Dealing with Data

More and more pharmaceutical companies are seeking alternate solutions to maintaining control and oversight of clinical trials, while looking for cost reduction strategies that can foster smarter upfront management of study budgets

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The clinical research market is focusing its attention on a new challenge: a risk-based approach to operations. On 24th August 2011, the FDA released for comments a new guidance document supporting a new risk-based approach to monitoring "Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring" (2). The guidance is intended to describe alternate strategies for monitoring that reflect a "modern, risk-based approach that focuses on critical study parameters and relies on a combination of monitoring activities to oversee a study effectively, the guidance specifically encourages greater use of centralised monitoring methods where appropriate" (3).

Current FDA and IDE regulations that obligate sponsors to oversee their clinical trials include 21 CFR 312.50 and 812.40, which stipulate that the sponsor is responsible for ensuring proper monitoring of investigation, and 21 CFR 812.25(e), which requires written monitoring of procedures. These are not specific about how sponsors should conduct monitoring. The standard "on-site" monitoring visit is an in-person evaluation carried out by sponsor personnel or representative at the site to identify data entry errors and missing data in source records and case report forms, assess compliance with protocol, test article accountability, and assess investigator supervision.

Centralised monitoring is a remote evaluation carried out by sponsor personnel or representatives at a location other than the site. Centralised monitoring encompasses standard checks of range, consistency, completeness of data; identification of unusual distribution of data; and checks related to compliance with the protocol. It also includes identification of higher risk sites to target on-site monitoring and routine review of data in real time.

There is currently a wide range of monitoring practices based on regular, often frequent site visits with up to 100 per cent source data verification. However, although this regime may seem robust, it is often not commensurate with risks and does not optimally address the most significant risks to trial integrity, particularly systemic errors. Furthermore, such a regime is resource-intensive. Accordingly, the FDA guidance was intended both to improve the effectiveness of monitoring and to reassure the pharmaceutical industry of the FDA's support of alternative approaches.

Monitoring as a Component of Risk Management

The goal of the guidance is to make clear that sponsors can use a variety of approaches to fulfil monitoring responsibilities, since 'no single approach to monitoring is appropriate or necessary for every clinical trial.' This is consistent with the notion of 'adaptive' as the approach should adapt to the needs of each particular trial.

Therefore, the guidance intends to assist sponsors in developing risk-based monitoring strategies and plans that focus on critical study parameters. It also encourages a combination of monitoring activities with greater reliance on centralised monitoring practices, where appropriate. In order to achieve this, companies should first conduct a risk assessment to identify and evaluate risks associated with critical study data and processes. Secondly, by taking into account the results of the risk assessment, a monitoring plan tailored to the precise needs of the trial can be defined.

Monitoring becomes a component of the quality risk management strategy applied through: planning – to identify quality objectives, relevant metrics and risks to quality standards; study conduct; measuring or monitoring results; and finally through responding to deviation.

From Theory To Practice

Time to market has always been a critical driver in the development of the clinical trials programme, but increasing competition in the pharmaceutical market is driving complexity in the design and conduct of clinical trials. Previous papers published focused on adaptive trial designs and the importance of electronic data capture (EDC) (4).

Adaptive trial designs will help reduce the lack of success in clinical research due to inappropriate sized trials, with a compression and merging of the standard clinical research phases. However, clinical operations still largely rely on systems that have not been optimised for real-time learning. The time has come for the design and application of integrated systems, facilitating real-time learning and near real-time decision making at a large scale.

Oversight Tools in a Standard Clinical Trial Environment

Clinical trials are increasing in complexity and this is reflected in the last five years massive engagement of 'central systems' to improve the management of operations.

In a standard modern clinical trial, the sponsor or CRO project manager usually deals with:

- Laboratory data (central laboratories)
- Randomisation (IwRS)
- Clinical trial supplies management (IwRS)
- Monitoring systems for primary efficacy variable and central reading (ECG, spirometry, imaging)
- Clinical trial management systems (CTMS)
- EDC (electronic data management eCRF) systems

Despite centralised systems improving data monitoring during the course of the study, current off-the-shelf products often lack flexibility to adapt to different trial designs and/or operations and the various databases involved cannot be integrated.

This lack of integration means that trial data can only be monitored through periodic (almost daily) access to up to five different e-systems to check the status of study subjects/activities. In addition to this, each one of these systems often asks for the same set of data (such as subjects and demography), which are repeatedly entered in each system. Multiple reporting of same data triggers an exponential probability of mistakes.

From IT to I²T

Data Management systems already deliver a good process for the resolution of discrepancies in trial data through periodic reconciliation between the different systems within the study database. But what about operations? Does an alternative exist which can provide project managers with the 360-degree view of the study status required to implement adaptive operations? Has a system been developed which provides a common platform interfaced and 'dialoguing' with all central systems used in the study? The answer is yes, the possibility exists.

Web-based platforms for the management of clinical trials have been in developments since 2008, which can be fully integrated with other central systems and databases. Integration is achieved through the following steps:

- Selection of data for system integration (user requirements) and definition of data format with the central service provider
- Definition of data transfer form through testing with dummy files
- Verification of data integration process (validation)
- Production (live integration with periodic data transfer into the specific project screenshots)

Tests and further real-life case studies executed until now confirm the added value (positive user feedback) of such an integrated platform. The application of an integrated platform gives the project manager, and other study team members, the possibility to access cumulative real-time data related to parameters such as subject status (progress), laboratory assessments performed during the study and shipment (test drug) status, all of which are sourced directly from the relevant 'parent systems' (laboratory, IwRS, other central systems). This ensures real-time data and reduces the number of discrepancies caused by multiple data entry.

In addition, raw data sourced from these systems could be used for *ad hoc* reporting defined at the beginning of the study to create: shipments (test drugs) status reports; patients progress reports; cumulative recruitment graphs; cumulative and site-specific recruitment graphs (bar graphs actual versus expected); country and site-specific performance metrics (screening failure rate, withdrawal rate); cumulative study metrics (global screening failure rate, withdrawal rate); monitoring visits schedule (planned versus actual); and laboratory assessments reports.

All of these reports can be downloaded as pdf files or extracted in Excel spreadsheets for status reports or other uses. These reports provide the basis by which the project manager can implement an effective adaptive operations approach to each trial.

The Added Value of Integrated Systems

eCRF Completion Reports
Standard eCRF completion reports (for example, number of eCRF pages

populated versus scheduled) in most current EDC systems are stand-alone documents. These standard reports do not usually link the pages populated to the actual progress (visits performed) of subjects enrolled in the study. In this way they only provide a generic 'completion' metrics versus the total number of eCRF pages expected for the total number of subjects to be enrolled in the study. As an example, perhaps the report details that 10 per cent of total pages are populated. Without integration of actual visit status (for example, from IWRS data), the project manager cannot deduce precisely the status of eCRF completion. Indeed, it could be that completion is 100 per cent, relative to actual subject progress (first protocol visits performed) into the study, or the situation could be much more critical. Such integrated information is essential for the project managers of operations or data management during the hectic moments of data cleaning to database (DB) lock, with figures changing day-by-day and hour-by-hour, following data entry performed remotely at investigational sites.

Laboratory Reports

Single laboratory reports cannot support the study medical team (Medical Monitor) to identify any trends in lab parameters, potentially linked to the subjects/patients exposure to the study drugs. Data transferred from the central laboratory database can be used to create cumulative or subject/patient-specific graphs to identify any expected trend in any parameters of the lab panel, or to compare any single test/subject at a determined visit versus that entire dataset for that parameter. This would trigger the early detection of any safety issues and its potential correlation to the study drug, fostering real-time decision by the clinical and safety teams about premature termination of the study, or potential amendments to the study protocol aimed to address new information.

Enrolment Reports

Drilling down to country and site level enrolment allows the clinical team to detect any specific negative or positive trend coming from that country or that site. These data could be further explored and considered to understand and identify reasons for better performance compared to initial forecasting (local clinical practice, local population, access to reimbursed medications), as well as to understand and identify reasons for worse performance compared to initial forecasting (untold competitive studies, subjects/patients switching to other concurrent trials, resource problems in study conduct). It is also possible to use recruitment data (country and site level) for further comparison and use through investigators database in strategic feasibilities, to streamline sites selection and geographical distributions. Finally, enrolment reports can adapt monitoring plans to early (pre-randomisation, whenever applicable) visits and increased frequency for top-recruitment sites.

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Queries Status Reports

These can be considered as surrogate indicators of quality in operations and data management activities. At site level, sites with the highest number of queries still opened can be detected and followed more carefully to avoid delays in data cleaning. These reports also identify time to queries resolution. At data management level, top recurrent queries are a very meaningful metric to identify misunderstandings by the clinical staff in data entry and/or clinical data interpretation. This can be an indicator for further changes of the eCRF structure, or to provide more instructions to investigational sites to clarify grey areas in data collection. Through newsletter or updated manuals, a new information can be spread over all the investigational sites to avoid any reccurrence.

These are only examples of the power of data integration in trial management oversight and reporting. In the future, integrated information technology will become more commonplace and reduce the risk of project managers' eyes crossing after less than 30 minutes of data comparison and discrepancies checks between five different platforms. This is the power of integration. Multiple source data which feeds into one management and reporting system can provide a fully integrated 360-degree overview of project status.

Risk Management and Adaptive Operations Through I²T

Monitoring is a key component of risk management in clinical trials and adaptive operations. The computing power of modern IT platforms, upgraded with systems integration applications, can provide useful tools and metrics. Professional experience and clinical research expertise is still critical to identifying meaningful metrics for the oversight of clinical research projects.

In the last five years, a variety of reporting features have been explored to elucidate the optimal indicators for activity status updates (timelines/quality) during the study. The approach proved to be effective, giving sponsors

the possibility to access multiple reporting in one platform, merging data periodically transferred from other vendors, DBs (central laboratories, IwRS, EDC systems). This breaks through the boundaries of stand-alone systems, reducing the time needed for reactions in the management of clinical trials.

This allows companies to effectively drill down into key individual site performance and subject progress metrics in the evaluation of performance and in the identification of critical situations (such as recruitment, number of deviations, screening failure and withdrawal rate, eCRF completion and active queries status) and issues to be promptly addressed and corrected. Resources are then effectively targeted on areas which most threaten subject safety, trial quality and integrity. This approach is consistent with the recommendation of the FDA guidance and the MHRA recommendations and this is a real-life example of the risk-based approach in the management of clinical research projects.

Conclusion

The concept of risk analysis and mitigation strategy (risk-based approach) has spread over all the phases of clinical research down to clinical trial operations. The increasing complexity of clinical trials and the condensation and merging of the former phases of clinical research in new adaptive clinical trial designs asks for new management models beyond standard monitoring practices. Technology and computing power resulted in the massive development and application of new tools in clinical research to support project management. Conversely, the use of multiple e-systems caused data redundancy and additional efforts to resolve discrepancies and the necessity of more resources (time and project team infrastructure) to access systems and check progress reports. If cost control and optimisation is at the basis of this revolution, the current pattern does not seem to be the best option, because this is not balanced by an increased use of resources (operations and management) at pharmaceutical sponsors and CROs level for project oversight.

While cloud computing and synchronisation technology is revolutionising the world of communication and IT with the release of off-the-shelf products, the scope of application is still extremely limited in clinical research, even though this is one of the market sectors which would benefit more. Stand-alone systems still represent a limit in information sharing and data pooling in clinical trial operations and new platforms need to be purposely programmed to acquire data from multiple systems (databases), integrate data and develop *ad hoc* reports, and to present a clear picture of the project status at activities level.

In a risk-based approach, even an early identification of the potential risks and their impact on planning phases then needs to be supported by active monitoring systems to check the frequency of occurrence and any trends. An integrated clinical research platform has proved to be a good solution to merge data sourced from various external systems/applications, to combine them and to create performance and quality indicators for risk-management, all available in a single tool. Integrated solutions for clinical research will help in risk and resource management but they will never replace the field-based operations. Although this integrated approach supports the effective delivery of adaptive operations, we must recognise that the daily work and expertise of CRAs and clinical staff remains at the heart of our efforts to ensure the safety of patients and the reliability of data.

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