FROM THE ANALYST'S COUCH

What drives operational performance in clinical R&D?

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Yellow chair by somsak nitimongkolchai/Alamy Stock Photo

Most pharmaceutical companies pay considerable attention to the operational performance of their clinical development enterprises. However, despite much anecdotal discussion of performance drivers — and reorganization designed to optimize them — there is little empirical information about which factors actually drive better performance. Here, we describe the output of a joint benchmarking effort between The Boston Consulting Group and KMR Group that takes a data-driven approach to identify design parameters associated with improved performance, and hence the actions that companies can take to optimize their clinical development operations.

Analysis

Our data set derives from benchmarking of 14 biopharmaceutical companies, which provided access to detailed quantitative information from their internal systems, as well as qualitative and quantitative information from interviews with leaders of development and clinical operations. The companies varied widely in size, with annual R&D spending of between ~US$200 million and >$5 billion. Their combined R&D spending in 2014 was >$50 billion, representing a significant fraction of industry activity. For each of these companies, we analysed the 2013 and 2014 data on Phases I–III and Phase IV interventional trials across all therapeutic modalities (including therapeutic vaccines but excluding prophylactic ones).

The study had two objectives: first, to understand operational performance holistically across efficiency, speed and quality; and second, to determine which factors across a range of design choices are actually associated with better performance. Regarding the first objective, we defined the three output variables as follows. Efficiency was defined by the residual between the observed and expected total clinical development spending. The expected spending was estimated by a best-fit model, using independent variables for the number of trials in each phase as the scaling variables. Speed was defined by the non-composite cycle time of trials achieving end-of-phase during the observation period, summed across Phases I–III. Quality was defined by the number of quality findings made by regulatory authorities per audit conducted. Regarding the second objective, there were 18 design choices designated as input variables, classified into five types — organization, strategic focus, new methods, resource management and scale — and then assessed for relationship to performance on the three output variables by means of single regressions and analyses of variance (ANOVAs).

It should be noted that the focus of this study was operational performance, which is just one of three major inputs to overall R&D productivity. The other two factors — the value of products produced, and the timing and amount of attrition in the pipeline — are powerful levers for driving R&D productivity, and companies should avoid optimizing operational performance at their expense (*Nat. Rev. Drug Discov.* **12**, 901–902; 2013). Having said that, many activities that companies pursue are ostensibly undertaken to improve operational performance, and our results indicate which of these activities are having the intended effect and which are not. Ultimately, the findings from this analysis should be used in conjunction with careful consideration of value and attrition effects.

Our first finding is just how far from optimized the operations in the pharmaceutical industry are. Compared with more mature, standardized industries where the performance of major companies is substantially similar (such as electricity services and metal fabrication), there is 12-fold greater variance in gross margins between pharmaceutical companies. We also see concomitant levels of variance in clinical R&D: the per-trial efficiency varies such that ±1 standard deviation (s.d.) is a difference of $4.0 million per trial, averaged across a typical mixture of trial sizes and phases (FIG. 1a). For a company of 'average' size in our data set, running ~130 trials, this translates to an annual cost difference of >$500 million. Although some variation is to be expected, given that the vagaries of human biology drive differences in individual trials, the level of variation is high. Against a standardized portfolio of trials, a 'poor' company performing at –1 s.d. spends 1.9 times as much, takes 1.5 times as long and has 2.3 times as many regulatory findings per audit as a 'good' company performing at +1 s.d. (FIG. 1).

Second, many factors posited as drivers of performance have limited impact. TABLE 1 summarizes the observed correlations between design choices and operational performance. We found no statistically significant effect on efficiency, speed or quality from factors such as company size, use of emerging markets and number of therapeutic areas. Yet these factors have been the focus of much attention (and restructuring effort), often for the sake of operational benefit. Because each company sees only *n* of 1 data on the impact of a choice across a time period when other changes occur simultaneously, it has been hard to determine whether such changes are having the intended effect. This study suggests they are not.

Third, eight factors (TABLE 1) were found to correlate with improvements in performance, and provide opportunities for action. Being on the 'right side' of any one of these design choices is associated, on average, with improvements of 18% in efficiency, 9% in speed and 26% in quality. Furthermore, these factors are typically associated with all three improvements (in efficiency, speed and quality).

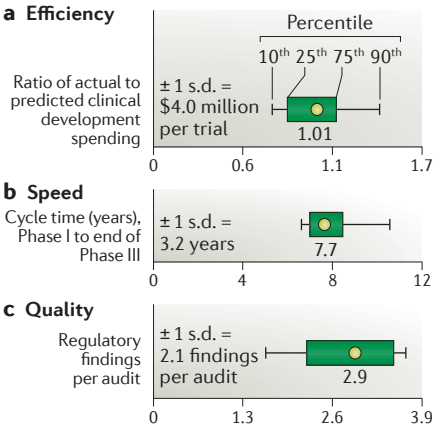

Figure 1 | **Variation in performance among 14 companies.** s.d., standard deviation.

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- A functional organizational structure rather than a business unit structure, a more consolidated geographical footprint, and more internal operations (that is, less outsourcing) were among these eight factors. These effects are independent of company scale, which had no observable impact. Note too that some aspects of design may harm per-unit efficiency, but could be justified if they drive better value or attrition profiles. For example, proponents of outsourcing may argue that minimizing fixed infrastructure makes it easier to be dispassionate about project termination decisions, and is hence worthwhile despite being associated with higher per-unit costs.

Discussion

Armed with these findings, companies are in a better position to seek performance improvements in two ways: first, by addressing specific design choices; second, by pursuing overall process optimization.

Three types of design parameter are at issue. In the first type, the parameters seem to reduce operational productivity without conferring any benefit regarding value or attrition, and this profile is not expected to shift over time. An example is a distributed geographical footprint. Such a design may well be the outcome of legacy integrations and other historical factors, rather than a deliberate choice. There might be legitimate constraints on changing these parameters, but companies could actively reassess the feasibility of making changes.

In the second type, the parameters are again associated with lower operational performance and with negligible benefit regarding value or attrition, but there is a legitimate argument that the impact could shift over time. An example is risk-based monitoring, which has been pursued with the aim of improving operational quality and efficiency, but to date it does not seem to be having the intended effect. Given that risk-based monitoring is relatively new, however, it is possible that this is a transient phenomenon driven by simultaneous investment in both risk-based and traditional monitoring, and benefits will materialize once companies learn how to use the risk-based approach.

In the third type, the parameters are again associated with an operational detriment, but there may be justification through benefits in value or attrition. Possible examples include a greater focus on precision medicine or on rare diseases. Although companies may ultimately opt to continue with these design elements, they need to be aware of the concomitant effects on operational performance and adjust their set-up appropriately to compensate.

Finally, regardless of choices on individual design elements, the huge variation in performance across the industry indicates a strong opportunity for process optimization. We have seen great success in redesigning operations along a 'lean' process flow — customized for R&D— to reduce complexity, avoid duplicated work, and to drive standardization, scalability and re-use.

Table 1 | **Impact of selected clinical R&D design choices on operational performance***

Design choice	Description	Efficiency	Speed	Quality
Organization				
Business unit structure	Division into business unit structure versus functional structure	▼	▼	–
Geographical centralization	Geographical centralization of functions (1–2 sites) versus decentralized (3+ sites)	▲	▲	▲
Early/late-stage division	Division into early- versus late-stage development	–	–	–
Strategic focus				
Number of therapeutic areas	Higher versus lower number of therapeutic areas	–	–	–
Modality focus	Higher % of trial subjects active with large versus small molecules	–	–	–
Rare disease	Higher % of subjects active with rare versus 'traditional' diseases	▼	▽	–
Personalized medicine	>20% of Phase I–III trials with personalized medicine focus	▼	▽	▽
New methods				
Emerging markets	Higher % of subjects active in emerging versus developed markets	–	–	–
Risk-based monitoring	>20% of Phase I–III trials using risk-based monitoring	▽	–	–
Adaptive trials	>20% of new Phase I–III trials using adaptive design approaches	▼	▽	–
Payer end points	>20% of new Phase I–III trials having end points specifically for payers/access	–	–	–
Resource management				
Outsourcing approach	Use of preferred provider versus functional service providers	–	–	–
Outsourcing investment	Higher % of outsourcing (of clinical development spending)	–	▼	▽
Staff continuity	Clinical team members pursuing projects across phases >20% of the time	–	–	–
Resourcing tool	Enterprise-level tool versus customized or no projections	–	–	–
Scale				
Clinical trial size	Greater number of subjects active per trial	–	–	–
Subjects per site	Greater volume of subjects active per site	△	▲	–
Company size	Higher overall R&D spending	–	–	–

*Solid upward green arrows or downward red arrows indicate a significant ($P < 0.05$) increase or decrease, respectively, due to the design choice. Hollow arrows indicate a corresponding directional ($P < 0.15$) effect.

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