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Strategic Resourcing
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INNOVATIONS FOR RAPID DATABASE LOCK

From PharmaNet/i3's Think Tank

Locking a clinical trial database rapidly is a priority for both sponsors and their CRO partners. A rapid database lock is a primary determinant of timely study completion and can materially impact study cost, the potential NDA submission and patent longevity. The need for immediate access to clean data throughout the course of the study is imperative. However, frequently, large numbers of queries near the end of a study delay the database lock.

To expedite the process leading up to the database lock, improvements are required. In November 2011, ***PharmaNet/i3*** engaged clinical research professionals in a discussion about potential process improvements during a ***Think Tank*** – a forum in which experts discuss and provide advice on specific challenges facing their work. The ***Think Tank***'s topic was: **How can sponsors and CROs successfully lock a database within twenty four hours of the LPLV (Last patient, Last visit) of a clinical study?**

The day-long interactive ***Think Tank*** was held near ***PharmaNet/i3***'s offices in Princeton, New Jersey, and attracted participants from a variety of US pharmaceutical companies. Those in attendance held positions in which they had the ability to make decisions, streamline processes, implement technology, and develop new methods to drive actionable solutions. Most importantly, all participants were closely involved with the database lock process; some were CRAs who held responsibilities for ensuring data was collected in a timely fashion throughout a trial while others were Data Managers who cleansed data for analysis.

The ***Think Tank*** promised participants a day of discussions related to the development of viable strategies for rapid database locks that the attendees could deploy in their own organizations. Certain recommendations were excluded from this white paper as the recommendations required industry-wide involvement and process changes. Participants were separated into four groups to facilitate the brainstorming process and were tasked with first identifying bottlenecks and delays, and then developing and prioritizing solutions.

The discussions focused on several process areas that the groups believed could be re-engineered to minimize the time- to-database lock. Issues and recommendations were categorized into four areas in which there was an opportunity for meaningful improvement: Business Processes, Communications, Technology and Investigator Site/CRA interactions. The summary of the discussion is below.

BUSINESS PROCESSES

The Business Process category included a variety of areas involved with planning the study, process management, forms development, resource allocation and training, i.e., activities critical at the beginning of any study. In these categories, the groups believed that there were specific activities that needed more attention in order to ensure that they were done correctly early in the study.

Planning

Better planning was identified as a priority. It was unanimously agreed that earlier and more thorough planning and process management were needed in all aspects of the study.

It was suggested that better protocol design, feasibility, and preparation could improve downstream performance by avoiding some of the primary causes of queries. A more robust design could be produced with the use of a protocol/study design and feasibility committee, which included end users. This would allow the team to "pre-test" the study design and forms for ease of use before deployment and help avoid the misunderstandings that resulted in queries later in the study.

Case Report Form (CRF) design was also considered a critical success factor for every project. By developing a more detailed protocol/study and a user-friendly companion CRF, there was evidence that human errors could be avoided. It is these errors - frequently submitted close to the study's end - that can result in the submission of large amounts of data which needs to be cleaned that delays database lock.

Resource Allocation

Resource allocation and management were also identified as critical to the timely database lock. From the

perspective of monitor visits, visits may not always be timely and remote monitoring may not be allowed for the study. Certain studies may call for a number of visits that don't fit with the actual need of the sites. To address these issues related to resources, the teams suggested the development of a flexible monitoring plan and a pool of reserve CRAs. The ability to monitor sites remotely could also add flexibility to the process and ensure the timely identification and resolution of queries.

Data managers are often assigned multiple projects and are not dedicated to a specific study until database lock is near. Identifying resources to perform reconciliation throughout each part of the process can maintain a steady flow of data and avoid the bolus of queries that arrive at a study's end, and the resulting delay in database lock.

Lack of time was generally cited as an obstacle to success: time to plan appropriately; time for sufficient training; time to communicate/coordinate with other groups; time to complete tasks when individuals are spread over several projects. Issues may be identified late in the process because the CRF is completed late, too few edit checks occur so that ill-conceived specifications are not identified, or the data manager has missed a critical problem. The ***Think Tank*** teams recommended enhanced resource planning to adequately account for the time required for training, communications and task completion and ensure realistic expectations for a timely database lock.

Training

Training was identified as one of the most critical aspects of the start-up of a project. Many aspects of training were discussed including regulatory, clinical research, study specific training, and the ongoing training and corrective action communications between monitors and their sites.

Training materials need to be available to support training sessions so that investigators have a reference guide throughout the study. This can help to avoid poor specificity in communicating queries and questions.

The lack of expertise or formal education in clinical research at certain sites makes meaningful training more critical. Training sessions developed solely to meet regulatory requirements are not entirely adequate to address this issue. CRA-based training sessions must thoughtfully outline expectations, roles, and responsibilities, teach sites to enter data onto the CRF/eCRF immediately and resolve queries promptly.

However, during training of the project team and investigators, it is critical to emphasize clear accountability for project roles and data in order to ensure the successful start-up and completion of the study.

Project teams should also be informed how performance will be tracked and what metrics will be reported against standards and/or objectives. Clear accountability and performance tracking adds transparency and can motivate the sites for continuous process improvements. It was also suggested that training be sequenced to align with the "real life" progress of a study for the benefit of both CRA and site.

All vendors involved in the study also need to be included in early training sessions so that they can plan appropriately. Printed guides or supporting material should be clearly written and available at the time of the training.

While it may seem obvious, "clean" data should be defined and investigator sites reminded of the importance of submitting their data on time. Obtaining a commitment to fulfill this requirement and tracking their performance is important. Special attention should also be paid to the early reconciliation of serious adverse events, which are often performed too close to database lock.

In addition to a comprehensive training plan for investigator sites, studies can also benefit from a contingency plan to address turnover at the investigator site and train replacement staff. Answering questions promptly throughout the study can also resolve the issue of turnover at a site where the initial site contact is no longer there or the replacement is unfamiliar with the particular issue requiring clarification. Investigator site personnel who need to write queries should be trained on how best to do so and with the necessary level of detail, balancing specificity and rigidity. Extra training on query writing can help reduce the number of unresolved queries that must be reissued, thus reducing delays In database lock.

It was agreed that there was a wide variation in experience levels with Electronic Data Capture (EDC) systems and software. In certain cases, a fear of technology lengthened the learning curve and can lead to a lack of commitment at the site level, which can affect time to database lock. Many EDC systems are not user-friendly or MAC-compatible which makes training so critical to the success of any project using an EDC system. It was believed that additional training could help

remedy a potential fear of technology and delays in data entry.

COMMUNICATION

The area of communications offered some of the biggest opportunities to accelerate the study database lock. There was a consensus across the brainstorming groups that open communication among all parties did not always occur and role-based silos frequently prevent many functional areas from working together as an integrated team. This often led to a host of downstream problems from late issue identification to missed interim deadlines.

The role of timely communications became even more important when goals, priorities, or timelines change; turnaround expectations were unrealistic or not communicated; or the impact of missed deadlines was not explained or understood.

Additionally, a lack of clarity was noted as a challenge. The same query may be worded one way by the CRO and in another way by the sponsor or site, creating an unnecessary communication loop to understand and answer the same question. Standards need to be well enunciated or understood, and supported with adequate training materials.

Expectations should be established, goals need to be defined, and timelines should be communicated to all members of the project team during the kickoff meeting so that each party has the same understanding. Investigator site personnel, CRO staff, sponsor representatives and third party vendors each need to have an understanding of their roles, responsibilities, and impact on the process. Additionally, each of the parties must be accountable for decision making in alignment with their roles. An appropriate feedback and performance review process as related to the study sites and study goals can also help to keep everyone on track.

TECHNOLOGY

Issues with technology fell into three main areas: the designated EDC technology, the system's reliability, capabilities and performance, and the use of customization to enhance study performance.

The System

It was cited that often the available technology does not match the needs of the study. A sponsor may require use of a particular system or cost constraints may limit system options. In other cases, the use of multiple systems led to confusion or issues with compatibility related to different standards. It was mentioned that there remained a need for enhanced EDC adoption.

Real-time standardized reports are typically not available and due to role-based access, sites cannot run reports to examine the details for their own sites. With site managers not having immediate data access or the ability to evaluate site performance to ensure it aligns with the key performance indicators (KPIs) for the study, it is more difficult to identify potential issues and address them autonomously. This lack of visibility increases the burden of the CRA and adds time and cost to the process.

Reliability/Capability

Servers have capacity issues as well as firewall issues. The teams reported that certain system updates may hamper the ability of individuals to perform tasks, such as queries. In certain situations, passwords expire frequently or without reminder, causing last minute delays and frustration for site staff who need new log-in credentials. When volume is too high or too many users are on the system, multiple service interruptions means data cannot be reviewed in a timely manner.

Customization

Electronic data is not available in a global format (CSDTM or SDTM) and individual customization usually is needed. Whichever system is used, the electronic CRF needs to be designed so it can flexibly meet the specific needs of the study. More edit checks could help to alert users earlier of potential queries.

SITE / CRA

Poor site selection is a root cause for many of the issues in this category. It is important to have clear selection criteria, select experienced sites and leverage a database with previous performance statistics.

Like many employees in the industry today, site personnel must do more with fewer resources, which may explain why sites do not resolve queries efficiently. However, lack of query resolution is also is due to the sites' receipt of too many queries at one time and their heavy enrollment near the end of the study. This peak in workload can overburden the site staff and they have difficulty accommodating monitor visits. It is important to create a discipline across the team to address queries earlier to avoid a bolus of queries at the end. Project teams need to streamline data review, conduct standard edit checks, and train staff to write and make self-evident corrections. Source data verification should not be on the

site's critical path because sites do not feel the priority of data lock. Their primary goal is patient care and this needs to be considered in all interactions.

There is no industry standard to calculate the amount of time a site should budget to perform all study-related duties, so time and prioritization issues arise frequently for CRAs. Because the CRA may not have adequate time to spend onsite, a close relationship cannot be developed which can result in a lack of strategic collaboration between site and CRA. However, it is this relationship that can streamline communications during the study and increase the level of understanding in the CRA-site relationship.

CRAs need to have adequate time to establish standards, reinforce, follow-up and measure site performance and have a vehicle to report this to the site staff. the problems of sites opening enrollment late and not closing on time could avoided with more frequent communication, better planning, and incentives for enrollment.

Better communication can ensure sites are notified when studies are amended or when changes take place. The entire communications process should be transparent and the sites considered and treated as an important partner with a shared objective for a successful, compliant and safe clinical study.

Top Solutions by Working Groups for Achieving a 24-hour Database Lock

Group A

- Incent data quality
- Continuously clean/lock data
- Plan and communicate
- Embrace EDC/EMR adoption/integration
- Conduct long-term planning through strategic partnerships
- Pay attention to site selection/professionalism.
- Develop metrics and make them transparent and available

Group B

- Challenge paradigm of CRF as an intermediary step in data collection
- Encourage industry standardization of data collection tools
- Develop a protocol/study design and feasibility committee to include end users
- Create a sequence of training to align with the "real life" - CRA-SIV-Enroll-IM
- Develop one form for SAEs across clinical and safety databases
- Provide reporting access for EDC to sites so they can look at their own metrics
- Develop industry cross-functional user council to provide input on minimal standards on system/reporting requirements

Group C

- Conduct regular, interim reviews to ensure that they match to KPI and adjust as needed
- Communicate expectations early
    - Define quality and "clean" data
    - Define roles
    - Communicate goals
    - Make certain that protocol is understood
- Provide early SAP with review by all stakeholders; specify what each stakeholder needs to review
- Conduct site selection to enable success; set expectations at the start, provide ongoing feedback, know the site history/performance

Group D

- Plan to prevent the bolus of queries at the end, and plan for periodic "waves of data" during the course of the study
- Streamline data review. Conduct standard edit checks, train staff to write and make self-evident corrections
- Program more edits into the system to reduce time; conduct more frequent/earlier review of the data
- Develop a flexible monitoring plan with a pool of reserve CRAs; allow remote monitoring
- Enable the source data to go directly into the EDC (BP, ECG, Labs, etc.)
- Define a lower SDV—collect only what you want; conduct adaptive monitoring.

About PharmaNet/i3

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