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Research Article

METRICS FOR LEVERAGING MORE IN CLINICAL DATA MANAGEMENT: PROOF OF CONCEPT IN THE CONTEXT OF VACCINE TRIALS IN AN INDIAN PHARMACEUTICAL COMPANY

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ABSTRACT

The clinical trials data is of critical importance in providing evidence to support a drug or biologic product efficacy and safety. Quality data, productivityand lower product costs are key considerations in drug development process and to maintain competitive edge. Clinical Data Management(CDM) is a multistage process where various activities must be considered and decision taken in synergy and not sequentially; planned and executed according to the GCP (Good Clinical Practices) guidelines with highest standards. During the course of development, implementation and standardization of CDM procedures in the context of vaccine trialsin an Indian pharmaceutical company, it emerged that multi-factormetrics based performancemonitoring of critical procedural stepshave synergistic impact in boosting overall in-time progression of the projectand meeting desired data quality.It is important to acknowledge domain knowledge in developing performance metrics by involvingmembers of cross-functional teams. This report summarizes possible methodologies which if adopted are likely to keep the team members updated with the project advancement. The proof of concept, createdin the form of metrics designed to drive performance improvement through appropriate levels of internal controls and characterizing progress made under each criteria, is expected to improve overall productivity by accomplishing the aim with desired quality and within stipulated time-frameby mitigating the errors.

Keywords: Clinical Data Management (CDM), Indian Good Clinical Practices(GCP), CDM Metrics

INTRODUCTION

India is emerging as the vaccine hub of the world. In consequence, there is an increased impetus in vaccine R &D and a steady rise in vaccine's clinical trials.[1,2]In the context of global scenario of drugs or biological products development major challenges that have been acknowledged are managing clinical trials data; reporting and documentation in compliance of GCP or international standardsand difficulties in meeting the regulatory requirements.[3,4]

A recent survey has shown that heterogeneity of CDM systems and deficits in quality management of dataexists in data management in clinical trials, apart from limited human resources and budgetary constraints. Current CDM guidelines are inadequate; regulatory directive define only GCP compliance for clinical trials. There is lack of specific and practicable technical GCP requirements that capture the range of CDM. The need for data standards has been suggested to ensure data quality management and meet regulatory review.[5,6]

Metrics', a verifiable measure, provides a quantitative assessment and keeps us updated with the issue (s) or performance of various procedural steps involved in executing a plan to meet desired goals. Quality process metrics, a multivariate approach, capturesoperational performance in terms of how something is being done relative to the known standards or practices to be established that may come from either internal or external sources. Metrics not only allows monitoringthe project progress but also identifying and predictingprocess gaps and outliers. While implementation of clinical data management (CDM) activities for vaccine studies in an Indian bio-pharmaceutical company[7], we have created metrics for not only assessing the progress or performance in context of the procedures adopted but also team members.

Thisarticle aims to outline the important metrics which might assist in CDM and would prove to be relevant by servingas a platform to evaluate the quality and productivity (a given activity cycle-time and cost reduction) to achieve the organization's goal.These metrics are expected to be extremely helpful to find out qualitatively and quantitatively the overall impact on the quality of outcome based on the factoror process under observation.It can be said that these metrics are indicator of CDM performance which can thus be translated to increased efficiency and therebydecreased processing time to achieve the goal with expected data quality standardsset forth by GCP (Good Clinical Practices).[8]

Although, there are no regulatory guidelines and framework which direct to have these metrics but it is expected that thesewill certainly provide lodgings for standardization of CDM practices by mitigating the forthcoming riskthroughtimely gap analysis. Overall it is anticipated that the recommendationsestablished will in turn support for the smooth and consistent performance and will be helpful to extricate the potential regulatory risk such as measuring noncompliance to protocol andSOPs (Standard Operating Procedures).

Of note, the ECRIN (European Clinical Research Infrastructure Network) data management working group conducted a two-part standardized survey on data management, software tools, and quality management for clinical trials;the overall inference drawn iteratedthe fact that the heterogeneity prevails in CDM.[2]This highlights the concern that each organization adopts its own internal practices for design, conduct, performance, monitoring, auditing, recording, analysis, and reporting[9]of study data. However, at the end, the goal remains common i.e. to have credible, accurate and reliable data. Under this heterogeneous environment, CDM activities can still be parked towards standardization by effective implementation of the said metrics as these can serve as a point of commencement of one common global CDM practice across the industry.[10] If we have common metrics to

gauge CDM performance, we might be compelledto implement common procedures to achieve process standardization.The scope of these metrics can be widened to harmonization, CDM task for different therapeutic segment of trials depending upon the in-house procedures adopted by the organization.

Defining Metrics

The challenge is to identify correct metricsto meet benchmarks for desired parametersand output, and how to perform measurements, and how to interpret results. The decision making should be guided and likely achieved by the process metrics being both quantitative (such as amount, cost, cycle-time, productivity, and excellence-error rate/quality) and qualitative (such as alignment with corporate strategy and in agreement with all the concern departments, individual teams and project teams, or level of technology involved).Consequently the set of all the metrics should be linked by aligning them to achieve the common goals and output.

In summary, CDM Metrics on the above mentioned parameters must be evolved based on organization requirements, study specific criteria (s) and keeping in mind the technologyinvolved in assisting the processes. Design of theses metrics should be such that to allow for efficient cross-study analysis in terms of its progress and performance.

Overview: CDM Processes

The complete CDM process can be summarized in several tasks; CDM processes which were adopted forvaccine studies (Myfive™ and Pneumococcal vaccine NUCOVAC®) conducted at Panacea Biotec Ltd., India, and have been earlier reported[11], are represented in Table 1. This table shows the generally categorized three different stages of CDM activities: Study Start-up, Study Conduct, and Study Closeout.[12]

Note: Adapted from Figure 1, reference, [13] only the major milestones for each stage are listed. For clarity, the tasks have been listed next to its proceeding activity; as a result some of the places can be seen as blank in the table.

Table 1: CDM Work Flow adopted for Vaccine study: major steps of each phase of CDM

Study Start-up	Study Conduct	Study Closeout
Finalization of CRF Received Final approved Protocol and CRF for Designing Creation of DMP (Data Management Plan)		
Creation of Annotated CRF (Case Report Form)		
If any of the Questions are not present in Global Library (Glib), Data Base Designer shall identify and send a request to Global Librarian for approval/creation		
-Study setup and Database -Designing Creation of Test Views	-CRF Data Tracking Log creation followed by 1st Pass & 2nd Pass Data Entry	Data Extract View Finalization (fine tuning): Send to Bio-Statistician, for SAS review
Test Data Entry/ User Acceptance Test (UAT) on Dummy Subjects	-Data Entry: based on Final Data Entry Guidelines document and processes for Handling of Lab Data (Non –CRF Data) -Data Reconciliation between 1st & 2nd entry to identify mismatch between the entries	-Data Coding, -Serious Adverse Events (SAE) Reconciliation With PVG (Pharmacovigilance) database -Creation of DHR
Creation of Self-Evident Correction (SEC) document for approval from medical monitor		LOCK (Study Access Revoke and relevant archiving task)
Finalization of DVP (Data Validation Plan) with the inputs from Medical Monitor	-Batch Validation Run for triggering the queries as per the predefined schedule on the data -Discrepancy Management (Review all queries and creation of Data Clarification Forms (DCFs)) -DCFs are sent along with the Tracking Log -Query Resolution	
Creation of Final Data Extract Views		Final Data Extraction for analysis & Submission
Master Data Management File (MDMF) Creation	MDMF Documentation continues as required	-Final MDMF Documentation -All Reports Creation
Move the study into the Production after relevant QCs of processes	Relevant QCs of processes at each step	QC of data and database (relevant before/after lock)

Metrics definition in the context of CDM study phase

Considering confidentially constraints, replicas of metrics parameters or measures of quantitative/qualitative assessment used for measurement, comparison or to track performance of various above described CDM tasks are presented. Metrics were categorized into 'Inter- Study Metrics' that compares between the studies, and 'Intra- Study Metrics'that exist only with a single study. For most of

the metrics, creation of separate Intra- Study Metrics was not required as these were derived with specifications of Inter- Study Metrics.For assessing each of the above described CDM stages,metricsand metrics- dashboards not limited to the followingwere proved useful in proactive decision making:

Proof of Concept: Study Start-up Phase

The details of major metrics adopted for Study Start-up Phase of CDM are described in Table 2.

Table 2: Major metrics adopted for Study Start-up Phase of CDM

Study Start-up	List of Major Metrics Adopted for Study Start-up Phase of CDM
-Finalization of CRF -Received Final approved Protocol and CRF for Designing	*Inter- Study Metrics* -Comparison of time between the studies for: • finalization of all the pages of CRFs • finalization of total number of global standard pages of the CRFs • finalization of total number of unique pages of the CRFs
Creation of DMP (Data Management Plan)	*Inter- Study Metrics* -Comparison of time between the studies for: • finalization of all the pages of DMP • finalization of individual sections of DMP
Creation of Annotated CRF (Case Report Form)	*Inter- Study Metrics* -Comparison of time between the studies for: • annotation of all the CRFs pages • annotation of total number of global standard pages of the CRFs • annotation of total number of unique pages of the CRFs • CRFs with percentage of annotations as per CDISC/in-house standards
If any of the Questions are not present in Global Library (Glib), Data Base Designer shall identify and send a request to Global Librarian for approval/creation	*Inter- Study Metrics* -Comparison between the studies for: • Total number of new questions created in the Global Library • Total number of existing questions used in the Global Library • Time needed to create new questions in the database *Intra- Study Metrics* -Page wise comparison of new questions in the CRF of single study
Study setup and Database Designing	*Inter- Study Metrics* -Comparison between the studies for: • Time needed to complete database designing for unique pages. • Time needed to complete database designing for global standard pages. *Intra- Study Metrics* -Page wise comparison within the study to find out the time needed for designing
Test Data Entry/ User Acceptance Test (UAT) on Dummy Subjects	*Inter- Study Metrics* -Comparison between the studies for: • Time needed to test the database designing. • Time needed to update the QC findings based on UAT. *Intra- Study Metrics* -Page wise comparison within the study to find out the time needed for UAT
Creation of Self-Evident Correction (SEC) document for approval from medical monitor	*Inter- Study Metrics* -Comparison between the studies for: • Time needed to prepare SECs document. • Number of data points for global standard pages, with common SECs. • Comparison of total number unique/new SECs across studies • Comparison of total number fields which was actually corrected based on SEC document, *Intra- Study Metrics* -Page wise comparison within the study , for the similar data points, for the applicability of SECs
Finalization of DVP (Data Validation Plan) with the inputs from Medical Monitor	*Inter- Study Metrics* -Comparison between the studies for: • Total number of new validation procedures created for Global standard pages • Total number of existing validation procedures used for standard pages • Total number of new validation procedures created for Unique pages • Time needed fordesigning of checks in the database for unique /standard pages based on: new validation procures or existing validation procedures • Predictive Analysis to identify the lead time needed to complete the pending task, based on historic data of similar studies and updation of QC findings. *Intra- Study Metrics* -Page wise comparison within the study to find out the time needed for designing of edit checks for the pages -Visit wise comparison of pages to see the applicability of number of common checks
Creation of Views for Data Extract	*Inter- Study Metrics* -Comparison between the studies for:

	• Time needed to complete designing of view in the database for unique pages/standard pages. • Total number of viewscreated in the database for unique pages/standard pages. • Total number of views with subsets, with difference in SAS Label or Default prompt in the database for unique pages/standard pages. • Total number of views which required updating based on the findings of bio-statistician. • Comparison of findings given by bio-statistician for different studies. *Intra- Study Metrics* -Page wise comparison to find out the time needed for designing of view
Master Data Management File (MDMF) Creation	*Inter- Study Metrics* -Comparison between the studies for: Time needed to complete documentation. *Intra- Study Metrics* -Page wise comparison to find out list of pending documents (needed at the study start) and time required to complete the same
Move the study into the Production after relevant QCs	*Inter- Study Metrics* -Comparison between the studies for: • Number of QC procedures performed • Time needed to complete applicable QC procedures. • Time needed to update the QC finding • Comparison of common QC findings. • Comparison of reason for repeating the similar findings *Intra- Study Metrics* - QC findings repeated for similar pages (visit wise comparison)

MatrixManagement: Study Start-Up Phase

Following are some of the key metrics dashboards, parameter-based viewsof metrics data showing key performance indicatorsbased on metrics data replica/extrapolation which can be used to monitor the trendsor actualto help improve processes performance at various phases of a study and make informed, reasoned decisions; address problem areas as they arise and opportunities taken. Of particular note, metrics and dashboards are data driven and quality of data matters.

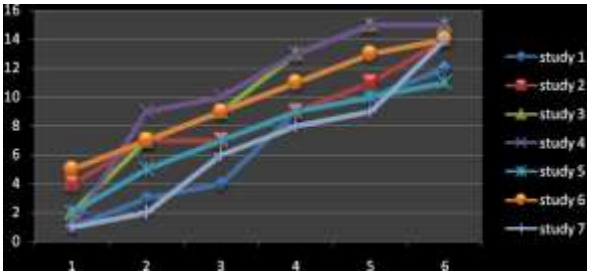

Fig. 1: Progress of CRF Finalization.

The above graphdepicts the progress of CRF finalizationover a period of time. Here Y- axis denoted the total number of CRF pages which have been finalized and X-axis denotes the time in weeks. Thus for study-1 at week-2 only three pages could be finalized, asagainst the study-6 where seven CRF pages have been finalized.

The above pie chart portrays the usage of new vs. existing questions for creation of study database.It is clear that study-1 uses the maximum number of new questions, whereas study-7 uses the least number of new questions. However, the usages of existing questions from Glib in all the studies are almost similar.

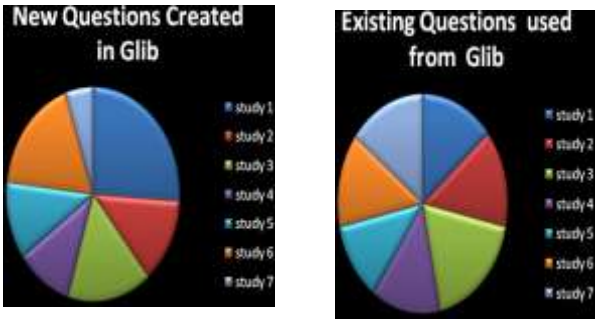

Fig. 2: Metrics for the use of New vs. Existing questions from the Global Library (Glib).

Proof of Concept: Study Conduct Phase

The details of major metrics adopted for Study Conduct Phase of CDM are described in Table 3.

Table3: Metrics adopted for Study Conduct Phase of CDM

Study Conduct	List of Major Metrics Adopted for Study Conduct Phase of CDM
-Creation of CRF Data Tracking Log -1st Pass & 2nd Pass: Data Entry(based on Data Entry Guidelines document) -Reconciliation between 1st & 2nd entry to identify mismatch between the entries	*Inter- Study Metrics* -Comparison between the studies for: • Number of CRFs submitted by the site for different active trials over a period of time • Number of CRFs still pending to be submitted by the site for different active trials over a period of time *Intra- Study Metrics* • Number of CRF pages still pending to be submitted • Number of CRFpages already submitted to the CDM

	• Number of CRF pages whose 1st Pass / 2nd Pass entry is pending • Number of CRF pages whose 1st Pass &/or 2nd Pass entry is done • Time needed by different data entry operators to complete the 1st Pass / 2nd Pass entry for similar number of pages • Comparison of data entry reconciliation report for finding out which operator is making maximum/minimum mistake during the entry. • List of pages with similar/systematic data entry errors
-Batch validation run on the data,for triggering the queries as per the predefined schedule. -Discrepancy Management : Review of all queries and creation of Data Clarification Forms (DCFs)	*Inter- Study Metrics* -Comparison between the studies for: • Total number of queries generated form a similar validation checkfor different sites • Identifying the queries with systematic errors • Identifying the sites with maximum /minimum number of queries • Time needed to review the DCFs by CDM personnel • Error rate *Intra- Study Metrics* • Identifying the queries with systematic errors for a site or for sites monitored by same CRA • Time needed to review & generate the DCFs by CDM personnel • List of pages with similar/systematic DCFs, visit wise comparison • List of duplicate DCFs
DCFs are sent along with the Tracking Log	*Inter- Study Metrics* -Comparison between the studies for: • Turn Around Time (TAT) for DCF resolution by the site/CRA • List of sites with maximum/minimum number of invalid responses • List of sites with maximum/minimum number of different responses for similar kind of queries • Studies with maximum/minimum, query aging time • Comparison of queries with missing data/missing CRF pages/number of out of range queries • Queries for number of Protocol Deviation/Violations& safety data • Queries based on Programming Errors • Number of critical queries *Intra- Study Metrics* • Turn Around Time (TAT) for DCF resolution by site/CRA • Query aging time • List of DCFs missed to be sent to the site by CDM team • List of misplaced DCFs by the site/CDM team • Inconsistencies across single CRF page based on logical rules • Inconsistencies between different CRF pages based on logical rules • Comparison of number of queries with invalid responses • Number of DCFs resolved in draft stage • Number of DCFs resolved as SECs • Number of DCFs resolved for spelling errors • Number of Valid DCFs with the resolution 'no required data verified from CRF' or irresolvable status
MDMF Documentation continues as required	*Inter- Study Metrics* -Comparison between the studies forthe time needed for documentscompletion, (live documents) and needs to be updated with study progress. *Intra- Study Metrics* • Page wise comparison within the study to find out list of pending documents (which needs to be updated during the study program) and time required to complete the same.

Matrix Management: Study Conduct Phase

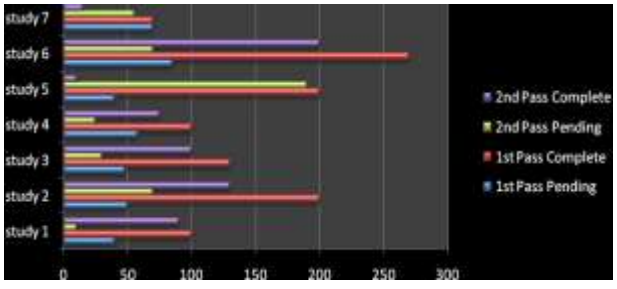

Fig. 3: Comparative Metrics for Depicting Data Entry Status.

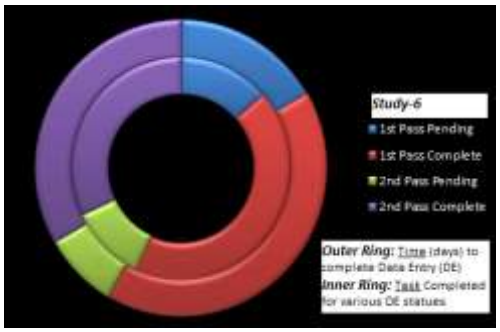

Fig. 4: Comparative Metrics for Depicting Data Entry Status vs. Time needed to accomplish the same (reference: Study-6).

The above chart (Figure 3) portrays the information about the various data entry statuses. It does the comparative analysis of the same between thedifferent studies. X-axis depicts the number of CRFs for various studies which are shown in Y-axis. Thus for study-6, 85 CRFs has the status of 1st Pass Pending, 270 has the status of 1st Pass Complete, 70 has the status of 2nd Pass Pending and 200 has the status of 2nd Pass Complete.

Table 4: Inference (Figure 4)

Study-6	1st Pass Pending	1st Pass Complete	2nd Pass Pending	2nd Pass Complete
Outer Ring:% time(days), to complete the task	17	42	8	33
Inner Ring: % of task completed	14	43	11	32

"Drill-down"details for study 6, for 1st Pass entry, 43% of the task was completed in 42% of the time. However, 8% of task was pending for 2nd pass entry for 11% of time.

Proof of Concept: Study Closeout Phase

The details of major metrics adopted for Study Closeout Phase of CDM are described in Table 5.

Table 5: Metrics adopted for Study Closeout Phase of CDM

Study Closeout	List of Major Metrics Adopted for Study Closeout Phase of CDM
Report Creation	*Inter- Study Metrics* -Comparison between the studies for • the time needed to create all the reports • the total number of pending reports • comparison of reason for uncompleted reports • % of work completion as per DMP • Final rate of errors in the database *Intra- Study Metrics* List of pending reports
Data Extract View Finalization	*Inter- Study Metrics* -Comparison between the studies for • List of final views • List of final views copied from different studies with the source study mapping marked *Intra- Study Metrics* List of final views which needed alteration for various pages, based on the study
Send to Bio-Statistician, for SAS review	*Inter- Study Metrics* -Comparison between the studies for • Metadata/data discrepancies or errors identified after SAS mock run for similar studies • Studies with maximum/minimum number of metadata/data errors • No of errors in data transfers *Intra- Study Metrics* • Visit wise comparison of data discrepancy or errors identified after SAS mock run in metadata/data
QC of data	*Inter- Study Metrics* -Comparison between the studies for • Missing QC reports • Comparison of QC findings for similar reports • QC findings repeated between the studies • New QC findings for similar reports • Time needed to update the QC findings • Error rate *Intra- Study Metrics* • Visit wise comparison of QC findings, checking for repeat or new findings • Visit wise comparison of time needed to update the QC findings • CRF pages with maximum QC findings
• Data Coding, • SAE Reconciliation with PVG (Pharmacovigilance) database • Creation of DHR (Data Handling Report)	*Inter- Study Metrics* -Comparison between the studies for • Different codes used for same verbatim term • Coding errors • Coding time • SAE Reconciliation time required • DHR with maximum number of comparable entries *Intra- Study Metrics* • Coding missed out for a page • Different codes used for same verbatim term • Obsolete version of dictionary used for coding • SAE identified during reconciliation
Final MDMF Documentation	*Inter- Study Metrics*

	-Comparison between the studies for: the time needed for documents to be completed at the end, before lock. *Intra- Study Metrics* • Page wise comparison within the study to find out list of pending documents (which needs to be updated during the study) and time required to complete the same • Number of documents created in different format than that mentioned in the SOP • Approvals not signed in the documents, due valid reasons • Time for completion of study specific archive task
• LOCK (Study Access Revoke and relevant archiving task) • Final Data Extraction for analysis & Submission	*Inter- Study Metrics* -Comparison between the studies for the • Time needed to complete locking tasksby CDM team • Time needed to complete locking tasks by IT department • Reason for delay in database lock • Reason for 'unlock'for the study

Matrix Management: Study Closeout Phase

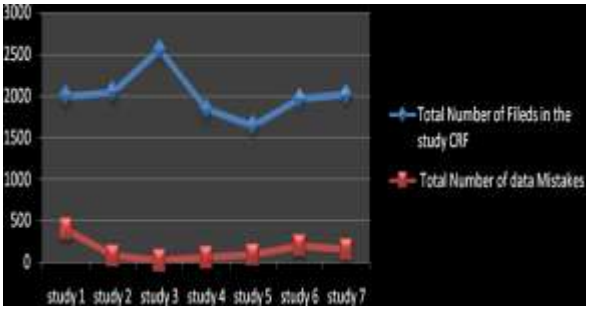

Fig. 5: Comparative Metrics for Depicting total number of data mistakes and total number of fields in the CRFs, study wise Y-Axis depicts total Number of CRF fields. Thus for study-6 the total number of fileds in the CRF is 1969 and the total number of mistakes are 197. Likewise, for study-3, the total number of mistakes are lowest i.e. 18 while the total number of fileds are 2560.

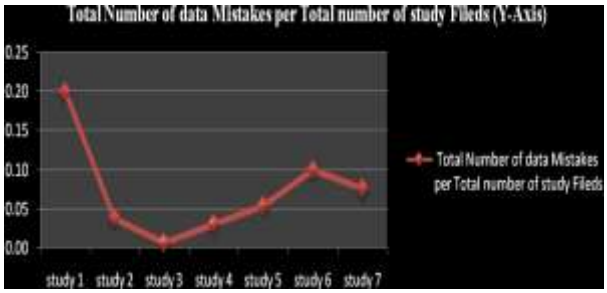

Fig. 6: Comparative Metrics for Depicting total number of data mistakes PER total number of fields in the CRFs, study wise.

In the above graph it can be seen that for study-6 the total number of data Mistakes per total number of study Fileds is 0.10. For study-3, the total number of data Mistakes per total number of study Fileds is 0.0.

DISCUSSIONS

Over the last few years CDM process has certainly evolved from traditional Excel® spreadsheets to CDM software solutions.[10]It has been noted that there is no standard for GCP-compliant data management processes and structures which is both generally applicable and practical.[5]"Proof of Concept"described in this study, a set of performance metricsreflecting the principles of 'GCP'or 'best practices', and expert feedbacks,if leveraged could enhance the chances of success of potential CDM task to achieve the desired outcome.The metricsdescribed based on our experience from the vaccine trials may be developed to effectively address CDM cross-functional tasks and thereby ensuring quality data. A need for consultation and consensus is suggested between the working groups those associated with the data, i.e. data provider, data owners, and data custodians prior to building metrics and dashboard design.[14]Common metrics will fetch for uniform dashboards thereby avoiding the generation of different reports by different teams for the same information, thus reinforcing the drive towards process standardization.Though the time, effortsand technological skills needed for initial implementation of thesuggested metrics may be high but accurate placement of the same, quality by design, drastic reductions in the costs-time cycle is anticipated.

In view of that, the metricscan be helpful to facilitate for consistence performance and increase efficiency throughtimely notification of outliers, based on:

- procedural gaps
- systematic errors
- metadata issues
- mistakes in data
- upsurge in error rate in the process
- chronological issues
- missing information
- incomplete documentation

Metrics must be created by balancing all the criterias; too much focus in one area may have undesirable impact on another. For example too much focus in quality of DCFs may affect the time to resolve all the queries in the discrepancy database, thereby delaying time to database lock.

Metrics which are developed based on historic data of similar studies, with the precise deployment of principles of predictiveanalysis will identify the lead time needed to complete the pending task.

CONCLUSION

To succeed in a CDM project, it is extremely important to have standardized operations, monitor project advancement, check if the desired tasks deployed to achieve the goals are advancing in the correct direction, in synchronization with the aims and objectives of the organization. Decision to adopt a particular metrics must be made at the time of project planning so as to draw maximum advantage.

Adopting the approach of keeping data handling and analysis simple, the metrics developed for forecasting the concerns of the stakeholders in CDM, could have a beneficial effect in saving time, cost, and efforts by serving as a decision making platform to allocate correct resources in a study.A way forward,concerted efforts to establish a set of standard CDM processes metrics reflecting biologic product (s) specific needs and broadly accommodating standards/guidelines such as those set by national or international professional, industrial or regulatory bodies.

DISCLOSURE

The opinions, interpretations stated in the article represent individual's viewpoint only, there being no conflict of interest.

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