Pharma Intelligence
Informa

The Challenging Environment Of Clinical Trial Oversight

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The clinical trial process continues to evolve with implications for study oversight. Industry trends are pushing clinical trials toward evaluation of drugs with smaller patient populations, which results in more complex protocols. Adding to trial complexity are continued patient recruitment challenges and the resulting steps being taken to expand the pool of available patients for trials. Finally, trial complexity is increasing as advances in both the science and the technology behind clinical research open new avenues of drug exploration and evaluation.

Biopharmaceutical companies today have fewer options for drugs that treat large patient populations with highly prevalent, chronic diseases. Many of these diseases now have available treatment options and bringing new drugs to market would require improving upon the performance of these existing treatments – a financially risky proposition. Instead we see pharmaceutical companies increasing levels of research around drugs that treat smaller segments of populations, including rare diseases. Contributing to the growth of rare disease trials are regulatory guidelines such as the Orphan Drug Act (ODA) in the US that provides financial incentives for manufacturers to develop drugs targeting rare diseases (a key incentive in the ODA is that pharmaceutical manufacturers receive 7 years of marketing exclusivity).[1] Rare disease trials typically have more complex protocols and their very nature means it is hard to recruit enough patients to meet the statistical power needed to prove the safety and efficacy of a new treatment.

Further impacting trial complexity is the overall increase in the number of clinical trial starts every year[2] coupled with continued patient recruitment challenges. To find patients in this environment and meet trial recruitment targets, many drug makers are expanding their trials to more countries and increasing the number of sites participating in trials. According to the Tufts Center for the Study of Drug Development, drug makers doubled the number of countries and increased the number of investigative sites by 63% to support Phase III protocols.[3] More sites and greater numbers of countries puts a greater burden on trial oversight.

Drugs are also being evaluated against an increasing number of endpoints, with one estimate showing an 86% increase in total endpoints over the past 10 years. This increase extends beyond traditional CRF or Case Report Form, and includes more investment and effort made to better capture and integrate imaging data, lab data, electronic patient-reported outcomes, electronic health records and “omic” data, etc. Integrating these data becomes important as companies strive to develop a more comprehensive view of the patient and their treatment response. However, it also requires enhanced coordination of a greater number of vendors and support systems as part of study oversight.

Clinical trial approaches are also evolving with the emergence of master protocols, basket trials and umbrella trials, which involve the use of multiple treatment arms in a single trial. Adaptive trials are also becoming more prevalent, with mid-study

changes to one or more aspects of the trial. All of these changes to clinical trial approaches result in more tasks, issues and deviations that must be managed and resolved.

Clinical trials are undergoing major changes in how they are structured, set up and executed. With these changes come an even greater need to manage and oversee these trials to ensure they are properly executed, on time and within budget.

Realities Of Clinical Trial Oversight

Medidata and Informa Pharma Intelligence ran a survey in September 2019 to better understand how the factors outlined above are impacting Clinical Operations teams responsible for managing and overseeing clinical trials.

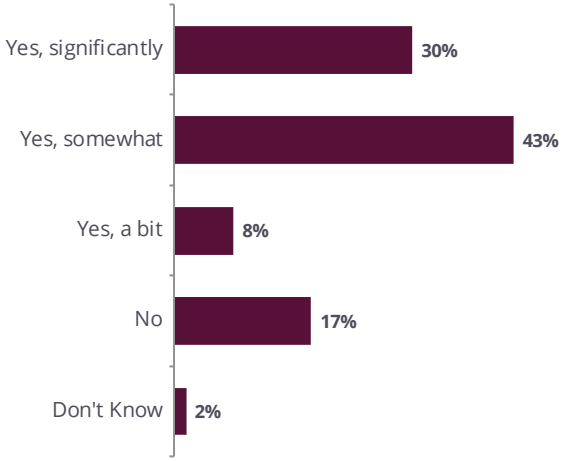
Respondents were clear that they were overwhelmed keeping up with the increasing demands. They indicated that they needed help dealing with the growing complexity of the clinical trial environment.

The survey results revealed that changes in clinical trial protocols most impacting day-to-day clinical trial operations were:

- increasing work with fewer resources;
- growing amount of data needing to be captured and evaluated; and
- rising difficulties in patient recruitment.

From the survey, respondents identified the changes most impacting their day-to-day job, with 65% highlighting being asked to do more with less, 65% identifying the amount of data needing to be captured and managed and 64% flagging patient enrollment challenges. Survey respondents also indicated that the increase in required endpoints (56%), trial sites (51%), number of countries (46%) and stakeholders (45%) had an effect on their daily activities. In addition, there are challenges in deciding what data to prioritize and invest in: "It's not any and all data that's needed, but relevant, quality data," according to a report that looked at precision medicine by Newsweek Vantage.

Figure 1. Oversight Workload Volumes



Question: Is the volume of work related to oversight increasing in your clinical trials?

Base: All respondents (n=132)

Briefly, please explain why: "the volume of work related to oversight is increasing in your clinical trials"
(summary of reasons & word cloud)[1]

1. Rising regulation
(increased requirements, e.g., ICH)

2. Project management
(more stakeholder & vendor coordination)

3. Resourcing constraints
(financial & staff expertise)

4. Workload expansion
(e.g., data collection, reconciliation, queries & analysis)

5. Project complexity
(e.g., synchronization, compatibility, bureaucracy & analysis)

Question: Briefly, please explain why: "the volume of work related to oversight is increasing in your clinical trials"

Base: All respondents (n=132). [1]Note: For all respondent verbatims see "Verbatims Comments" slides18 - 20.

As shown in Figure 1, 81% of the Medidata and Informa Pharma Intelligence respondents said that they had experienced some type of increased workload related to clinical trial oversight. The main reasons given for why workloads were increasing included efforts needed to meet increasing regulatory requirements, resourcing restraints such as tight budgets and difficulties recruiting qualified personnel; increasing nature of data collection and data entry; and growing project complexity driven for example by stakeholder and vendor coordination.

The increase in volume of work for clinical trial oversight includes "more and more responsibilities in the oversight of providers. More and more expert advice on technical/scientific/medical aspects of clinical trials and more and more coordination between the different stakeholders," said a survey respondent from a small to medium-sized contract research organization (CRO).

When asked where they focus their time, almost half of respondents stated that at least 25% of their time was spent on tasks and issues with minimal impact on outcomes. One respondent indicated they are spending time on tasks that are "repetitive and of no clinical significance." When asked the reason why they spent time on tasks with minimal impact one respondent indicated this was due to "inadequacy of CRO processes" and another respondent identified "lack of understanding of what is important."

The survey also showed that only 2% of respondents claimed to have completed all their tasks and issues on time. An additional 25% of respondents completed 75–99% of tasks on time, and another 48% only completed 50–74% of tasks on time. The Medidata and Informa Pharma Intelligence survey results offer compelling evidence that study teams have more work than they can handle and need help prioritizing. Respondents are "spending time" on issues that don't have an impact on outcomes – arguably non-value add tasks – and are unable to finish their work on time. This suggests there are important issues not being addressed in a timely fashion, or even at all.

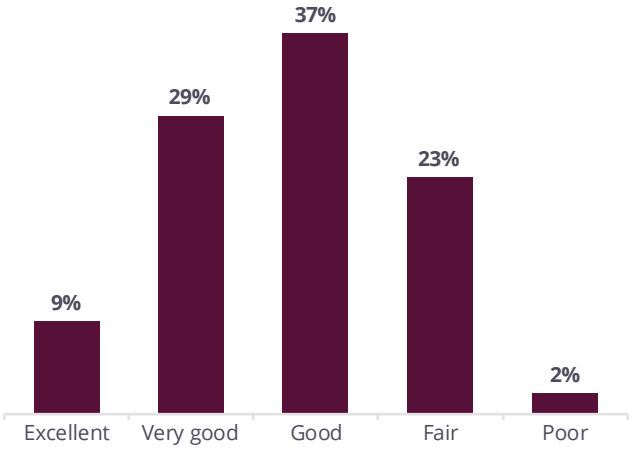
Complexity Of Project Management And Collaboration

With the growing number of vendors, contractors and other staff now involved in clinical trials, collaboration is becoming a bottleneck in the process for some organizations. As shown in Figure 2, 25% of respondents believe their collaborative ability is inadequate, and only 38% see themselves as achieving best practice. After financial constraints (16%), the largest barriers to collaboration were working in different systems (16%) and inadequate staffing levels (14%).

Increasing vendor and contractor involvement was identified by the survey respondents as a notable issue. As protocol complexity increases and different clinical trial approaches are adopted, more vendors are required to access expertise. In addition more data sources are being sought to get a better view and understanding of the patient and how they are responding to treatment. This adds to the number of stakeholders and overall difficulty of project and protocol management.

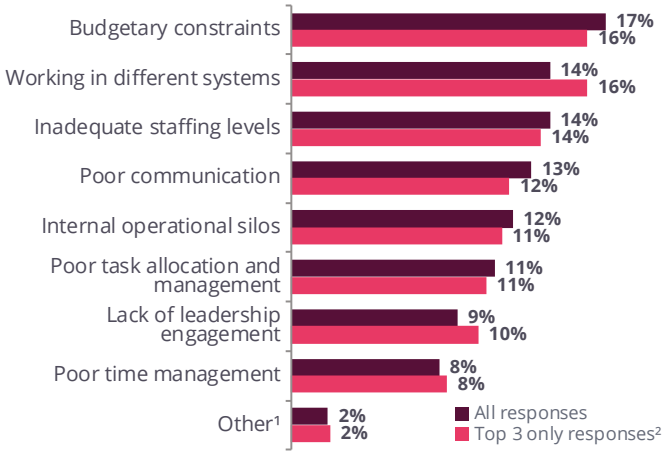
A survey respondent from a small to medium-sized contract research organization observed that: "Typically, there are more third parties than 10 to 20 years ago, documentation of oversight is more demanding, vendors utilize sub-contractors and oversight extends to them, etc."

Figure 2. Clinical Trial Collaboration



Question: How would you characterize your organization's ability to effectively collaborate across functions in clinical trials?

Base: All respondents (n=132). ¹Includes: "Fair" & "Poor."



Question: What are the primary obstacles to more effective collaboration in clinical trials? (Please select the top three.)

Base: All respondents (n=131); multiple answers permitted (n=382). ²Top 3 only responses: All respondents (n=79); multiple answers permitted (n=237). ¹Other includes: Working with academia, Use of technology, Inadequate corporate management, None, High CRA turnover, Lack of consensus because of poor data and analytics, Acceptance of third party superior knowledge and usage, Cultural differences and IT/technical issues. ²Note: question changed to "Top 3 choices" on September 13.

Data, Data And More Data

The complexities of handling and analyzing data were cited by 30% of survey respondents as a main factor interfering with effectively using trial data to assist with strategic decision-making. In particular, respondents struggled with both the number of stakeholders required to jointly review and analyze data, and with inadequate reporting and analytics. One respondent from a mid-sized biopharma company cited a number of challenging factors related to having to work with large amount of data:

"Higher complexity and vast amount of data from different data sources, the requirement to reconcile data from different vendors and datasets, more vendors and datasets mean higher risk of protocol deviations and queries, different systems to monitor and source data verification in the same clinical study make monitoring and quality checks more complex."

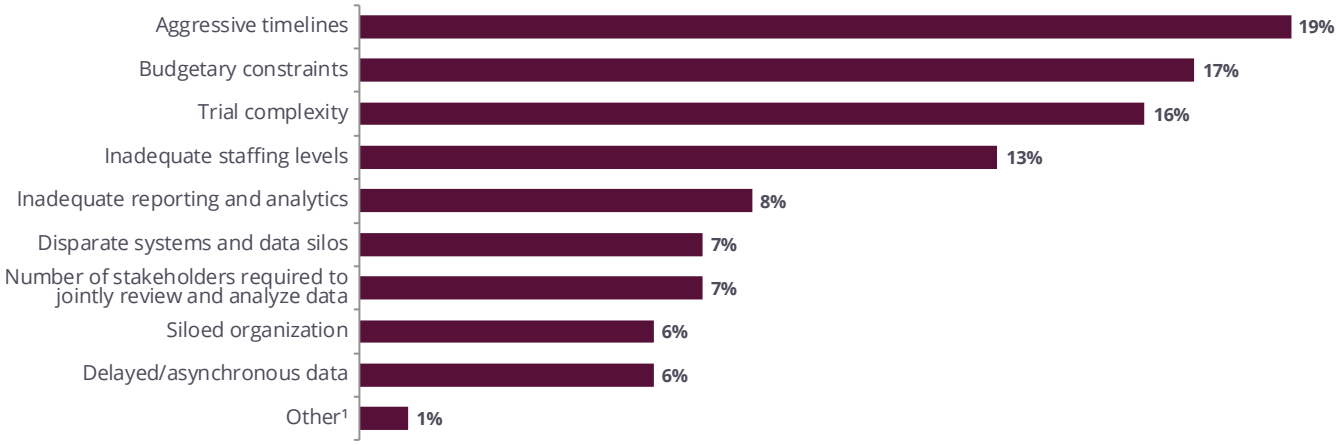
Survey participants also reported difficulties with delayed/asynchronous data and disparate systems and data silos. Organizations need to evolve to a position where data and technology solutions become key enablers of their initiatives.

A top priority for biopharmaceutical executives must be increasing investment in their IT systems. In the Newsweek Vantage report this was cited by 34% of executives – and 47% of those in large organizations – with a further 28% saying that their organizations were increasing investments in data analytics and management solutions.

Identifying Issues Quickly

The survey also found that factors interfering with strategic decision-making can hamper an organization's ability to identify issues quickly. Sixty-five percent (65%) of respondents said they did not

Figure 3. Identification of Operational Issues



Question: Which factors pose the biggest challenges in terms of identifying operational issues more quickly? (Please select the top three.)

Base: All respondents (n=132); multiple answers permitted (n=350). [1]Other includes: Working with academia, Evolution in regulatory requirements, Changes in definition of reportable events and how the information comes in and Individuals failing to take ownership for their tasks and oversight.

see themselves operating at best practice levels when it comes to identifying issues quickly.

As shown in Figure 3, aggressive timelines (19%) were cited as the biggest challenge from respondents, followed by budgetary constraints (17%) and trial complexity (16%). Respondents that felt their organization was less effective at identifying issues quickly attributed this to:

- a lack of proactivity;
- issues being difficult to identify because of complexity;
- software limitations;
- organizational bureaucracy;
- increasing workloads; and
- limited resourcing.

Coupled with tasks not getting completed on time (only 8% of respondents completed 75%+ of all tasks on time), this indicates that study teams do not have the capabilities to prioritize their workload and focus on operating effectively. This appears to be due to a lack of effective program and study management. One respondent noted: *"We have no process for issue/deviation management and no metrics to follow up on performance and quality. Recruitment is the only metric that is followed closely."*

Context And Understanding

The Medidata and Informa Pharma Intelligence survey results indicate that professionals in clinical operations are struggling with an overload of tasks and information. There are more vendors, sites, people and components of a trial requiring oversight, and as a result clinical operations staff struggle to complete their tasks on time. The survey reveals there are insufficient resources to provide high-quality oversight, that too much time is spent on non-impactful tasks and that the tasks being undertaken are not completed on time.

Results show respondents are looking for a better understanding of which tasks are important to address, so they can prioritize their workload. One respondent went so far as to say there was a "lack of understanding as to what is important/ impactful/concerning." Without placing these tasks into a broader context, all tasks are treated as equally important to complete, and as result the most important issues don't receive the necessary priority. With better insights into what is happening within their trials, respondents can better spend their time on activities that directly and meaningfully connect with trial outcomes.

By reviewing within the overall clinical trial, respondents would be able to review all issues at the site, country and trial level. With this context clinical operations staff can better identify high priority and systemic issues for resolution. Tasks and issues can be reviewed side by side and prioritized relative to one another. For example, high-screen failure rates at one site may indicate a training issue. However high screen failure rates at multiple sites may indicate a more fundamental problem with the protocol and inclusion/ exclusion criteria. Placing these issues in context allows respondents to better assess how to approach these issues.

Communication And Silos

Resources are unlikely to scale with increasing trial complexity and in some cases may be required to decrease. The big opportunity, as Newsweek Vantage points out, is to be found in using digital platforms to connect people in new ways, enable greater efficiency and achieve better evidence generation. It noted that to take these steps requires investing in bigger, more sophisticated systems, which is not easy to achieve for businesses that are making decisions in silos with limited communication.

In order to seize this opportunity and succeed, there are steps organizations can take. Using digital platforms can increase communication and improve the collaborative efforts needed to resolve cross-functional issues in a timely manner. There is significant benefit to be gained from breaking down silos and opening lines of communication with the purpose of achieving more effective collaboration.

While appropriate skills and abilities are required for efficient and smart clinical trial oversight, it is also important to emphasize relevant technologies and systems. Data and technology solutions, particularly advanced clinical trial management systems (CTMS) can become key enablers of initiatives and rationalize synchronization and assist data assimilation.

Early Remediation

Respondents described processes and systems that were reactive in nature, with problems and issues identified and addressed after the fact. They indicated a limited ability to proactively identify issues and address them early. Clinical operations staff indicated a desire to identify the top issues rapidly and to quickly take actions necessary to resolve them. Instead time is spent on repetitive and low value add tasks.

To address these challenges it is important to consider adoption of a unified platform that can provide the foundation for remediating issues quickly. In addition to eliminating many of the low value tasks related to duplicate data entry and reconciliation, a unified platform can accelerate the collection and review of data and tasks. Issues can be identified in a fraction of the time and resolved

quickly. Clinical operations staff can reduce and even eliminate the time spent on gathering and aggregating information across multiple people and systems, and instead focus on identifying, prioritizing and quickly resolving the top issues.

Conclusion

Within a rapidly changing clinical environment, the complexities of running clinical trials and their oversight will only increase. In this scenario a new technology-based model is needed to adjust to the realities and demands of clinical trials both now and in the months and years to come. Technology solutions, such as a next-generation Clinical Trial Management System, can address the needs of clinical operations staff who need help with increasing workloads and declining resources. By providing greater context on the issues at hand, improving collaboration among the increasing number of participants in a trial and proactively and quickly identifying and remediating problems before they become larger issues, technology can play a critical role in improving the experience of clinical operations staff.

Resources:

[1] Source: https://www.ajmc.com/newsroom/5-things-about-the-orphan-drug-act. Accessed November 24, 2019.

[2] Source: https://clinicaltrials.gov/ct2/resources/trends#RegisteredStudiesOverTime

[3] Source: https://static1.squarespace.com/static/5a9eb0c8e2ccd1158288d8dc/t/5b4de76e352f53bd7a416e1b/1531832174796/julaug-summary.pdf