of these areas across the data set for phase III trials. Personnel spending makes up 37% of the total costs for the average phase III trial, whereas outsourcing and grant/contracts spending each make up approximately one-fifth of the total trial cost.

The data enable cost performance to be assessed in three ways: first, comparing a company's clinical trial cost portfolio with that of the overall group to better understand how its cost profile differs from that of its peers; second, evaluating the cost of a given company's trial portfolio relative to its particular therapeutic area focus, and third, examining the trial cost profile in terms of operational efficiency. Although the data on individual company performance in the data set are confidential, the pooled data presented here are useful for understanding key cost drivers, as well as how much clinical trials actually cost.

Median clinical trial costs. For the first type of assessment, data on the median costs for each trial phase can be used. If a company is found to expend more per trial, the cause may be explained by factors such as therapeutic area profile, trial design choices or inefficiencies in operational processes. However, the end result is that if a company runs more expensive trials for any reason it will be considered less productive; that is, not able to run the same number of trials per dollar.

For the trials in the data set, the median cost of conducting a study from protocol approval to final clinical trial report was US$3.4 million for phase I trials involving patients, $8.6 million for phase II trials and $21.4 million for phase III trials (FIG. 2).

Unsurprisingly, much of the variability in these costs is related to trial protocol design choices and factors such as the number of subjects, sites and visits ($P \leq 0.0001$) (TABLE 1). We also used statistical techniques to identify key factors that influence cost that are based on a company's strategic choices, such as the selection of the countries in which to conduct the clinical trials. This analysis revealed, for example, that increasing the number of countries and use of emerging markets increased cost (TABLE 1). A greater share of patients in emerging markets also tends to lengthen cycle times (*Nat. Rev. Drug Disc.* **16**, 157; 2017), particularly in phase III. This indicates that while these countries are useful to help broaden patient populations, they raise challenges by both expanding timelines and increasing costs.

Another key factor associated with higher cost was trial duration (TABLE 1). In particular, each additional month for phase III trials translates into a median $671,000 spent. With this as a baseline, even small cycle-time reductions could have meaningful benefits on overall clinical development budgets.

There were also factors that had no statistically significant effect on overall trial cost, such as whether a trial used an adaptive ►

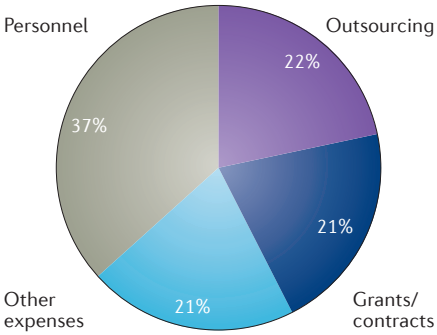

Figure 1 | **Components of the costs of phase III trials.** Data are from 273 studies conducted in patients from 2010–2015 (see Supplementary information S1 (box) for details.

design, was for a rare disease or involved a biologic product (TABLE 1). Nevertheless, although rare disease studies were not associated with differences in total trial cost, they did have a statistically significant ($P = 0.0003$) higher grant cost per subject, due in part to smaller patient pools and more complex design. Similarly, studies with large molecules also had significantly higher grant costs per subject ($P = 0.004$).

Operational performance. Although the design factors are essential to any cost assessment, they do not shed light on the operational performance of companies; that is, how well they execute clinical trials according to their chosen design. To evaluate operational performance, we used multivariate regression to derive a statistical model that accounts for essential factors related to protocol design (that is, a lean model (see Supplementary information S1 (box) for details). The lean model uses the following core clinical trial design parameters: study size (using volume of sites), therapeutic area and treatment duration. For phase II and III trials, the lean model explains approximately two-thirds and almost 90% of the variance in overall study cost, respectively. The remaining unexplained proportion of the variance (that is, 33% and 10%) is due to the impact that operational choices and execution have on the overall cost for each study.

Operational efficiency for each company in the data set was calculated using the actual-to-predicted (that is, model-derived) spending ratio. This showed that despite the majority of costs being explained by protocol design parameters, there are still substantial inefficiencies within operations across the industry. The disparity in operational efficiency (±1 standard deviation) between companies in the data set equates to a roughly $700 million annual difference in overall clinical trial costs for the average-sized company in this data set.

Table 1 | **Influence of selected factors on clinical trial costs**

Factor	Description	Total trial cost*
Sites	Number of sites randomizing	▲
Subjects	Number of subjects randomized	▲
Visits	Number of subject visits	▲
Duration	Duration of trial (time from protocol authorization to final clinical trial report)	▲
Molecule size	Large versus small molecules	NS
Rare disease	Rare versus not-rare disease	NS
Adaptive design	Adaptive versus not-adaptive design	NS
Emerging market activity	Emerging market activity versus no emerging market activity	▲
Emerging market subjects	Percentage of subjects in emerging markets	▲
Regions	Number of regions	▲
Countries	Number of countries	▲

*Factors indicated with red arrows were associated with increased clinical trial costs ($P \leq 0.0001$) (see Supplementary information S1 (box) for details, including individual P values). NS, not significant. Source: KMR Group.

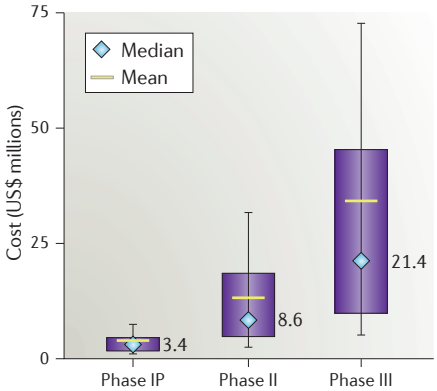

Figure 2 | **Costs of clinical trials.** Data are from 726 studies conducted in patients from 2010–2015. Medians and means are indicated with diamonds and lines. Boxes indicate the 25th to 75th percentiles and whiskers indicate the 10th and 90th percentiles. Phase IP, phase I study involving patients. See Supplementary information S1 (box) for details.

Finally, we identified common characteristics between high- and low-performing companies and found several interesting themes. For example, those companies that spend a higher proportion of their clinical development budgets on outsourcing performed better when comparing the costs of phase I trials ($R = -0.46$), but worse when comparing the costs of phase III trials ($R = 0.38$).

Additionally, companies that conduct trials for rare diseases to a greater extent tend to be less productive in phase III ($R = 0.67$).

Improving performance

Understanding the factors that drive clinical trial costs is a nuanced and complex effort that requires a solid methodology to ensure comparability across both companies and trials. We hope that the data provided by our analysis helps companies in benchmarking their performance and identifying specific areas for improvement.

In general, there are three broad groups of factors that can be targeted to improve cost performance: choices for trial design parameters (such as size of study, number of end points and treatment duration), operational choices (such as outsourcing and use of emerging markets) and cycle-time reductions. Although opportunities for individual companies to improve their performance need to be understood through thorough evaluation of their own data on these factors, our analysis indicates some areas that could be particularly useful to focus on. These include factors such as the use of outsourcing at different stages of the clinical development process, the use of emerging markets and operational aspects that reduce cycle times. Understanding the relationships between all the factors will also be crucial to making optimal choices.

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The authors declare competing interests: see Web version for details.

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