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22 The Impact of Risk-Based Monitoring on the Design and Conduct of Electronic Data Capture (EDC) studies: Industry Perspective for Clinical Data Management. By Nomfundo M November
I hope you are enjoying your summer and the warm weather! The year is going by quickly and the SCDM staff, Board and Committee volunteers have been busy making our 25th Anniversary year the best ever!

As a quick reminder, in my April letter, I shared SCDM’s new vision and mission:

**SCDM Vision (our aspirational view of the Society):**
Leading innovative clinical data science to advance global health research and development

**SCDM Mission (what we do):** Connect and inspire professionals managing global health data with global education, certification and advocacy

We’ve been working to bring our new vision and mission to life with multiple initiatives. Two of these initiatives, both from the Innovation Committee, were rolled out this past quarter and announced on social media channels—LinkedIn, Facebook, Twitter, Instagram—and via our website.

The first is the new white paper “The Evolution of Clinical Data Management to Clinical Data Science” that speaks directly to the drivers that are leading to seismic changes in our discipline. The paper offers key concepts and thought provoking ideas of what a future in Data Science may look like. The Committee Chair, Patrick Nadolny, participated in a future of CDM panel discussion at the PharmaSUG conference in June, sharing the SCDM vision and the paper. SCDM intends to publish more papers in the next year on changes to the CDM role and how technology will be an enabler to achieving it. Laying out our vision of data managers advancing global health research through the expanding world of data science and inspiring data management professionals to embrace it is our first step in realizing our vision and mission!

The second initiative launched that directly supports our new vision and mission is the eSource Implementation Consortium. Its mission is in its name ‘implementation’—by bringing together academia, pharma and technology vendors to use emerging techniques and standards to facilitate dataflow from Electronic Health Record systems (EHRs) to clinical data management systems or warehouses, they will demonstrate best practices and encourage the adoption of eSource. This consortium is now open to all.

Continued on page 3
Here are some other exciting events and news to share that promote our mission of education, certification and connecting:

- **Coming up we have 4 global conferences to attend!**
  - *SCDM India Single Day event*, Sept 14, 2019, Pune|India
  - *SCDM Annual Conference and Leadership Forum*, September 29- October 2, 2019, Baltimore|US
  - *SCDM EMEA Conference and Leadership Forum*, October 23-25, 2019, Berlin|Germany
  - *SCDM India Annual Conference December 6-7, 2019*, Karnataka | India

- **Additional educational offerings are coming- from new chapters in the GCDMP to new webinars and online courses!**

- **Lastly, be on the lookout for an updated website that is easier to navigate and a new community platform to collaborate with each other to share best practices and for committees and taskforces to work together more easily and reach their goals quicker.**

We hope you are energized by our vision and mission and opportunities to be a part of SCDM! Now is the perfect time to get [involved with your Society](#), to help your career, to give back to others and have some fun along the way!

I hope you are as excited as I am to be a part of a thought leading organization who is defining a new direction from Data Management to Data Science! Please contact me ([linda.king@astellas.com](mailto:linda.king@astellas.com)) or our Executive Director Triphine Dusabimana ([triphine.dusabimana@mci-group.com](mailto:triphine.dusabimana@mci-group.com)) if you’d like to find out more about volunteer opportunities, the Society’s new vision and mission or would like to share your ideas and thoughts on our future. More about our new vision and mission throughout the year!

See you in Baltimore in September!

Kindest regards,

**Linda King,**  
SCDM Board Chair, 2019
Dear readers,

Data Management has come a long way from where it was when SCDM started 25 years ago. Looking back over those years, SCDM has always been in the forefront - bringing ambitious minds together to drive best practices within the evolving CDM industry, and to create an atmosphere for exchange of information and experience.

The tradition continues. Committees with an eye toward the future are active, pooling the experience of our CDM industry colleagues and leaders to describe a vision of a transformed clinical research data landscape and the future tools and roles and the skills needed there. Here are just two recent examples of this. In June, the SCDM Innovation Committee published its White Paper: “The evolution of clinical data management to clinical data science: A reflection paper on the impact of the clinical research industry trends on clinical data management,” a comprehensive discussion of the trends and future clinical research landscape - important content to open up the scope of our view!

Also in June, SCDM announced that its eSource Consortium, which was established in 2017 under the auspices of SCDM, will now be open to all academic, technology and industry sponsor participation. The consortium’s industry-changing mission is to agree upon standardization of clinical research datasets, enabling faster adoption of direct data transfers by academic sites and industry sponsors. A current task is to develop Data Exchange Specifications for eSource data of core safety domains as well as some efficacy domains.

So in this same vein of exchange, we are pleased to present you with the 2nd edition of Data Basics for 2019, our “Summer Issue”. We bring you articles from authors worldwide, sharing their initiatives and the hard earned experience they’ve gained.

In our lead article, the author presents a case study about an innovative approach for collecting and classifying protocol deviations programmatically and how data managers and site monitors benefit from this process.

Although Risk based monitoring (RBM) is discussed often these days as a ‘standard’, the author of our 2nd article decided to use a survey to collect information systematically about the how widespread an impact that RBM has actually had on everyday practices for Clinical Data Managers. In her article, she shares with us her important survey findings.

We conclude this issue with an article from several bio statistical colleagues from the University of Kansas. They explore the benefits and challenges for executing the computer system validation when implementing an EDC system. While this is not a new exercise for big pharma companies, this is not yet so common at academic institutions, making this interesting reading for folks looking to bring in new systems.

We hope you find this varied content stimulates further exploration and exchange on the most important topics within your own organization! Exchange helps us each grow individually, continuing to strengthen CDM contributions to all of our organizations as a whole, now and into the future.

Nidhin & Janet
2019 Online Course Schedule

Catch up with your learning in 2019! You might have missed some great opportunities. Check out our course and webinar schedules, and their updates on the SCDM website. For more information and to register, please see here webinar and online courses.

### 2019 Online Course Schedule

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### 2019 Webinar Schedule

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INTRODUCTION

Many times, while working within the confines of previously established processes for collecting, sharing and analyzing data, I imagined a path through which the results would be more accurate and achieved more efficiently. Approval granted by a forward-thinking leadership team and with the aid of knowledgeable, dedicated colleagues, it is possible to develop a process that is accurate, efficient, and user-friendly across line functions.

During clinical trials, there are always planned or unplanned protocol deviations (PDs). ICH GCP requires that PDs are documented. ICH E6 (Section 4.5.3) states “the investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol [1].”

As protocols become more complex and regulatory requirements become more stringent, PDs are on the rise [2]. The increase of PDs may compromise subject safety and skew statistical analysis. Pharmaceutical companies should accurately collect and classify PDs in order to facilitate statistical analysis of the study data. Missing PDs, inaccurate recordings or ineffective Corrective and Preventive Actions (CAPAs), may lead to the occurrence of higher impact incidents such as misconduct and even fraud in clinical trials.

Regulatory audits commonly reveal deficiencies in the recording and reporting of PDs. These challenges provide high hurdles for data managers. In order to optimize the process, PDs can be detected real time within the Electronic Data Capture (EDC) system by using standard and customized programming of PD Electronic Case Report Forms (eCRFs) and online edit checks.

BACKGROUND

Current industry practice is to utilize the Clinical Trial Management System (CTMS) to record PDs and the EDC system to record clinical data. The two systems are not always integrated which sometimes leads to a juxtaposition between the two data sources. Additionally, study team members may not always have visibility into the CTMS system. The PD process from data collection to Clinical Study Report (CSR) reporting involves multiple line functions such as Medical Monitors, Data Managers (DM), Clinical Research Associates (CRAs), Operations, Safety, Statistics and Programming. Improving this process to be more effective and symbiotic can improve the integrity of the study.

Lack of standardization of CTMS configuration across Clinical Research Organizations (CROs) results in discrepancies across portfolios. Performing trend analysis of data across studies becomes cumbersome and time-consuming. Collection of PDs generally occurs during monitoring visits or during data reviews, which are scheduled periodically depending on the size and complexity of the study. The detection and accuracy of PDs is time sensitive. As time passes from PD occurrence, discrepancies can occur. Earlier detection and resolution of PDs makes it possible for preventive actions to be more effective and protocol deviations details to be more precise.

Global clinical research inherently generates differences in data collection processes. In complex multisite global trials, PD categorization, and classification of PDs as major or minor are subjective based on a CRA’s discretion. With the best of intentions, this process produces a situation where PDs can vary across sites for a given study. There is also a risk of missing critical PDs during monitoring visits on sites with high subject enrollment. Missing critical PDs may pose a risk to subject safety and cause compliance concerns.

In the past, the responsibility of Data Managers (DMs) has primarily been to review listings, identify trends and detect outliers in data. The future of DMs requires increased involvement in a wide range of cross-functional processes including operational management of PDs, regulatory compliance, statistical analysis and programming. Data Management’s ownership in all aspects of clinical data collection and analysis brings us closer to making lifesaving drugs available to patients faster and in a more compliant manner.
OBJECTIVE

Most clinical teams spend an extensive amount of time reviewing hundreds of rows of text-heavy PDs and fixing errors manually using back-and-forth communications with the CRO team. Despite all the effort, there is always the risk of missing critical deviations. At Agios, a cross-functional team got together to work on a solution to make this process more efficient and standard across studies. We proposed a solution to collect all deviations in the EDC system using standard tools and programming across the portfolio. There was initial skepticism and speculation of moving from CTMS to EDC, as EDC systems are not traditionally designed to accommodate the intricacies and complexities required to capture PDs. Implementation of this process required crossing boundaries and understanding all levels of functional requirements from field monitoring to local IRB practices to statistical analysis. We received feedback from the early adopters of this process which helped us make this process more robust.

METHOD AND PROCESS

The method described in this article utilizes online edit checks, custom functions and algorithms to capture and manage PDs within the EDC system using eCRFs specially designed for collecting PDs. PD entry roles are created to provide access to CRAs and DMs to record and manage PDs within the EDC system. Data entry privilege for the PD entry role is restricted to the PD eCRFs by the database developer. The site coordinators and investigators do not have access or visibility into the PD eCRFs.

PDs are detected and recorded in real time by online PD edit checks and custom functions as sites enter subject data in EDC. When a PD occurs, an online PD query fires to the site and a programmed custom function records the potential PDs into one of the PD eCRFs. DM confirms the reportable PDs from the list of potential PDs recorded in the PD eCRF, after evaluating site’s response to the PD queries and other related data points. This reduces the amount of monitoring necessary and the delay in detecting PDs. In addition to the detection of PDs by online PD edit checks, this method also allows CRAs to manually record PDs found during source document verification (SDV) and monitoring visits. CRAs enter the manual PDs by selecting options from a dynamic drop-down search list that is programmed based on the classification algorithm documented in the PD specification document.

A custom PD report is available at real-time in the EDC system and can be reviewed by any team member. This method allows team members to detect trends, safety signals, site training issues, etc

PROCESS

1. PD Specification Document

The process starts at the beginning of a study with the creation of a PD specification document. Requirements are gathered from a detailed review of the study protocol and collecting feedback from the Medical Monitors, Statisticians, CRAs and Programmers to ensure that the documentation is robust. This document serves as a blueprint to build the PD process in the EDC system and provide reference to the study team to collect, monitor and analyze PDs. The specification is created by the study DM. All Potential PDs that might occur throughout the life of a study both from a protocol and GCP standpoint are included in this specification. Each PD in the specification is assigned a PD ID, PD category or class, major and minor designation, identification method such as programmed or manual and impact on statistical analysis. [Figure 1].
2. PD Functionality

During the study start-up phase, the PD functionality and programming are included in the initial development of the EDC system. The EDC build includes the development of PD eCRFs, online PD edit checks with custom functions, PD report and PD entry roles.

The PDs defined as ‘Programmed’ in the PD specification are built as online PD edit checks. The edit check specification document for a study includes the regular edit checks as well as the PD edit checks. All PD edit checks and their associated query texts are assigned a PD ID per the PD specification document to differentiate them from the regular edit checks. It is critical to differentiate the PD edit checks for both programmers and DMs, as these checks are programmed and processed differently from regular edit checks. Programmers build the PD edit checks with custom functions to allow for the recording of the potential PDs in the PD eCRF. The programmed PDs fire in the eCRF when data entered for a subject meets a programmed PD edit check condition. When the PD edit check fires, a query is generated to the site and simultaneously the custom function also records the corresponding PD into a unique row of the Administrative PD eCRF with unique details of its classification and the data point of origin. DMs are required to confirm the Potential PDs in the PD eCRF based on the site’s response to a PD query.

PDs defined as “Manual” in the PD specification are programmed as dynamic drop-down options in the PD eCRF. PDs that are built as dynamic drop-down options are manually entered by the CRA into one of the PD eCRFs designed for manual PD entry.

A custom report is built into the EDC system that outputs all the PDs from the Programmed and Manual PD eCRFs. This report is generated on an ad-hoc basis by study team members, thereby increasing visibility, traceability and transparency. CRAs also use this report to include PDs into their monitoring visit reports and site follow-up letters.

Figure 1. Protocol Deviation Specification Document
3. PD eCRFs

The three PD eCRFs used to record and manage PDs in EDC are Administrative, Programmed, and Manual. (Figure 2).

a. Administrative PD eCRF: This eCRF is used as a staging area for all the potential PDs that are generated by the PD edit checks and the custom functions. All potential PDs remain unconfirmed in this eCRF, until a DM evaluates and finalizes each PD. All fields with the exception of the field ‘PD Confirmed’ are programmed to be automatically derived in this eCRF based on the PD specification document. Depending on the site’s response to a PD query, DM confirms the potential PD in this eCRF by selecting “Yes” or “No.” If a PD is confirmed as “Yes,” the custom function automatically pushes that PD from the Administrative PD eCRF to the Programmed PD eCRF for management by the CRAs. If a PD is confirmed as “No,” that PD is not pushed into the Programmed PD eCRF and remains in this eCRF as an unconfirmed PD.

b. Programmed PD eCRF: This eCRF serves as the final area for all programmed PDs that are pushed from the Administrative PD eCRF. The CRA reviews this eCRF to verify accuracy of the confirmed PDs and enter the additional required fields such as “IRB submission status,” “Follow-up actions,” etc.

c. Manual PD eCRF: This eCRF allows manual entry of PDs by the CRA. PDs that are complex to program or require source document verification are recorded in this eCRF. All PDs identified as “Manual” in the PD specification document are built in as dynamic drop-down options in this eCRF. The drop-down options are programmed as an algorithm to keep the PD classification standard across all studies irrespective of the identification method and EDC platform used. The dynamic selection options available for a field in this eCRF is based on the selections made in the previous fields, eCRFs entered in EDC for that subject, and the fields available within that eCRF (e.g., if PD Class selected is Study Treatment deviation, then list of options for the Protocol Deviation field should only include PDs that are categorized under that PD class “Study Treatment Deviation” and list of options for visit should be the Dosing Administration Folder). Critical fields such as PD ID, PD Class (Major/Minor) and Source are automatically derived by the custom functions and does not require manual selection. Free text entry in this eCRF is limited to certain fields, allowing CRAs to be both flexible and compliant with the standards.

Figure 2. Protocol Deviation eCRFs: Administrative, Programmed and Manual eCRFs
4. PD Data Flow in EDC [Figures 3 and 4].

i. Subject data is entered into EDC eCRFs by the site coordinator. If the data entered in an eCRF meets the condition of a programmed PD edit check (e.g., a Lab result at screening meets an exclusion criteria) a PD query is generated to the site and simultaneously a corresponding potential PD is populated in the Administrative PD eCRF. A custom function automatically derives the PD ID, Visit, Form, Field, Log Line number, Time-Point, PD description, PD class, PD code associated with each PD in the Administrative PD eCRF. The potential PDs are generated in the Administrative PD eCRF have a PD confirmed status of “Blank,” until the confirmation status is updated to “Yes” or “No.”

ii. Site responds to the PD query either by correcting the data entered or confirming via query response that the data entered is correct. Based on site’s action to the PD query, one of the below options are executed for the potential PD in Administrative PD eCRF:

**Option a:**
If the site confirms the data entered is valid, DM manually confirms the potential PD as “Yes” in the Administrative PD eCRF and closes the PD query. The PD confirmed as “Yes” is pushed by the custom function from the PD Administrative eCRF to the Programmed PD eCRF.

**Option b:**
If the corrects the data entered in response to a PD query, and the PD edit check condition is no longer met, the custom function immediately updates the potential PD status to “No” in the Administrative PD eCRF. The PD confirmed as “No” is retained in the Administrative PD eCRF. If the site again changes the data entered and the PD edit check condition is again met, the custom function updates the PD confirmed status from “No” to “Blank.”

**Option c:**
If the site changes data entered associated to a PD edit check after the DM has confirmed the PD as “Yes” in the Administrative PD eCRF, the custom function detects that change and update the PD confirmed status from “Yes” to “No,” and inactivate the PD from the Programmed PD eCRF, that was previously pushed from the Administrative PD eCRF to the Programmed PD eCRF.

**Figure 3. Protocol Deviations Data Flow in EDC**
RESULTS

This process of capturing PDs in EDC has been implemented across several oncology and rare disease studies at Agios. PD trend analysis reports and metrics are currently being developed using data visualization tools connected to the EDC system. These reports and metrics enable study teams to detect outliers and trends across trials and sites over time [Figures 5, 6 and 7]. The ability to identify trends and detect root causes of PDs provides the ability to make corrective actions on time and reduce the occurrence of PDs.

A standard suite of documents including PD eCRFs, developer’s guide, PD specification, PD plan and training material has been developed to make the process efficient, standard and scalable. SDTM mapping and programming of PDs have seen a significant improvement in efficiency. Study teams now spend less time sorting and correcting recorded PDs, which allows more time for implementing correcting actions. The standardization and automation of this procedure increases resource productivity, as well as save time and money.
Increasing the Efficiency of Protocol Deviation Collection and Reporting in Clinical Studies
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**Figure 5.** Protocol Deviations by Category and Site

**Figure 6.** Protocol Deviations by Major, Minor and Site
CONCLUSION

The next steps on this path include creating system alerts for major PDs, Key Performance Indicators (KPIs) and tracking reviewed PDs. As we continue to improve the process, we envision seamless implementation on new studies.

The initial implementation of this process was challenging because it required all operational requirements be included in the EDC system which is not always flexible. There is always some resistance in transitioning from an established, known process, to a new process that not only requires training but changes to current practices and SOPs. Changes are not always comfortable, yet the industry made the transition from paper to EDC and now to Machine Learning and Artificial Intelligence (AI). As Agios continues to make the PD process more robust, we hope there will be other contributors in the industry to add technological advancements to other current platforms/processes.

FIGURES

- Figure 1: PD Deviation Specification
- Figure 2: PD eCRFs: Administrative, Programmed and Manual
- Figure 3. Protocol Deviations Data Flow in EDC
- Figure 4: Protocol Deviation Confirmation and Routing in EDC
- Figure 5. Protocol Deviations by Category and Site
- Figure 6. Protocol Deviations by Major, Minor and Site
- Figure 7: Protocol Deviations Trends across Oncology Studies
KEYWORDS: Protocol Deviation, Standardization and Automation, Major and Minor Designation, Detecting protocol deviations in Real Time, Detect Outliers and Trends Across Studies, Online Edit Checks.

REFERENCES:

ABOUT THE AUTHOR:

Loona Borgohain  
Associate Director, Clinical Data Management  
Agios Pharmaceuticals

In the world of clinical data management every number on a spreadsheet and every curve on a plot represents a life. When I received my master’s degree in Biomedical Engineering, I knew that I wanted to make a difference and be challenged every day. I believe my experiences from being a programmer to my current position as an Associate Director of Data management in Oncology at Agios, I have fulfilled my aspirations. I have worked for CROs and Pharmaceutical companies gathering some rewards and accolades along the way. I have also been fortunate to be involved in fighting complex, aggressive, and often fatal cancers. The reason that I am fired up every day, is because I know that I am closer to bringing a lifesaving drug to a patient. I know because I see the data.
Case Study: Electronic Data Capture System Validation at an Academic Institution

By Dinesh Pal Mudaranthakam1,2, Ron Krebill1, Ravi D Singh3, Cathy Price1, Jeffrey Thompson1,2, Byron Gajewski1,2, Devin Koestler1,2, Matthew S Mayo1,2

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RESEARCH SUPPORT:
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INTRODUCTION:
There has been a great amount of innovation in research informatics since the transition from paper records to digital formats. The impetus for such initiatives was to increase the efficacy, reliability, and portability of research data. In the first generation of innovation, data were transcribed into commercially available databases or spreadsheets that provided the capacity to construct a harmonized data table. While this methodology has a rudimentary utility, its adaptability is significantly limited. Each study has unique design and operational characteristics that may not be adaptable to a pre-existing database or spreadsheet data architecture. Furthermore, when dealing with clinical research data, there are other important considerations that these initial approaches cannot cope with.

Electronic Data Capture was a progeny of the federal Paperwork Reduction Acts of 1980 and 1995. In a broad sense, both acts were road maps for the standardization of information collection and optimized storage information structure that could be shared among federal departments to support the functions of the federal government. By October 2003, federal agencies were able to warehouse and maintain digital transactions from individuals or entities. However, outside the federal government, most academic and private service entities were slower to adopt EDC systems. Lack of human and financial capital resources, changing regulatory policy, and technological innovations were significant barriers to EDC implementation.
Electronic systems are an efficient platform to capture and warehouse data. However, it is also important to note that system users and regulatory bodies should be able to trust the data in these systems. A properly validated EDC provides the financial study sponsor and regulatory bodies a level of confidence that the data at each functional level is trust-worthy: data capture, warehouse management and data export.

The process of validation ensures a robust evaluation of the user interface transcription to the database level as well as the export interface transcription from the database level to an external file. The United States Food and Drug Administration (FDA) has published an electronic data system validation guidance, 21 Code of Federal Regulations Part 11 21 CFR Part 11, [1],[2] that codifies requirements for each of the components of the system. Below is the bare minimum system validation checklist prescribed by FDA as part of 21 CRF Part 11.

- **Subpart A – General Provisions**
  - Scope
  - Implementation
  - Definitions

- **Subpart B – Electronic Records**
  - Controls for closed systems
  - Controls for open systems
  - Signature manifestations
  - Signature/record linking

- **Subpart C – Electronic Signatures**
  - General requirements
  - Electronic signatures and controls
  - Controls for identification codes/passwords

For the specific definition of Title 21, please refer [https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=11](https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=11)

One of the critical components of 21 CFR Part 11 is the implementation of electronic signatures. Guidance is provided by the FDA for validation and implementation of electronic signatures. In general, electronic signatures must be constructed from at least two unique identification components: identification code, and user password. Both of these components are directly associated with a unique system user. Electronic signatures are considered legally binding and the equivalent to a person’s handwritten signature[3] when a system complies with 21 CFR Part 11.

In 2012 The University of Kansas Cancer Center and the Department of biostatistics jointly adopted a commercial electronic data capture system known as eResearch. The use of the electronic data capture system allows direct data entry for research activities by researchers, which reduces the issues associated with capturing research data on paper. The goal of EDC implementation was to gradually expand the services Biostatistics and Informatics Shared Resource (BISR) to highly regulated FDA and pharmalogical treatment trial. The groundwork for 21 CFR Part 11 certification began in 2016 and was completed in April 2018. The purpose of this paper is to provide an overview for achieving system validation (21 CFR Part 11 compliance) for an Electronic Data Capture system at an academic institution.

**MATERIALS AND METHODS:**

A compliant system is expected to perform according to the defined user and functional requirements, is secure from unauthorized or accidental change, and accurately records authorized changes while maintaining an audit trail of user actions. To evaluate our EDC system’s capacity to comply with the requirements of 21 CFR Part 11, the BISR contracted an independent Information Technology (IT) compliance consultant to conduct a gap analysis. The gap analysis identified the current EDC system’s deficits and capabilities with respect to the requirements of 21 CFR Part 11. This three-day process included the majority of the stakeholders who interacted with or supported the system.
Stakeholders included personnel such as data managers, information security, system engineers, application administrators, quality assurance specialists, and regulatory experts. The external team of experts interviewed all stakeholders and summarized the needs of the system to become 21 CFR Part 11 compliant. The summary report of the gap analysis served as a template to create the Validation/Evaluation Plan once BISR decided to move forward with achieving compliance.

**SYSTEM VALIDATION:**

System Validation is a set of actions used to check the compliance of any electronic system element with its purpose and functions. These actions are planned and carried out throughout the life cycle of the system. In this case, we have performed a retrospective system validation since it had already been successfully deployed and was currently in use at the University of Kansas Medical Center[4]. The system validation coincided with a system upgrade that was underway at the time. BISR was responsible for the validation since they both own and manage the system[1]. Annual reviews are conducted by an external consulting team to verify that any future system upgrades and changes are performed per the BISR standard operating procedures surrounding system validation compliance.

**METHOD:**

An evaluation plan was developed after determining that the eResearch system was deemed a system requiring evaluation. Evaluation of the system ensured that the system performs according to the defined user and functional requirements, is secure from unauthorized or accidental change, and accurately records authorized changes while keeping a compliant audit trail. This effort is to verify that eResearch is compliant with all requirements of 21 CFR Part 11, as summarized in Table 01[5].

**Table 1: Summary of Evaluation Package Resources & Responsibilities**

<table>
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<tr>
<th>Role</th>
<th>Responsibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS: Package Sponsor</td>
<td>Provides consulting and expert knowledge on compliance process, as well as GCP training. Trains users on how to set up testing environment and monitor testing conditions.</td>
</tr>
<tr>
<td>QC: Quality Control</td>
<td></td>
</tr>
<tr>
<td>PM: Package Manager</td>
<td>Identifies and leads a Package Team:</td>
</tr>
<tr>
<td></td>
<td>• Approve the Test Plan and the Test Summary Report, along with managing the testing environment.</td>
</tr>
<tr>
<td></td>
<td>• Drives the Package process and identifies ad-hoc members as needed.</td>
</tr>
<tr>
<td></td>
<td>• Drives item preparation, establishes and manages package archive, and checks the quality of documents in production for their ability to pass audits.</td>
</tr>
<tr>
<td>TC: Test Coordinator</td>
<td>• Authors Test Plan and other test documentation, including the Test Summary Report.</td>
</tr>
<tr>
<td></td>
<td>• Identifies and trains testers informal testing practices.</td>
</tr>
<tr>
<td></td>
<td>• Manages a formal testing process.</td>
</tr>
<tr>
<td>T: Testers</td>
<td>Execute test scripts informal testing.</td>
</tr>
<tr>
<td>SUP: Supplier[s] of products, services, platforms, or consulting the support</td>
<td>• Perform assigned tasks agreed to as specified in the contractual agreement, by standards and guidelines.</td>
</tr>
<tr>
<td></td>
<td>• Provide documented evidence for their contribution to the Evaluation package.</td>
</tr>
</tbody>
</table>
Through the validation process, the following documents were developed, and the testing was performed (see Figure 1) [8].

Validation Plan (Lifecycle: Plan): The Validation Plan described the scope of the project, including defining the modules in scope of the validation within the eResearch system. Some eResearch system modules were excluded from the Validation Plan as they were not actively utilized at the current time by the stakeholders.

Validation Risk Assessment (Lifecycle: Plan & Risk analysis): This document identified potential risks and defined actions that were taken to mitigate these risks, if applicable.

User Requirement Specification (URS) (Lifecycle: Specify): URS addressed the technical controls, procedural controls, capacities, accuracy, security, fault tolerance, physical environment, and training requirements.

Functional Requirement Specification (FRS) (Lifecycle: Specify): FRS addressed the functional controls, procedural controls of the system, how it operated and the expected functionality.

Test Plan (Lifecycle: Plan): Test Plan addressed all the testable user requirements and functional requirements. Additionally, this plan identified the best practices [6] that were followed during the execution of each test plan.

**Figure 1:** System Validation Lifecycle
Installation Qualification (Lifecycle: Verify): An IQ package is addresses validating the system after the software has been successfully installed. In our case, we inherited the IQ package from our vendor, who was responsible for installing the application on premise.

Operational Qualification (Lifecycle: Verify): An OQ package certifies the system is in a stage where it is operational for regular business as expected. IQ and OQ packages set forth the execution of a defined set of tests using test scripts that contain the instructions, expected results, and acceptance criteria. These packages also include a section to record the results of the testing of each script.

Master Traceability Matrix (Lifecycle: Verify and Report): The Master Traceability Matrix shows the relationship between each user requirement and corresponding test script(s). The traceability matrix summarizes that each URS and FRS was successfully tested.

Validation Summary Report (Lifecycle: Report): The Validation Summary Report summarizes the results of the software validation project including a summary of the plan execution and the decisions as to whether the system qualified or not.

**Table 2: List of Standard Operating Procedures and Testing modules**

<table>
<thead>
<tr>
<th>SOPs developed</th>
<th>URS Test Matrix</th>
<th>FRS Test Matrix</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Procedure for Controlled Documents</td>
<td>• User/Access Management</td>
<td>• Users/Access Management</td>
</tr>
<tr>
<td>• Service and Repair</td>
<td>• Study Management</td>
<td>• Customization – code developed for an internal purpose</td>
</tr>
<tr>
<td>• Server Back Up/Monitoring</td>
<td>• Study Team Management</td>
<td>• Randomization</td>
</tr>
<tr>
<td>• System End User Training</td>
<td>• Patient Management</td>
<td>• System Features</td>
</tr>
<tr>
<td>• Good Data Management Practices</td>
<td>• Patient schedule Management</td>
<td>• Study Access controls</td>
</tr>
<tr>
<td>• Vendor Access</td>
<td>• Patient Adverse Event</td>
<td>• Patient Status controls</td>
</tr>
<tr>
<td>• Change Management</td>
<td>• Patient Form</td>
<td>• Custom Reports</td>
</tr>
<tr>
<td>• Document Standards</td>
<td>• Form Library</td>
<td>• Audit Reports</td>
</tr>
<tr>
<td>• Controlling End-User Access and Access Request</td>
<td>• Reports</td>
<td></td>
</tr>
<tr>
<td>• Resolving Patient Record Duplication</td>
<td>• Quality Checks</td>
<td></td>
</tr>
<tr>
<td>• Server SSL Cipher Strength Levels and Security Analysis</td>
<td>• Help and Library</td>
<td></td>
</tr>
<tr>
<td>• Ad-Hoc Query Reporting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Calendar Creation Notification and Milestones</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Electronic Case Report Development</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Procedure for Incident Management</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Disaster Recovery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Adding a new Study</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Case Study: Electronic Data Capture System Validation at an Academic Institution

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Additionally, the team performed and documented a complete disaster recovery test to validate the backups and recovery capabilities. The team also participated in Good Clinical Practices training, which reinforced the importance of following controlled procedures to maintain the system in a validated state.

Table 03 is a summary of Time and Cost investment for system validation [7].

**Table 3**: Time and Cost analysis for system validation

<table>
<thead>
<tr>
<th></th>
<th>Time</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gap Analysis</td>
<td>30 days</td>
<td>~$8,000</td>
</tr>
<tr>
<td>Develop and review – Standard Operation Procedures (SOPs)</td>
<td>60 days – (2 full-time employees spending a couple of hours every day; consultants review)</td>
<td>~$19,000</td>
</tr>
<tr>
<td>Develop Test Scripts</td>
<td>20 days – (1 full-time employee spending a couple of hours every day; consultants review)</td>
<td>~$3,000</td>
</tr>
<tr>
<td>Execution of Test Scripts</td>
<td>20 days – (this included multiple stakeholders such as regulatory team, study coordinators, administrators, etc.)</td>
<td>~$3,000</td>
</tr>
<tr>
<td>Training</td>
<td>One day – In-person training for 3 hours, which included two parts basic and advance Part 11 training</td>
<td>~$1,500</td>
</tr>
<tr>
<td>External Consultant</td>
<td>150 days – worked with the BISR team at every step</td>
<td>~$26,200</td>
</tr>
<tr>
<td>Grand Total</td>
<td>~150 days to develop and implement required elements for system validation, certification</td>
<td>~$60,700</td>
</tr>
</tbody>
</table>

Note: Table 03 is a rough estimate of the cost at a research institute performing a one-time 21 CFR Part 11 electronic data capture system validation. This cost could vary across other institutes depending upon team size, skills, and network infrastructure. The above table does not include annual reviews, or additional day-to-day costs of complying with additional processes that might be required to achieve system compliance.

**CONCLUSION:**

The overall validation process yielded benefits as well as challenges. The greatest challenge was keeping momentum to keep the system validation project in alignment with the timeline. Not only did the process reinforce the importance of having these controls in place, but it also introduced efficiencies in our day-to-day process for managing and maintaining the electronic data capture system. This process also encouraged the team to be more flexible with covering cross-functional responsibility as the need arose to take on additional tasks. By following specified procedures, the end users were ensured that they were generating reliable data that could be used to advance their research with confidence.

Along with the benefits, there were a few challenges that the team had to overcome to complete the system validation process promptly. Challenges included the sponsor identification for system validation. Receiving valuable stakeholder input promptly and active involvement was sometimes difficult due to conflicting schedules.
ACKNOWLEDGMENTS/FUNDING
The research reported in this publication was supported by the National Cancer Institute Cancer Center Support Grant P30 CA168524 and used BISR core.

KEYWORDS:
System Validation; Electronic Data Capture (EDC); Food and Drug Administration compliance (FDA); Electronic Signatures; Audit Trail; Standard Operating Procedures (SOP).

REFERENCE

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ABSTRACT
The conduct of clinical trials has seen various changes since the introduction of risk-based monitoring. In addition to the Food and Drug Administration’s (FDA) guidance on the risk-based monitoring (RBM), factors such as low cost and improved data quality have influenced the adoption of the RBM model by the clinical research industry. RBM relies heavily on the real-time availability of data, and the industry’s shift towards electronic data capture (EDC) has also provided the key tools through which this model can be realized. Cross-functional collaboration is undoubtedly required to carry out the RBM process and each group (namely: Biostatistics; Clinical operations and Pharmacovigilance) have a role to play, including clinical data management (CDM).

A survey was conducted to gauge the response of clinical research professionals with regards to the impact of RBM on the design and conduct of the industry lead EDC studies and its influence on CDM activities. The survey focused on the areas of database build; data management plan (DMP); edit checks; data collection; data quality and the role of data management. RBM experience expressed in number of years, confirmed the expected trend of its adoption across the industry. The overall results of the survey indicated that most participants felt the impact of RBM on various CDM processes. Nevertheless, there was some difference in opinions based on the job role for certain survey questions.

KEYWORDS
Risk-Based Monitoring, clinical data management, electronic data capture, database, data management plan

INTRODUCTION
Clinical trial conduct has evolved over the years into a complex and multi-faceted activity. Considerations around regulatory compliance; ethical conduct; patient safety and technological advancements have influenced the way clinical trials are designed and conducted. The introduction of RBM has been a recent contribution to the changing landscape of clinical trial conduct, came with the release of the FDA guidance document on this topic. It points out that overall study quality could be achieved if more focus is placed on the possible risks towards critical data and processes which are necessary for the fulfilment of study objectives, rather than routine site visits and 100 percent source data verification [1].

With EDC systems, the data are available in near real-time, which allows for an instant overview and reporting of clinical trial data. As such, EDC plays an important role as one of the tools required for RBM studies [2]. The RBM model relies on a cross-functional approach to trial conduct, and this includes CDM, whose power to recognize data patterns makes them a key proponent in the RBM process [3].

The study sought to answer the following questions:
1) How did the discipline of CDM adapt in order to accommodate risk-based monitoring?
2) In what ways did the EDC design and build activities and the overall CDM activities support RBM?
3) Is it possible that the changes seen in CDM today would have occurred despite the introduction of RBM?

STUDY DESIGN:
Simple random sampling was applied to select the participants from a group of pre-identified clinical data managers and programmers. No survey was found that could address the purposes and objectives of the study, so a new questionnaire was created.
The survey design was based on a 5-point Likert scale with 24 questions that were divided into groups based on the various data management activities, namely: database design and development; DMP and edit checks; data collection and quality and the overview of RBM impact.

In terms of data analysis, the independent and dependent variables previously defined are the job role and participant attitudes, respectively. The null hypothesis (H0) for all the questions assumed that no relation exists in terms of the answers provided by clinical data managers and programmers. A p-value of less than 0.05 was determined to be statistically significant. Descriptive statistics in the form of frequencies and percentages were used to examine the data.

RESULTS:

Demographics:

Respondents were from various countries, however, the majority were from the United States and South Africa, with 24.5% and 53.1%, respectively.

**Figure 1.** Country of employment

Requests for participation were distributed evenly between clinical data managers and programmers. However, from all the respondents, a large majority were clinical data managers at 71.4 %, with programmers only making up 28.6 % of total participants.

Most respondents possessed over 3 years of experience working with clinical studies that utilized the RBM model. This fact confirmed the expected trend of more organizations adopting the RBM model since its introduction in 2012.
Table 1: Frequencies of RBM Experience vs. Job Role (N = 49)

<table>
<thead>
<tr>
<th></th>
<th>Clinical Data Manager</th>
<th>Programmer</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 1 year</td>
<td>% of Total 18.4%</td>
<td>% of Total 6.1%</td>
<td>% of Total 24.5%</td>
</tr>
<tr>
<td></td>
<td>Count 9</td>
<td>Count 3</td>
<td>Count 12</td>
</tr>
<tr>
<td>1 - 3 years</td>
<td>% of Total 22.4%</td>
<td>% of Total 4.1%</td>
<td>% of Total 26.5%</td>
</tr>
<tr>
<td></td>
<td>Count 11</td>
<td>Count 2</td>
<td>Count 13</td>
</tr>
<tr>
<td>More than 3 years</td>
<td>% of Total 30.6%</td>
<td>% of Total 18.4%</td>
<td>% of Total 49%</td>
</tr>
<tr>
<td></td>
<td>Count 15</td>
<td>Count 9</td>
<td>Count 24</td>
</tr>
</tbody>
</table>

Survey responses overview:

With the exception of 2 questions, the summated scores for each of the Likert scale questions revealed that RBM played a significant role in the changes seen within the various CDM processes.

**Figure 2. Summated responses for all Likert scale questions**

DISCUSSION:

Overall, the attitudes of the CDM professionals were positive in relation to the impact of RBM on CDM activities.

i) Database Design and Development:

The Clinical Data Interchange Standard Consortium (CDISC) standards have played a role in the increased adoption for EDC and have also played a role in the standardization of database set-up [4][5]. The ability for integration between systems and databases is an important factor in RBM studies [6]. Most participants agreed that a link exists between the introduction of RBM and the increased adoption of CDISC. One of the best practices for CRF design has been to collect mainly critical data specified in the protocol, especially the data associated with safety and efficacy endpoints [7]. As such, majority of participants disagreed with the statement that the collection of critical datasets within the database is seen mainly in RBM studies.
Since the RBM model is based on the identification of possible risks, by extension this would apply to CDM activities. However, in the context of database development, most programmers opposed this view, whilst clinical data managers agreed. A reason for the disparity in attitudes is because both roles have a different part to play in the set-up of a clinical trial database and therefore the process of identifying risks is not the same. Data managers collaborate with clinical operations and other functional areas in developing the risk assessment categorization (RACT) tool. The activities of programmers in relation to RBM involve “data analysis and modelling; report generation process and programming for trend analysis” [8].

ii) DMP and Edit Checks:
Classification of critical data and the process of data collection & acquisition, data handling, data review & reconciliation and quality assurance are just some of the activities outlined within the DMP. 76% of data managers agreed that the DMP authoring process had become aligned with the identification of risk as a result of RBM.

In terms of edit checks, many participants did not experience a change in the complexity of programmable edit checks for RBM studies. A review by Medidata Solutions revealed an increase in the rate of auto queries programmed within clinical trial databases, as well as a 16% increase in the rate of auto queries over a 3-year period that corresponded to a 28% decrease in site monitoring visits [9]. Although that review did not conclude that this was due to RBM, most participants agreed that the total count of edit checks increased for RBM studies, as compared to non-RBM studies.

iii) Data Collection and Quality:
Most participants agreed that there was no marked increase in the number of eCRFs for RBM studies. Alternative methods of data collection, such as electronic patient-reported outcome (ePRO) and electronic medical records (EMR), and the increased ability to integrate these e-source platforms into EDC systems may have negated the need to expand the data collection modules associated with eCRFs.

Source data verification (SDV) has long been one of the main methods by which site monitors could ensure data quality. Therefore, the participant agreement regarding the change in SDV requirements since the introduction of RBM was expected. Many EDC platforms such as Medidata Solutions do facilitate the set-up and tracking of targeted or reduced SDV as seen with RBM studies [10].

iv) Overview of RBM Impact:
The core aim of this study was to confirm the attitudes of CDM professionals on whether RBM had made an impact on CDM activities. A large proportion of participants were in favour of this statement. Likewise, most participants also showed an understanding of what role they played within the overall RBM process. Interestingly, respondents disagreed with the statement that changes seen within CDM would have come about despite the occurrence of RBM. The evolution of any function or process is inevitable if it is to remain relevant. Therefore, further research is required in order to define and attribute accurately the impact that RBM has had on CDM processes.

Respondents disagreed with the statement on whether critical data collection was most prevalent in RBM studies. This can be explained by the general practice of designing eCRFs to collect data which answer the protocol questions and satisfies the statistical analysis requirements, rather than all the data which is generated during a trial [11].

CONCLUSION
This survey explored whether RBM had an impact on EDC and CDM processes. The theoretical framework based on available literature and research proposed that the introduction of risk-based monitoring would to some extent play a role in the changes seen within CDM and the processes performed by this function. Overall, the attitudes of data management professionals were positive in relation to the study’s aims.

Results gained from this research can provide focus areas for organizations to examine how CDM processes can be leveraged to facilitate RBM. By understanding the role of CDM within the RBM model, there is an opportunity for industry to involve CDM in the process of risk assessment, whilst also developing a risk-based approach in the planning and execution of CDM activities.
The Impact of Risk-Based Monitoring on the Design and Conduct of Electronic Data Capture (EDC) studies: Industry Perspective for Clinical Data Management.

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KEYWORDS: Risk-Based Monitoring, clinical data management, electronic data capture, database, data management plan.

REFERENCES

ABOUT THE AUTHOR:
Nomfundo M November
I am a clinical research professional from South Africa. I graduated with a degree in Medical Microbiology, and then later completed a Master’s degree in Clinical Research. I have over 9 years’ experience within the industry – 3 were in clinical operations as a Clinical Trial Assistant, and the rest in Clinical Data Management.
I thoroughly enjoy the technical aspects of CDM and feel privileged to be a part of the clinical research industry.
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