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TRIAL WATCH

Trends in clinical trial design complexity

The challenges of measuring the safety and efficacy of investigational drugs that target chronic, difficult-to-treat or rare diseases in more narrowly defined patient subpopulations have increased the scope of clinical trials and the burden to execute them in the past 15 years. Other factors affecting protocol design include capturing more patient-reported outcome measures, and the collection of comparative effectiveness and biomarker data. Here, we provide new benchmark data on trial complexity with the aim of enabling drug development sponsors to compare against their own organizational practices and informing clinical research practitioners of evolving protocol design practices.

The analysis is based on 9,737 clinical trial protocols that received ethics review board approval between 2001 and 2015, drawn from Medidata's PICAS database, which contains detailed protocol and investigative site contract data from more than 170 global pharmaceutical and biotechnology companies (76% of the protocols were provided by large companies and 24% by mid-sized and smaller companies (see Supplementary information S1 (box) for details)). Design elements associated with executional feasibility — including the number of procedures performed, the number of planned study volunteer visits, the work effort to administer procedures and the cost per study volunteer visit — were evaluated and compared across two time periods — 2001–2005 and 2011–2015 — separated by 10 years to characterize trends. This approach was used to allow longer time horizons in which to gather more meaningful insights while reducing any outlier effects in any given year.

The results of this analysis show that protocol design elements associated with protocol execution have grown rapidly. The mean number of distinct procedures carried out per protocol increased significantly for phases I, II and III, most notably among phase II and III protocols (FIG. 1a). The frequency with which each distinct procedure was performed grew at an even faster rate, leading to a higher growth in the mean number of total procedures. During this period, however, the mean number of planned visits per study volunteer grew at a far more modest rate, resulting in more procedures performed per study volunteer visit and a greater burden on volunteer participation.

Phase I protocols were the most complex, with the highest mean number of distinct procedures (36) and total procedures (253) carried out in the 2011–2015 period. Phase III protocols saw the highest relative growth in total procedures carried out, increasing by 70% from a mean of 110 procedures in 2001–2005 to 187 in 2011–2015 (FIG. 1a). A mean of 22 distinct procedures were carried out for each phase III protocol in 2001–2005, compared with 35 in 2011–2015 — a 59% increase. The mean number of planned study volunteer visits increased by 25%, from 12 visits per protocol in 2001–2005 to 15 visits per protocol in 2011–2015.

The work required to administer phase I, II and III protocols at investigative sites also increased substantially over the 10-year time period (Supplementary information S1 (box)), as did the mean total cost per study volunteer per visit (FIG. 1b). Although the costs for many procedures such as blood tests have come down during the past decade, the total cost per volunteer visit has grown considerably because of the increase in the total number of procedures carried out. Phase II studies saw the highest increase in the mean nominal cost per study volunteer visit (61%), followed closely by phase I (49%) studies. Phase III studies showed more modest growth in mean cost per visit, with an increase of 34% over the 10-year period.

These study findings are striking given research linking protocol complexity to longer cycle times, higher numbers of protocol amendments and lower patient recruitment and retention rates (for example, *Contemp. Clin. Trials* **28**, 583–592; 2007). The collection of excessive and unnecessary clinical data may also compromise data integrity and analysis, lead to higher error rates, drive longer study durations and delay submissions to regulatory agencies.

A growing number of pharmaceutical and biotechnology companies and contract research organizations have taken steps to optimize their protocol designs in order to improve feasibility, ease site and subject participation burden, reduce the number of unplanned and unbudgeted protocol amendments, and gather more meaningful clinical data. These initiatives include protocol review committees, protocol-authoring practices connecting procedures to primary and key secondary end points, common protocol-authoring templates, and soliciting feedback on draft protocol designs from patients and investigative site staff before approval and execution. Studies at the Tufts Center for the Study of Drug Development have not yet detected a measurable industry-wide impact from these initiatives, although early anecdotal reports indicate that these initiatives are beginning to yield reductions in the number of protocol amendments and in the burden on investigative site administration (*Ther. Innov. Regul. Sci.* **47**, 651–655; 2013).

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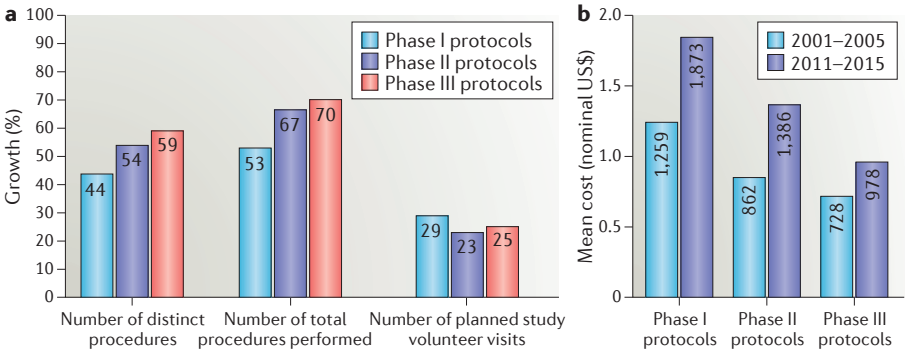

Figure 1 | **Trends in the complexity and costs of clinical trials. a** | Growth rates for protocol design metrics between 2001–2005 and 2011–2015. **b** | Cost per volunteer visit for the same two periods. Increases in protocol complexity have offset cost savings from procedural efficiencies and technology improvements. See Supplementary information S1 (box) for details.