Protocol Design Trends and their Effect on Clinical Trial Performance

A new study suggests that changes in protocol design may be adversely affecting clinical trial performance. Kenneth Getz discusses the results.

During the past ten to fifteen years, sponsor companies have sought to collect increasingly large amounts of clinical research data. There are several reasons for this. For example, the focus of investigational treatments has shifted to chronic diseases, where clinical endpoints have become more difficult and time-consuming to measure and patient populations have become more targeted. Competition between drug developers has also intensified, leading sponsors to gather more data to differentiate products within crowded markets.

Anecdotal reports from sponsors, contract research organisations and investigative sites indicate that protocol designs have also become far more demanding and complicated. However, trends in protocol design and their impact on clinical trial performance have never been formally measured. Therefore, in 2007 the Tufts Center for the Study of Drug Development (Tufts CSDD) in the US conducted a study to characterise and quantify protocol design change and its impact. The study found that changes in protocol designs are placing a greater burden on site personnel and study volunteers, and suggests that clinical trial performance is being adversely affected.

Methodology

Data analyses were conducted on 10,038 protocols drawn from Medidata Solutions Worldwide’s (formerly Fast Track Systems, Inc) proprietary database. This database contains detailed protocol data across all phases and therapeutic areas, from more than 75 pharmaceutical and biotechnology companies. Protocols were selected if they had received institutional review board approval between 1999 and 2005.

To assess the impact of protocol design change on investigative site work burden, Tufts CSDD adapted the Relative Value Unit (RVU) methodology created by and used by Medicare since 1992. Tufts CSDD assigned a work burden measure (WEU) to each procedure for all 10,038 protocols. It also gathered data from 57 unique protocols – 28 protocols conducted between 1999 and 2002, and 29 conducted between 2003 and 2006 – to analyse the impact on clinical trial performance. This analysis was limited to Phase II and III protocols investigating chronic illnesses and conducted in the US, in order to control for therapeutic area and geographic variability.

Results

Protocol design change

Between 1999 and 2005, the annual growth rate in the number of unique procedures per protocol across all therapeutic areas was 6.5%. Across all therapeutic areas and phases in 2005, the median number of unique procedures conducted per protocol was 35. Phase IV postapproval studies showed the highest annual growth rate, at 9.1%. Wide variability was observed across therapeutic areas, with protocols for studies in ophthalmology, pain management and gastrointestinal (GI) indications displaying the highest annual growth rates in the median number of unique procedures across all phases.

The annual growth rate in procedural frequency during 1999-2005, across all phases and therapeutic areas, was 8.7%, indicating that the number of times that a unique procedure is conducted during the duration of the study is increasing faster than the growth rate in the number of unique procedures conducted annually. Annual growth in procedural frequency was highest for protocols in Phase II (12.1%) and lowest for protocols in Phase III (6.1%). In 2005, each unique procedure was conducted an average of 5.4, 6.5, 4.0 and 3.1 times, for Phases I, II, III and IV trials respectively.

During 1999-2005, the administration of questionnaires and subjective study volunteer assessments was the fastest growing procedure type across all phases of development, but most notably in Phase III and IV studies. Lab tests and blood work, and office consultations and examinations, saw the largest relative declines as a proportion of all procedures performed per protocol.

The number of exclusion criteria per protocol remained fairly constant between 1999 and 2005. The average number of inclusion criteria, however, jumped nearly three times. Overall, the distribution of eligibility criteria by category remained consistent.

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Impact on performance

During 1999-2005, investigative site work burden increased annually by 10.5%. The largest annual growth in work burden – 33% – occurred between 2003 and 2005. Annual growth in investigative site work burden was highest in Phase I.

Clinical trial cycle times were substantially longer for protocols conducted in the later time period (2003-2006). The average overall duration of clinical trials increased by 74%. Patient enrolment cycle times increased. Median cycle time from first patient/first visit (FPFV) to last patient/last visit (LPLV) rose by 53% and median cycle time from FPFV to LPLV by 65%. Additionally, patient enrolment rates for protocols conducted during the later time period were much poorer. Volunteer enrolment rates (ie percentage randomised following screening) dropped from 75% in 1999-2002 to 59% in 2003-2006. Study volunteer retention rates (ie the percentage completing the study following randomisation) dropped from 69% to 48% across the comparison time periods.

The average number of protocol amendments increased only modestly between 1999 and 2006: from two in 1999-2002 to three in 2003-2006. The average length of the case report form increased by 227%, from an average of 55 pages per protocol conducted between 1999 and 2002 to an average of 180 pages per protocol conducted between 2003 and 2006.

The median number of adverse events reported rose dramatically, from 667 in the 1999-2003 cohort to 1,481 in the 2003-2006 cohort – an increase of 122%. There was also a 12-fold rise in the median number of serious adverse events reported – two per protocol in 1999-2002 vs 25 per protocol in 2003-2006. These sharp increases may be due, in large part, to changes in the way that adverse events are defined and counted.

Discussion

The results of this study show the various ways in which protocol designs are becoming more demanding and burdensome on investigative site personnel and study volunteers. The combination of changes in the number, frequency and type of unique procedures per protocol is driving higher levels of investigative site work burden. Growth in site work burden is, therefore, a function of both increasing complexity of protocol design and the rising administrative demand to execute these procedures. Although causality has not been demonstrated, the results further suggest that clinical trial performance has been adversely impacted by changes in protocol design.

The Tufts CSDD study results challenge the notion that development cycle time acceleration and efficiency can best be achieved through aggressive investigative site management. Opportunities to achieve higher levels of clinical trial performance perhaps rest most on internal sponsor improvements in protocol design. The downstream impact of simplifying protocol designs will probably ease investigative site work burden, and drive speed and efficiency substantially.

The results highlight the importance of upfront planning to anticipate the effects of protocol design elements on clinical trial success. Internal assessment of protocols in phases and therapeutic areas that have seen the highest growth in the number of procedures, eligibility requirements and work burden may be a good initial and practical place to target efforts to simplify and streamline protocol designs.

An earlier, 2006 Tufts CSDD study showed that investigative site compensation per protocol procedure has been declining by nearly 8% annually. Combined with the current study results, sponsor companies need to assess whether compensation levels are commensurate with protocol requirements and whether they are motivating for investigative site staff.

Whereas our analysis of protocol design trends is based on a large, representative sample of more than 10,000 protocols, our impact analysis is based on a relatively small (N=57) convenience sample. We are presently exploring the feasibility of a follow-up impact study involving a much larger sample. Subsequent analyses are also planned to evaluate protocol design approaches that are correlated with higher levels of clinical trial performance and to understand the impact of design changes on a global basis. In the current operating environment, research sponsors place a premium on accelerating drug development cycle time while optimising efficiency and quality. The results of the Tufts CSDD study shed light on the critical role that protocol design plays in clinical trial performance and on new strategies and practices to improve the protocol design process.

References