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Using Study Metrics to Monitor Several Aspects of Clinical Studies Virtually Real-time

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ABSTRACT

Monitoring the operational performance of the different functional areas of clinical studies can be cumbersome and time-consuming. Furthermore, not having the information needed to make informed decisions can be disadvantageous for managers and members of the team. Therefore, there is an incentive to establish a way of monitoring study metrics at the start of the study and monitor progress on an ongoing basis. This paper will present some of the metrics that can be implemented to monitor progress, virtually real-time, from different functional areas of a clinical study such as clinical operations, data management, safety, and biostatistics. The use of these metrics should enable teams to increase productivity, work smarter, and make better decisions.

INTRODUCTION

While the concept of using metrics to guide strategic planning and decision-making does not appear to be a new concept in industries such as manufacturing, information technology, and academia, the lack of literature on the use of metrics in clinical research, particularly in the pharmaceutical or biotech industries, indicates that this practice is not well-known or common practice within the clinical research industry. The clinical research industry can benefit from this practice as metrics can be used as tools for supporting actions that allow studies to evolve toward successful outcomes, promote continuous improvement, and enable strategic decision making. The principal objective for the implementation of study metrics in clinical research is to promote the quality of study data. However, to achieve this objective, the metrics should be study specific, quickly understood and broadly accepted by the various stakeholders. Stakeholders can include team members from different functional areas, including clinical operations, data management, safety monitoring, biostatistics, and programming. Each stakeholder should have the opportunity to provide input into the creation and definition of different metrics. With this framework in mind, this paper presents and briefly discusses a non-exhaustive list of metrics that can be implemented early on in the study to monitor progress and performance from different functional areas of a clinical study. While the majority of the study metrics discussed in this paper are at the site level, some of the metrics presented are at the subject level. Furthermore, a brief discussion of the origin of data sources that can be used for the metrics is included.

SITE LEVEL METRICS

By looking at the metrics at a site level, an emphasis is placed on maintaining the overall study quality. This view provides a macro-level perspective on the progress of the study and allows team members to identify and mitigate potential problems by looking at variability across sites. The following are some of the site-level metrics that can be implemented and monitored for each of the functional areas.

CLINICAL OPERATIONS

Clinical operations are a critical component in any clinical study. The clinical operations team is involved in a study from start-up to close-out. They are tasked with ensuring proper study planning, conduct, patient safety, and data quality. Some of the services they provide include site identification, qualification, and selection; patient recruitment and retention; site monitoring and management, among others.

Table 1 provides some of the metrics that can be implemented to monitor the progress of site selection, qualification, and monitoring. By looking at the number of site qualification and initiation visits to-date, and using the total number of expected visits for each category, the percentage completed can be calculated at a given time point to monitor some of the site start-up activities. More importantly, most of the metrics presented in this table can help the Clinical Team Lead (CTL) make informed decisions on how to allocate resources. Tracking the performance of interim monitoring visits (IMV) throughout the length of the clinical trial can be done by looking at the number of IMV as a portion of expected total IMVs. Moreover, by looking at the date of the next scheduled IMV and the total number of case report form (CRF) pages to be

verified, the CTL can estimate the number of Clinical Research Associates (CRA) that are needed at the site and/or number of days the CRA needs to be at the site to perform the verification duties. Similarly, by looking at the projected date for last patient/last visit (LPLV) at each site, the CTL can work with the CRAs on the logistics of scheduling the close-out visits.

Table 1. Site selection, qualification, and monitoring

Metric	Description
1. Site Qualification Visits Completed*	*Number of site qualification visits completed to-date*
2. Site Initiation Visits Completed*	*Number of site initiation visits completed to-date*
3. Interim Monitoring Visits Completed*	*Number of interim monitoring visits completed by CRA to-date*
a) Next Scheduled IMV	*The projected date for next IMV*
1. Number of pages to be verified at next IMV	*Number of pages to be verified by CRA at next IMV*
2. Number of days at the site	*Number of days CRA spends at the site*
b) Projected Last Patient/Last Visit	*Project date of last patient/last visit at the site. This date is projected by using the visit windows in the protocol*
1. LPLV at "X"	*Where X can be a time point of interest from the protocol*
4. Close-out Visits Completed*	*Number of close-out visits completed to-date*

Note: * indicates that percentages are calculated by dividing by the total expected number of visits for each category

Table 2 presents some of the metrics that can be implemented to monitor the progress of patient enrollment, retention, and management. Enrollment activity can be captured by the number of randomized patients, screen failures, and randomized/not dosed. Alternatively, the team may choose to report the total number of enrolled subject. Moreover, if applicable, these metrics can be broken down by cohorts. Patient retention rate can be captured by looking at the number of patients who discontinued or withdrew from the study early as a percentage of randomized subjects. This metric is particularly important as it can provide an early sign of whether or not the number of patients needed to achieve statistical power (if mentioned in the protocol) can be attained given the rate of discontinuation. This early sign allows the team to take corrective measures to mitigate retention problems. Furthermore, by looking into the reasons for discontinuation and time to discontinuation, the team can try to pinpoint the underlying cause(s) for patient discontinuation.

Table 2. Patient enrollment, retention, and management

Metric	Description
1. Patients Randomized	*Number of patients randomized to-date*
a) Screen Failures	*Number screen failures to-date*
b) Randomized/Not Dosed	*Number patients who were randomized, but not treated*
2. Patients Discontinued/Withdrawn	Number of patients who discontinued/withdrew from the study early
a) Reason for Discontinuation	*Reasons for discontinuation (as in eCRF) presented in descending order of frequency*
b) Time to Discontinuation	*Time to discontinuation presented in time intervals (as appropriate for study)*
3. Patients in Efficacy Population	*Number of patients who have evaluable data for the study end-point (not necessary is efficacy is not being evaluated)*
4. Patients Completed All Visits	*Number patients who completed all scheduled visits (as mentioned in the protocol)*
5. Number of Protocol Deviations (PD)	*Total number of PDs recorded to-date. Each PD can be presented in descending order of frequency*
6. Number of Patients with PDs	*The number of patients with PDs. Each patient can have more than one deviation*

Note: eCRF = Electronic Case Report Form

Tracking the number and types of protocol deviations is often crucial in clinical studies. Therefore, the team may choose to look at the deviations as the total frequency of deviations at the site and the number of patients with deviations. The individual deviations recorded at the site can be reported as subcategories under each category, in descending order of frequency. For the number of patients with deviations category, the team should be aware that each patient can have more than one deviation.

DATA MANAGEMENT

Data management (DM) is a critical phase in clinical research, which leads to the creation of high-quality and reliable data. Similarly to team members from clinical operations, team members from DM are actively involved from study start-up to close-out. They are tasked with the CRF design, database design, data validation, manual data review and reconciliation, medical coding, and database locking.

Table 3 illustrates some of the metrics that can be used by DM to monitor and manage the progress with data entry, validation, queries, and database locking. By monitoring the progress of data entry, the team members can determine the status of CRF page completion and missing pages. While the number of missing pages is not included in the table, this number can be determined by subtracting the number of pages entered from the number of pages expected. The metrics for data queries can help team members track the status of data queries and data queries that are not resolved within specified time limits. By tracking the duration of queries open, members of the DM team can follow up with sites on the specific data queries that have not been resolved within a specified time window. Additionally, while not included in the table, the team may choose to include metrics to monitor the cleanliness of the study data by tracking metrics for data validation activities such as edit checks, generally specified in the Data Validation Plan.

Table 3. Data management metrics

Metric	Description
7. CRF Data Entry*	
a) Pages Entered	*Number of pages entered*
b) Pages Verified	*Number of pages verified*
c) Pages Ready for Freeze	*Number of pages ready for freeze*
d) Pages Frozen	*Number of pages frozen*
e) Pages Signed	*Number of pages signed by Principal Investigator*
f) Pages Locked	*Number of pages locked*
8. Total Queries Issued	*Number of queries issued to-date*
a) Queries Answered, not Closed	*Number of queries that have been answered, but not closed*
b) Queries Closed	*Number of queries closed*
c) Queries Open	*Number of queries that are still outstanding*
9. Duration of Queries Open	*The duration of open queries, which can be specified as ranges such as 0-7 Days, 8-14 Days, 15-21 Days, 22+ Days. These ranges can be tailored to fit the study specifics*

Note: * captures data entered (to-date) by site staff into the Electronic Data Capture (EDC) system

SAFETY MONITORING

Monitoring patient safety throughout the study is a critical component in clinical trials. The safety monitoring team, which generally consist of a medical monitor and a safety monitor, ensure that patient safety and compliance with the requirements of the study protocol are always at the forefront by following the established standards (e.g., Guidelines set by the International Conference on Harmonization Good Clinical Practice) in order to protect the rights, safety and well-being of participants (Yao et al, 2013).

Table 4 shows some of the metrics that the team can implement to monitor the safety of patients throughout the study. While reporting the total number AEs by site may suffice, calculating a percentage based on the number of overall visits at the site can provide a way to monitor variability across sites. While not presented in the table, the team may also be interested in looking at the types of AEs that are being reported. The list may be limited to reporting a limited number of most frequent AEs. When looking at the types of AEs, the Safety team may get an idea for whether there are unusual or unexpected safety concerns. This information may also allow the team to identify any bias in the type of AEs the sites

are reporting (or not reporting). By looking at the site variability, the team can identify possible under- or over-reporting of AEs, which can result in an imprecise safety profile for the product being studied. By identifying inconsistencies in the way AEs are reported by sites early in the study, the safety team can take corrective actions to address the problem. This metric can be broken down by reporting by severity (i.e., Mild, Moderate, Severe). While the occurrence of such items is uncommon, tracking the number of SAEs, pregnancies, and INDSRs/SURARs can also provide useful information to the team. The safety team may also be interested in the number and type of protocol deviations, included in Table 2.

Table 4. Safety Monitoring

Metric	Description
1. Number of Adverse Events (AEs)	*Total number of adverse events reported by the site*
a) Mild	*Number of mild adverse events*
b) Moderate	*Number of moderate adverse events*
c) Severe	*Number of severe adverse events*
2. Serious AEs (SAEs) Reported	*Number of SAEs reported to-date*
3. Pregnancies Reported	*Number of pregnancies that occurred while on-study*
4. INDSRs/SUSARs Reported	*Number of Investigational New Drug Safety Reports or Suspected Unexpected Serious Adverse Reactions reported by the site*

BIOSTATISTICS AND PROGRAMMING

While biostatistics and programming are generally two separate teams, their functions are so interdependent, particularly with the creation of the study statistics, that they are often considered one team. Statisticians play a crucial role in clinical trials and the drug development process. While they are generally involved in the study start-up process, such as providing input with the protocol development and CRF design, their involvement, particularly for the programming team, is minimal until the study reaches a point where the planned analyses need to occur.

The Biostatistics and Programming team works closely with the DM team and often communicate with the Clinical team to ensure successful trial design and analyses. While the metrics provided in previous tables are of interest to the team, they are particularly interested in monitoring the metrics mentioned in Table 2 such as the number of patients randomized, in efficacy population, completed, discontinued, reason for discontinuation, and time to discontinuation, as these statistics are generally included in the statistical analyses. Though not included in this paper, the biostatistics and programming team may want to create metrics to track the progress of creating the statistical datasets and displays.

SUBJECT LEVEL METRICS

Whereas looking at site level metrics provides a macro-level perspective on the progress of the study, subject level metrics can be used alongside site-level metrics to provide a micro-level perspective on the progress of the study. Table 5 provides some of metrics that can be of interest and are captured at a subject level. These metrics can help team members easily identify the subjects/records of interest based on the information identified at the site level. For example, if wanting to identify the list of subjects who discontinued the study early for all sites, the team can create a list by filtering on “discontinued” subjects on the “Current Status” metrics. If wanting to do the same for a particular site, the team can filter further by filtering on “Site.”

By looking at “Last Visit/Date,” the team can identify where a particular subject is relative to the study scheduled visits. This metric not only provides a quick snapshot of where subjects are within the scheduled visits but also indicates the date of the subject’s last visit, which can be used for several purposes such as validating the disposition date recorded in the “Date of Completion or Withdrawal.” For example, if the subject has a current status of “completed”, the date recorded in “Date of Completion or Withdrawal” should, generally speaking, match the date recorded in “Last Visit/Date” as the visit showed here should equal the study disposition visit (assuming disposition is recorded on the last scheduled visit).

By looking at subject level metrics for data management, the DM and Clinical team can identify and focus on the subjects who may have a low number (or percentage) for data entry and validation as they work towards the process of locking the database.

Table 5. Subject Level Metrics

Metric	Description
1. Subject Identification	
a) Site	*The site Identification number and PI name (e.g., 01- Smith)*
b) Subject study Identification	*Subject Study ID (as assigned in EDC)*
c) Cohort number, if applicable	*Cohort number to which subject belongs, if applicable*
d) Screen Fail	*Identifies whether or not a subject is a screen failure (Yes/No)*
2. Subject Status	
a) Current Status	*Subject status (e.g., screen failure, randomized, completed, discontinued)*
b) Date of Completion or Withdrawal	*Date of completion or withdrawal (missing if ongoing)*
c) Last Visit/Date	*Last completed study visit and date*
3. Subject Level Data Management	
a) Pages Expected	*Total number of expected pages (based on subject status)*
b) Pages Entered	*Total number of pages entered by site staff*
c) Pages Verified	*Total number of pages verified by CRA*
d) Pages Requiring Verification	*Total number of pages requiring CRA verification*
e) Pages Ready for Freeze	*Total number of pages ready for freeze*
f) Pages Frozen	*Total number of pages frozen*
g) Pages Locked	*Total number of pages locked*
h) Open Queries	*Number of queries that are still open for the subject*

DATA SOURCES

Since the bulk of the data used to create the metrics presented in this paper are clinical data that is collected by the eCRF and entered in the EDC system, the information needed for most of these metrics should be available in most clinical studies. The metrics from Table 2 are solely programmed from EDC data. Tables 1 and 3, however, require more specialized data sources, which may or not be readily available in the company. Table 1, for example, uses data from an internal tool used by Rho® where the CRA visit activity is recorded. However, depending on the existence and how it was set up the company, most of the site selection, qualification, and monitoring information may be available in the Clinical Trial Management System (CTMS). The data used to create the data management metrics presented in Table 3 and 5 is facilitated by a business object reporting tool within the Clinical Data Management System. Lastly, while the data needed for the safety monitoring metrics presented in Table 4 can be available in the safety database, some of this information may also be included in the EDC database.

When deciding what metrics to implement for a study, it is essential to keep in mind the availability and frequency of the data that is needed to create the metrics. The availability of the data dictates how fast the metrics can be updated and the new information is available to the team.

CONCLUSION

While the metrics presented in this paper are by no means an exhaustive list of the items that may be of interest to a clinical study team, the purpose of the metrics discussed in the paper is to show the benefits of using metrics as a mean for supporting actions that allow studies to evolve toward successful outcomes, promote continuous improvement, and enable strategic decision making. As mentioned throughout the paper, the use of metrics can help members of the different functional areas make informed decisions for their functional area and identify potential problems before they compromise the quality of the study data. It can also provide benefits for Project Managers such as allowing them to stay abreast of the status of the study as a whole and provide quick updates to other stakeholders inside or outside of the company.

Although the format in which the metrics can be presented to the team is not discussed in the paper, it is essential to consider the platform that would work best for the needs of the team. Some of the platforms that can be used include dashboards and Excel reports. As mentioned in the previous section, the availability of the data dictates how fast the new information becomes available to the team. So, the team should take this information into account when creating the metrics.

REFERENCES

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