Society for Clinical Data Management
DATA DRIVEN

Data Basics

To advance excellence in the management of clinical data

A PUBLICATION SUPPORTED BY AND FOR THE MEMBERS OF THE SOCIETY FOR CLINICAL DATA MANAGEMENT, INC.

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Letter from the Editors

Michelle Meany and Chandra Wooten

Dear SCDM Members,

Welcome to the Spring Issue of Data Basics!

The role of the Data Manager seems to be ever-changing. With ongoing technological advances and increased outsourcing at many levels, the roles and responsibilities of data managers continue to evolve. One of the biggest challenges facing data managers today is that of creating and managing numerous partnerships between diverse groups of people, both within one's organization and outside of it. You will find several interesting articles in this issue that address the theme of "Reaching across the Organizational Divide."

If you want to get a handle on SAE reporting, be sure to check out "Complexities in Reporting SAEs: What Do the Regs Really Say?" on page 12. For an update on the latest data collection technology, read "Patient Reported Outcomes: Data Collection using Digital Pen Technology" on page 8.

The Publications Task Force is always looking for new articles on topics of interest. This year's issue topics are listed below with their deadlines. If you are interested in submitting an article and have any questions, please feel free to contact anyone on the Editorial Board. The topics for upcoming issues are as follows:

Summer: Virtual Teams/Project Management – Working in the Virtual World
Submission Deadline: 04/06/2010

Fall: – Data Quality
Submission Deadline: 07/06/2010

Winter: Pharmacogenomics and Metabolomics
Submission Deadline: 10/05/2010

We hope you enjoy this issue.

Sincerely,
Michelle Meany & Chandra Wooten
Data Basics Co-Editors

Building the Infrastructure to Support Multiple FSP Relationships

Cindy McLaughlin, Data Management Vendor Manager for Biogen Idec

In late 2005, Biogen Idec's data management department made the decision to deploy a new business model using Functional Service Providers (FSPs) to achieve operational milestones and has initiated three separate FSP relationships since 2006. The advantages of this approach include achieving flexibility and scalability using external resources, and having real-time access to data as FSPs work directly on Biogen Idec systems and follow Biogen Idec processes. Additional goals were to obtain quality, cost-efficient work from the FSPs and build more strategic and effective outsourcing relationships.

These multiple FSP relationships have required a significant infrastructure to facilitate efficient operations. Some key components included a department reorganization, creation of flexible resourcing contracts, defined processes for resource

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Letter from the Chair

Ralph J. Russo

Dear Member,

The theme for this issue of Data Basics is "Reaching Across the Organizational Divide." The nature of data management puts all of us "in the middle" of various functional groups or activities each day. In addition, technology today allows virtual work arrangements that can create a divide between members of the same data management team. Whether we're looking for our statistician's guidance on protocol parameters, coordinating data cleaning across geography, or working with our clinical colleagues to prepare for an investigator meeting, we need to bridge the divides that exist to be successful.

SCDM's educational offerings can help you develop strategies to deal with the demanding task of managing across divides. If you are working in or managing a virtual team, or just trying to manage the teams needed for SAE reconciliation, consider attending one of our upcoming Career Development path webinars to learn how to cope with these challenges.

The society's strategic goals also strive to bridge divides. The Board of Trustees has developed partnerships with organizations that focus on different aspects of clinical trial execution and management. We are exploring how we can expand our educational opportunities in India and other regions of the world to better serve data managers no matter where they choose to work. We are reaching out to organizations that are involved directly and indirectly to the industry we serve. We'll see the benefits of these partnerships in 2010 and beyond. ■

Ralph J. Russo

Building the Infrastructure to Support Multiple FSP Relationships

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and account management, an established governance structure and financial controls.

The data management reorganization was structured to drive the execution of the pipeline and meet the needs of the FSP business model. The data management leadership team determined that success with the FSP model is built upon joint ownership, consistency in process and technology and tight integration of data management and FSP resources.

The leadership team assessed internal core competencies, identified subject matter experts, principals and administrators and created a new vendor management function within data management. Other department functions include operations, which comprises an early- and a late-phase center of excellence; program management; clinical technology; training and compliance; and medical coding. All functions collaborate and depend on each other for effective FSP management.

New roles and responsibilities were defined for each function and subsequently affected most, if not all, data management documentation. Relationship management documentation includes the following:

- Vendor governance job aid
- Managing FSP resources job aid
- Managing data management contracts & purchase orders job aid
- Roles & responsibilities matrix
- Engagement handbooks that include a partnership communication & escalation plan
- Steering committee charters
- Flexible resourcing contract

To ensure success and promote clear expectations working in this new organizational structure, this documentation was revised

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and changes communicated to the FSPs.

A series of relationship management tools in the form of applications and databases have also been deployed to assist in these partnerships. These tools aid in user account management, resource and project management, performance management and financial management.

Another key component of the new infrastructure included the creation of an open-ended, flexible FTE contract. Prior to the implementation of these contracts, the majority of time was spent managing changes in study assumptions due to protocol amendments and out-of-scopes. Consequently, implementing other key requirements of working in this model was time-constrained. The Biogen Idec contracts management group was instrumental in challenging how contracts are typically structured and simplifying the change management process. This outside-of-the-box thinking has saved a tremendous amount of time and effort and no longer do we manage change on a micro level.

The flexible contracts cover all current and future work and specify resource levels instead of individual projects and tasks. Data management activities are not itemized in the contract, but rather are referred to in standard operating procedures (SOPs), work instructions and job aids. The management of the ever-changing assumptions and task lists are managed outside of the contract. Resources are viewed as Biogen Idec contractors and once trained work can begin in a matter of minutes or hours. The Biogen Idec vendor manager monitors resource utilization and the spend against the purchase order.

Because the contracts are created with flexibility as a central characteristic, they allow for resource allocations needed for fluctuations in study timelines. The contracts also significantly reduce the need for change orders. Amendments can be created to increase or decrease the core resource levels and to date, amendments have not been needed.

The Biogen Idec IT department deployed a consistent data management outsourcing desktop for all three FSPs. The data management team established specific Biogen Idec – FSP eRooms to share project information. This web-based communication tool is used daily for effective team communication. The Biogen Idec IT department also provides support to the FSPs via a clinical systems support desk where calls are logged and triaged appropriately.

As the volume of work increased, it was necessary to establish a resource management process to follow when onboarding new external team members for resource approval, account management and training. The FSPs are able to access all training documentation via the Data Management Resource eRoom. This serves as an organized, centralized resource and facilitates change control as only the current versions of approved data management documents are stored in this eRoom.

All data management and FSP team members are entered into a master team contact list that resides on the main page of each FSP eRoom. A combined Biogen Idec-FSP data management team also jointly discusses future workload and resources. Data management's goal is to establish open, transparent relationships with its FSPs which in turn will return value to the partnership and operational activities.

Successful relationship management is based on vendor governance and oversight which is required at all levels within Data management. Three levels of vendor governance have been established. The first level is the project team, in which data management and FSP team members are respon-

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sible for resolving day-to-day issues. If issues cannot be resolved by the joint project team, those issues are escalated to the Outsourced Operations Committee. This committee is a functional-manager level. It meets monthly to discuss operations management and ensure consistency across project teams. Issues that need to be further escalated are brought to the attention of the Data Management Steering Committee. This committee, which meets quarterly and consists of director-level management, is focused on departmental strategy and business development activities. Regular review of objective performance feedback and metrics occurs at each level of vendor governance. Annual relationship management surveys also collect subjective relationship feedback.

Biogen Idec has also established monthly functional team meetings for both programming and data management. All internal data management staff and FSPs jointly participate in these monthly meetings and the meetings are chaired by the principal clinical programmer and principal clinical data manager. The objectives are to serve as an open forum for the discussion of functional area questions and changes and to ensure the use of common tools and consistency across projects and partners. All FSPs hear the same message at the same time and this forum manages the delivery of all functional area changes. With transparency and streamlined communication with the FSPs, data management promotes and receives efficiency and value.

In order to assist with budget monitoring and planning, financial controls and budgeting tools have been established. After entry of each vendor's monthly invoice amounts, these tools allow for vendor management to know at a moments notice the status of the budget and purchase order as well as the summarization of total project costs. Because the contracts are setup to secure resources, the vendor manager also tracks FSP resource utilization and charts this information to aid in forecasting for future workload and costs.

Building a consistent infrastructure to support this new model was important, but it is equally important to analyze the results and ensure the model is meeting the expectations of the business. The following is a summarization of observations and experiences of working in this business model.

Biogen Idec data management's internal headcount has increased slightly over the years while access to external FSP resources has flexed to meet the pipeline demands and changes. Data management has leveraged the experiences and strengths of the FSPs to provide additional value to the relationship by working not only on production but process improvement work as well.

Ever so important in the FSP model is to maintain consistency with technology, process, people and projects as that will lead to efficiencies and return value to the sponsor. Otherwise, the sponsor and FSP will spend additional time communicating and managing the changes by updating documentation, providing additional training and handling gaps in knowledge transfer. That extra time spent reduces operational and cost efficiency. The development of strong partnerships with experienced FSP team members delivering quality work ensures that sponsor's expectations can be met.

Keys for successful partnerships include building a consistent infrastructure with one set of clear expectations for all FSPs. This allows sponsors to be better able to compare, assess quality and determine value. It also allows for efficient management of multiple partnerships. An infrastructure that has built-in flexibility and simplifies the change management process throughout the relationship will bring efficiency to the partnership. Both the sponsor and the FSP must promote excellent communication as it allows for team members to openly discuss challenges and risks, and manage change. With these proactive steps taken, more often than not the partnership will result in met expectations and relationship satisfaction.

Since continued success depends on continuous improvement, the focus moving forward is to deploy better systems that can streamline processes and result in significant time savings for data management. Such systems might include software or tools to better manage external resources, metrics management, as well as budget planning and analysis. Most importantly, a key thing we can do is enhance partnership communication via quarterly newsletters and team meetings. The objective is to ensure that project team members are recognized for the partnership's project-specific accomplishments as it is that day-to-day effort that returns rewards to the entire relationship. ■

Cindy McLaughlin has 16 years of data management experience and began her career at Seragen and PAREXEL International where she held database technical lead and management positions. Over nine years at Biogen Idec, Cindy has served as clinical systems analyst, manager, clinical systems and vendor manager.

Reaching Across the Organizational Divide – A More Organic Paradigm

Dawn Shewchuk, RN, BSN, CPC, CCDM

It is probably fairly common knowledge that problems and difficulties in the business world arise from poor communication across groups and teams. Despite best efforts at transparency and harmonization, information silos often impede success.

Many articles address bridging across top level, middle management, or multi-levels or bridging via an "information trough" running down silos at all levels. Frequently these articles are garnished with photos depicting rigid skyscrapers or concrete silos with metal bridges built-in to connect one to another. The imagery is of sturdy vertical structures connected by horizontal bridges, fixed in place, ready to withstand the elements.

Other articles suggest softer methods of bridging the organizational divide. Communication is usually the recommended antidote. Teamwork and connecting groups through collaboration and other means is foundational. This article will address a more organic idea for reaching across the organizational gap.

In discussing these concepts with a highly imaginative colleague, it was suggested to view the organization as a tree. Further, to reach across the organizational gap is to branch out to reach other branches, or to reach the other side of the tree. How would I get from my branch to another branch on the other side of the tree?

I found this strikingly different from "the silo model." Anyone can picture the diagrams –vertical "buildings" with solid horizontal "bridges" in place to get from Point A to Point B. The tree model however, suggests reaching out individually or collectively, and growing in non-fixed directions.

Our tree paradigm discussion further evolved to liken reaching as a vine instead of a branch. A vine grows and can be trained directionally. It can be flexible and change directions. It can grow up, down, across, wrap around, recede back.

Therefore, I propose another opportunity to reach across the organizational divide in addition to bridges, communication and teamwork is to grow across, or at least towards the other "branches" of the organization by education and information sharing. I will attempt to explain using coding as an example of how this additional method could help to reach across and collectively achieve the desired results.

Coding medical data is done for several reasons:

- Consistent data classification across all protocols within a project, as well as globally across all projects
- Classification of verbatim text into predefined categories so statistical reports can be generated for data analysis
- Providing a central repository for all terms and codes
- Meeting reporting needs – CIOMS, Annual reports, NDAs
- Contribute to product package inserts

Sometimes challenges arise between functions or teams. What would happen if different groups such as Drug Safety and Clinical coded the terms differently?

Suppose medical data were recorded differently between protocols within a project. What impact would that have on the project? For example, if cancer progression was being measured, and terms were recorded as cancer of a certain body site progression, how would that be coded according to the organization's coding conventions? Would it be split to code both the cancer of the body site and cancer progression? Would it be coded to only the cancer of the body site? Would it be coded to only the cancer progression? What would happen if some protocols within a project captured both the body site and the progression and others captured just the progression?

In the examples above, the obvious solutions would be harmonization. The more harmonized the processes, the more problems can be alleviated. Such as:

- global standards across projects and organization
- global dictionaries
- same coding conventions
- same database platforms across the organization
- same language only accepted
- autoencoding
- algorithms

It may not always be possible to meet all of the above conditions. In those cases, communication and teamwork are required to bridge the gaps. Serious Adverse Event Reconciliations and Dictionary Migrations are two examples of what could be required in those cases. Teams should discuss ahead of time to plan how data is captured, coded, and reported and how this will impact their results.

For our coding example above, improving knowledge of these issues could avoid potential gaps or failures in the organization's individual or collective goals. Reaching to other areas we want to collaborate can be done by growing ourselves like a vine toward that branch we want to reach. Individuals or groups could check resources within the organization. Study the organization's training modules, SOPs and coding conventions. How will these impact the team's trial, project, or deliverables? What dictionaries are used? Get to know the dictionaries. For example, in the MedDRA dictionary, check which System Organ Class (SOC) the Lower Level Term (LLT): Blood pressure high goes to. Then, check the same for the LLT: Blood pressure increased. Get to know which if any of these types of situations would impact results.* Ask questions. Call or email a resource in the organization.

Other opportunities for education include online, the Society for Clinical Data Management Web site, *Good Clinical Data Management Practices*, textbooks,

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Will the Roles of CRAs and Data Managers Ever Merge?

Pratik D. Kulkarni, MSc, CCDM, Data Manager, Syne Qua Non

If you are a data manager who toiled on paper studies for all these years and are now handling an EDC study, this question must have definitely crossed your worried mind. The fact of the matter is that clinical trials have seen major changes in the past few years in terms of new processes, technologies and even the models in which clinical drug development is outsourced. The roles of CRA and data manager are central in a clinical study team and there will always be a curiosity to see how these roles develop. Many clinical research professionals have worked both as a CRA and a data manager, and many continue to explore interchanging between these roles to have a larger understanding of the clinical trial process. It is understandable that many data managers and CRAs try to switch their profiles, as it offers a logical continuation to the existing knowledge they gain of the trial process. Even though the core competencies of the job role of a CRA and a data manager are different, they share more similarities between them than any two other roles in a clinical study team. Besides, the similar entry level academic expectations make the role of CRA and data manager quite interchangeable. The interdependence is also a result of their more or less equal stakes in the clinical trial process. All of this makes the question of whether the role of CRA and data manager will merge, a very interesting pursuit.

The changes in technology, especially EDC, have made this proposition a very realistic possibility. All pharmaceutical companies, smaller biotechnology companies and even the CROs have been moving away from a paper-based process. EDC implementation may be a cost intensive process, but it offers a whole array of enabling factors, including efficient validation systems, effective management of real-time data, and the most important one for any company- quicker turnaround times between data collection and data analysis.

With the changes in technology one has to change the ways in which the business is conducted. EDC has brought a whole new concept of electronic signatures, resulting into a complete makeover of many existing SOPs, processes and trainings. But that is just one side of the story; an equally interesting aspect would be to assess how this technology impacts the conventional structure of a clinical trial team.

The Past

CRAs and data managers shared similar stakes in the clinical trial process, but traditionally the role of a CRA and a data manager were demarcated.

CRA – An individual largely responsible for site initiation, recruitment of the patients, overseeing site compliance with regulatory requirements, and performing source data verification. Additionally, with the remainder of his time and energy he liaises with the data manager to resolve any data issues.

Data Manager – An individual who "kicks" in at the protocol and CRF finalization stage and is responsible for annotating the CRF, creating the database structures, drafting an edit check plan, running edits, creating queries and managing them.

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Reaching Across the Organizational Divide – A More Organic Paradigm

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external courses, or workshops. There are blogs, listservers, and social media. Be sure to know and consider the source when using the latter types of resources.

Educate others, share knowledge or skills which could benefit other individuals or teams across the organization. Many articles can be found in references such as *Drug Information Journal* and SCDM regarding clean data being vital for coding. Joseph in a presentation to the Society for Clinical Data Management in 1999 postulated the simplest way to improve coding is to control the verbatim term. Education and information to foster consistency can be extended at investigator meetings to all team members.

After a while, my colleague and my discussion of "the organizational tree" turned silly, picturing "vines strangling the tree" and "no one watering the tree". In these times, we must work more efficiently. Trees overcrowd each other, sunshine and water may be scarce. Branches may wither and die if they are not given a severe pruning first.

It takes further energy and resources to communicate, work with teams, educate ourselves, share information, and teach others. It requires effort and initiative, but that sort of reaching that grows ourselves can take us where we want to go. ■

Dawn Shewchuk entered the world of medical coding after 10 years in clinical nursing. An inclination toward the technical led toward medical informatics, then the Clinical Data Management Certificate Program at UCONN College of Continuing Studies. She is certified by the American Academy of Professional Coders and CCDM.

Will the Roles of CRAs and Data Managers Ever Merge?

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The data manager's responsibilities went until the database "lock", after which statistics took over the analysis of the data. Over the years, the CRA and data manager established their work processes with the CRA largely managing the site and the data manager managing the data. Their paths rarely crossed.

The Present

This earlier structure is now being challenged because of the implementation of EDC. It has created a convergence in the traditional role of a CRA, data manager and even the project manager. As the clinical trials progress on the EDC platform, a merged role will start to appear over the years. Presently, even though many CROs and pharmaceutical companies have implemented EDC, they still subscribe to the traditional structure by having both data managers and CRAs on a trial. However, the roles of an "EDC empowered" CRA and data manager have changed as compared to the traditional roles. The main reason for this change is that the EDC offers real-time access to data to all stakeholders of a clinical study team. The CRA can review the data by logging into EDC even before reaching the site and is then better prepared to handle the data issues. By remotely monitoring, how "clean" the data are, the CRA can now decide how frequently each site is to be visited and also determine what kind of training will be required at each site. With EDC, the CRA is almost completely eliminated from the process of query management. The satisfactory resolution of the queries is completely managed between the data manager and the site personnel; the CRA is only required to change the status of the page to "locked" once he deems it to be clean. On one hand EDC has increased the CRA's understanding of the data manager's profile because they share a common system, and on the other hand it has lessened their burden of resolving data issues.

The corollary of a common system can also be extended to data manager having an increased familiarity of the CRA's day-to-day activities. Not only can a data manager can keep a close watch on which pages are getting locked, but also advise the CRAs on the sites requiring maximum attention and keep them abreast with the status of the recruitment process. The automated edit checks incorporated in the EDC has minimized the data manager's grind in the process of discrepancy resolution. The instructions given by the EDC system are accurate to the extent that sites can rectify the errors by themselves. Data managers can now concentrate their efforts in understanding data trends, ensuring medical coding, and organizing reconciliation with external data. Any key inputs by analysing such data and reporting to the CRA can make a big difference towards cleaning the database faster.

The Future

What we are currently seeing is just the beginning of the role overlap. As EDC systems mature, more changes will be made to the basic design. In the time to come one can expect the EDC to have enhanced features to enable more automation, with more complex and comprehensive edit checks. All such changes would mean the CRA and data manager would be required to do much less on the system. This may in turn lead to the evolution of the traditional roles to the next level. Increasingly it will become a rule for both CRAs and data managers to be well versed with both ICH GCP as well standard data management practices like GCDMP. The personnel working on such combined roles will be helping the site to fill the CRF in the protocol defined manner, communicate with them and provide clean data. This will ensure the data are being cleaned almost simultaneously with visit schedules. Even under the present day technology, it is possible to implement a combined CRA role for less complex Phase 1 studies with small patient populations. A complete merger may not be possible for large complex studies as yet, but one cannot deny the fact both CRA and data manager are now required to know a larger spectrum of the process.

Conclusion

There are practical challenges that come with adapting to a new structure. A very important prerequisite of a merged structure is the fact that it will work most effectively if the pharmaceutical companies choose similar vendors for monitoring and data management. A close communication between the CRA and data manager is the key to the success of a possible merged role. However, not all outsourcing models allow for such an arrangement. Besides, there are many CROs successfully operating on specialist and niche data management services and still remain preferred vendors with large sponsor companies.

But the changes in technology and the constant pressure to cut trial costs may lead to the emergence of the merged structure. Some companies are already experimenting with conventional roles. The position of clinical data liaison in Criterium Inc. establishes such a merged role. With the passage of time, more such roles will start to appear in the market. CROs and service providers that offer value proposition at lower costs through innovative approaches will continue to be the chosen suppliers for pharmaceutical and

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Patient Reported Outcomes: Data Collection Using Digital Pen Technology

Ellen Loonan Goldberg, CCDM, Director, Electronic Clinical Data Systems, Writeresult, LLC

What is a patient reported outcome? A patient reported outcome, or PRO, is "…any report coming directly from patients (i.e., study subjects) about a health condition and its treatment… without the interpretation by the clinician" (FDA 2006)

PRO questionnaires are used to measure multiple aspects of how a patient experiences a health condition or treatment. How does a patient feel while experiencing a condition or how do they function during the study treatment? What is the emotional impact of a condition or how does a condition affect a patient's ability to execute his or her daily activities? The PRO data provide a patient's perspective on a condition or treatment, as well as evidence of a treatment benefit from the patient's viewpoint.

PROs can be generic, condition-specific or treatment-specific; they are used across many therapeutic areas. These questionnaires are designed for the patients to complete themselves without influence from other parties. To achieve this goal, the patient completes the forms without assistance from the investigator, study coordinator or relative/friend, and in a quiet room without distraction. PROs are available in multiple languages and contain accepted standardized questions collected globally.

Historically, PRO responses were completed by the patient on paper and sent to the clinical data management department for double key entry. This process was lengthy and time consuming, as you can imagine, especially when forms for entry were shipped from thousands of miles away. How do we reduce the time to database lock?

Another option that can be employed to collect PRO data is electronic data capture (EDC). Many patients, especially in global studies, do not have computers or computer experience. Many patients may be uncomfortable using new technologies and are reluctant to sit at a computer and record their responses. Additionally, site personnel do not have the time to enter their patients' questionnaire responses from paper into the computer used for EDC.

Use of hand-held devices is also an option to collect PRO data. This technology can cause anxiety in patients who are not experienced in current technology or may have poor manual dexterity due to their existing conditions.

The approach my company took for collecting PRO data was to have patients use a digital pen to capture their patient reported outcome responses. The pen is slightly thicker than a standard ball point pen but it's comfortable for patients of any age. Since the digital pen uses a ballpoint ink refill, patients across many therapeutic areas have been content using it to write their responses; it is not necessary to press down hard. One pen can be used for all patients at one site.

How does the pen work? Data are captured in the pen's memory. A camera and pressure sensor in the pen record the way the patient writes each stroke to facilitate automatic interpretation of the responses. The pens are rechargeable and hold enough charge, and they have enough memory, to store many PROs before the investigational site transfers the data to data management.

The site is given a CD containing software for transferring the data from the pen. Once this software has been installed, the study coordinator can easily transfer data to data management where verification and cleaning occur. All the investigational site needs to do is plug a pen 'cradle' into the USB port in their computer, and insert the pen into the cradle. The data will automatically transfer from the pen to data management via the Internet. High-speed Internet access is not required; this is helpful in global studies where only dial-up access is available.

All transferred data are automatically interpreted using optical character recognition (OCR) methods. Numeric, alphanumeric and checkbox fields can all be interpreted. Even visual acuity scales (VAS) can be measured automatically by the system. The interpreted responses are automatically merged with their corresponding PRO form template enabling the PRO image to be viewed by the clinical data coordinator (CDC). Viewing only one screen, the CDC then compares the PRO image with the system's interpreted values. The CDC can then override anything that was not correctly interpreted. The verified data can then be committed. The data is stored in the database within minutes from anywhere in the world. If there are any values that are not legible, the CDC can query the site. Data written with digital pens on PRO forms can be locked quickly.

We have incorporated another tool into this process. Once the form data have been transferred, the PRO form is visible via the Internet. This process is extremely useful for CRAs and sponsor managers who are responsible for the site data. The CRA can review the completed patient PROs before their monitoring visit; this enables them to use their time at the site more efficiently. PDF files of the PRO forms can also be archived onto CDs for U.S. Food and Drug Administration review.

Digital pen technology has proved to be our most efficient method of collecting patient reported outcomes, whether they are recorded in the investigator's office, or written at home by the patient.

- The patients view this as a normal practice since they're writing on paper with a pen.
- It's fast and easy for the sites to transfer data.
- The sponsor and sites can see the PRO forms via the Internet

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Clinical Research Data Tasks and Definitions

Meredith Nahm, MS, Duke Translational Medicine Institute and School of Health Information Sciences, University of Texas at Houston; Constance Johnson, PhD, Duke University School of Nursing; Anita Walden, Duke Translational Medicine Institute and School of Health Information Sciences, University of Texas at Houston; Todd Johnson, PhD, School of Health Information Sciences, University of Texas at Houston; Jiajie Zhang, PhD, School of Health Information Sciences, University of Texas at Houston

The first formal list of clinical trial data management tasks was published in *Data Basics* in 1999[1]. This task list helped scope the *Good Clinical Data Management Practices* (GCDMP) resource, and provided a foundation for the certification exam. The GCDMP and certification exam, however, are cornerstones of a field that is rapidly changing. For this reason, periodically revisiting the foundations, such as the growing evidence base and the task list, is important to our field. We started work in Fall 2007 to re-survey those tasks associated just with the collection and management of data in clinical research. Limited to just the tasks that directly operate on data, this work is considerably more narrow than the original task list; for example, project, vendor and people management tasks are not included. However, this work went a step deeper in searching for authoritative definitions for each task and defining those tasks for which no definition could be found. Additionally, this work went beyond tasks common to industry sponsored clinical trials to include the broader field of clinical research as defined by the National Institutes of Health.*

We postulate that although different methods and different terms to describe them are used across clinical research, there is a level of abstraction at which tasks can be defined that 1) uses common terminology across clinical research, and 2) is specific enough that it is useful. Use of common terms to describe our methods is critical to promoting best practices and to leveraging the rich literature available across clinical research data management. A primary goal of this work is to provide the tasks and definitions to the curation team for the Medical Subject Headings (MeSH), to improve the indexing of our literature base and ultimately decrease the fragmentation that exists. The initial drafts were developed and vetted through the 2008 and 2009 SCDM Annual Conferences, and the Society newsletter, *Data Connections*. With this report, we release the updated version.

Background

Limited work has been done to formally and systematically describe the activities and objects used in managing clinical research data. The initial SCDM task list[1] consisted of 67 tasks grouped into nine categories. The 1999 task list was used as one input to this work, although it contained no definitions. Later, in 2004, SCDM released its Certified Clinical Data Manager (CCDM) certification exam and associated core competencies[2]. The current exam consists of 112 tasks grouped into 26 categories, called core competencies.[2] Both SCDM task lists are based on common job responsibilities and necessary skills for the profession. As such, the lists appropriately include job tasks that are not direct operations on data. In addition, the membership of SCDM has historically comprised individuals from industry with only a minority from government-funded research or academic institutions, thus, the lists may not cover some components of the broader clinical research projects, e.g., epidemiology, registries, investigator initiated studies and health services research, for which data are managed in these arenas.

A different approach to identification of clinical research related tasks was taken by Deitzer, et al, who abstracted tasks from 20 cancer clinical trial protocols, systematically generating a list of 102 activities employed in the conduct of the sampled clinical trials.[3] This list, however, is significantly broader than operations performed on clinical trial data, i.e., all tasks abstracted from cancer protocols, and was cancer-specific.[3] In addition to the extant task lists, the Data Management Association (DAMA)[4], the Clinical Data Interchange Standards Consortium (CDISC)[5] and SCDM[6] maintain glossaries, however, the majority of terms are nouns, rather than activities. For example, the term "data collection form" may be defined by one of these authoritative sources, but the task of designing a data collection form was not. Likewise, while the Biomedical Research Integrated Domain Group (BRIDG) information model covers regulated clinical research, nouns are covered, but tasks generally are not. The ontologies of clinical research (OCRe)

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The National Institutes of Health define clinical research as including patient-oriented research, epidemiological and behavioral studies, outcomes and health services research.* **Patient-oriented research: *This type of research involves a particular person or group of people or uses materials from humans. This research can include studies of mechanisms of human disease, studies of therapies or interventions for disease, clinical trials or studies to develop new technology related to disease.* **Epidemiological and behavioral studies:** *These types of studies examine the distribution of disease, the factors that affect health, and how people make health-related decisions.* **Outcomes and health services research:** *These studies seek to identify the most effective and most efficient interventions, treatments and services.*

Clinical Research Data Tasks and Definitions

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and clinical investigation (OCI) are similar in that respect. A classification of tasks or activities and associated authoritative definitions does not yet exist for operations undertaken in the collection, processing, and management of research data. Maintaining such a task list is important to a discipline because it scopes and defines competencies required for practice in the discipline, as well as provides a link to the evidence-base on which practice recommendations should be made.

Methods

Development of Tasks and Definitions

The work presented here was initially developed based on an extensive literature review, mapping to the SCDM certification exam core competencies, mapping to the SCDM Task List, and the author's domain expertise. In keeping with work-centered modeling principles, the tasks presented here are purposively explicit and implementation-independent descriptions of the work performed in clinical research data management.[7] As such, they may be useful in requirements specification for technology design, as well as an essential step in usability evaluation.[8, 9, 10, 11]

Importantly, this work covers the tasks performed in collecting and managing data that directly impact the data. The objects used to perform these tasks, such as a case report form, are not explicitly shown here, but are defined in other places, e.g., GCDMP, CDISC Glossary. Additionally, detail about different methods that may be used, e.g., interactive double data entry as opposed to use of third person compare is represented in the definitions. Importantly, the current version does not distinguish between different technologies, i.e., EDC or paper methods; we care only about the methods involved, not whether or not a Web-based system was used, or whether the device was a hand-held or a laptop personal computer. The decision to remain technology independent was made because our interest is in the data and operations on the data. As such, the tasks and definitions remain stable over time and may be helpful in describing and providing a foundation for evaluation of new technologies and methods. Also of importance, we capture the tasks only, and do not portray the iterative nature of clinical research data management work, e.g., we do not distinguish between developing data validation checks versus making changes to existing data validation checks. In keeping with our scope of tasks that directly impact data, some included tasks, are not performed by data managers in some organizations, e.g., medical record abstraction, data entry, clinical measurements, source document verification. These tasks are included because they operate directly on the data and because the data manager needs knowledge about the methods employed, and may have input into those methods.

Initial versions were modeled using formal top- and mid-level ontologies, i.e., web ontology language (OWL) and the Basic Formal Ontology (BFO). However, because we do not think this ontology (tasks, their relationships and definitions) will be used in machine reasoning, the tasks are not represented here. Further, the representation here was far more conducive to the planned review and use of this work.

Focus Groups, Peer Debriefing and Comment Collection 2008-2009

Focus groups are unstructured interviews with small groups of people who interact with each other and the group facilitator. [12] They have the advantage of leveraging group dynamics to stimulate discussion, gain insights and generate ideas in order to pursue a topic in greater depth.[12] Three focus groups were held at the 2008 SCDM Annual Conference to assess the draft tasks and their definitions. From the 552 registered attendees, 101 were randomly selected to receive invitations to the focus groups. Invitees could attend any of the three scheduled groups. There were three to six people in each group, a total of 14 participants. The ontology was split into sections of approximately 15 tasks. These tasks were split among the group participants. Attendees reviewed their chosen section and then participated in discussion around the following questions:

- Are there tasks missing from your section? If so, what are they?
- Are there definitions of terms in your section that you are uncomfortable with? What changes or other sources for definitions would you suggest?
- Are there synonyms for any of the terms in your section that you are aware of?
- Is the hierarchy correct? If not, what would you change?

Comments were recorded by the participants in hard copies of the task graphic and definitions. Written comments were received from all participants. Additionally, the recordings from the groups were reviewed for additional comments not recorded on the hard copies. Following the conference, updates were made to the ontology and associated definitions. This protocol was reviewed and approved by the Duke Medical Center, *IRB Pro 00009183*.

The updated version was included in the January 5, 2009, *Data Connections*, distributed to SCDM membership. No additional comments were received.

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Clinical Research Data Tasks and Definitions

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Due to the informal nature of the comment request, we could not assume that the lack of comments was an indication that the representation of the tasks was accurate. Under a protocol amendment, information packets were provided to the attendees of the SCDM 2009 Annual Conference to obtain further review and comment. The packets included: 1) instructions for commenting (similar to those from 2008), 2) a graphical representation of the tasks (similar to Figure 1), and 3) the associated definitions. There were 642 registered attendees for the conference, including vendors and speakers. All attendees were encouraged to comment by recording their comments directly on the hardcopy and placing it in a comment box during the conference.

Results

From the 2009 Annual Conference, 60 comments, not including typos and formatting, were received from 12 reviewers. Forty resulted in changes, 20 did not. The updated graphical representation of the tasks is included as Figure 1. The small numbers at the bottom of the task boxes in Figure 1 show the mapping to the SCDM certification exam core competencies. Type and part hierarchies are shown for tasks, no other hierarchies were pursued. Seventy-five tasks are represented, of which 55 have authoritative definitions, i.e., from a regulatory authority, standards body, professional society, or published book. The updated definitions are included in Appendix 1. Responses to the comments from the 2009 Annual Conference are provided in Appendix 2.

Discussion

We release the initial version to the membership for trial use, similar to an HL7 Draft Standard for Trial use (DSTU). We anticipate several uses of the tasks. The first is comparison to GCDMP sections as they are updated; such a comparison will point out areas where the section could provide more domain coverage. The second use is as a source for terminology. Having a common source will increase the likelihood that researchers and practitioners mean the same thing when they use the same word, particularly across industry and academically oriented studies and across other types of clinical research. Third, the tasks and definitions will remain available as a context for research in the field, and could also be a resource for software selection, development, and evaluation by providing categories for a more detailed functional analysis. The fourth use is in better indexing the literature base for our discipline. These results will be provided to MeSH in hopes that some terms and definitions will be adopted. Better indexing of our literature will help us all retrieve more complete references, and thus leverage more of the evidence base when we need information on a particular task. In a futuristic scenario, it is easy to envision clicking on a task box and linking through to a PubMed result set with published articles on the topic.

Conclusion

From this work, we conclude that there is a level of abstraction at which clinical research data management tasks can be defined that is both useful, and common across many application areas of clinical research. This work represents one small step in bridging the gap 1) between the practice of clinical research, data management and the supporting evidence base, and 2) between different practice areas within clinical research.

Acknowledgements

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Complexities in Reporting SAEs: What Do the Regs Really Say?

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"If a patient is randomized to the study but never receives study drug, must site staff report serious adverse events (SAEs) for this patient?"

This excellent question was recently asked in the CDM group on LinkedIn. The responses ranged from assertions that regulations require that either serious or all AEs must be reported starting at informed consent (IC), to suggestions that, in the absence of any internal company guidance, they should be captured as they can be eliminated from the analysis based on the "definitely not related" assessment.

I think the answer is probably "it depends!" As with most aspects of clinical research, deciding what to collect and to report requires understanding the risks associated with the different choices. That requires understanding, among other things, the context of the question, where and when the research occurred, and who intends to use the data and for what. Below you will find my thoughts on some of these factors.

(Incidentally, if anyone can point me to a place in a regulation where it defines "on study" as beginning with signing IC, and/or where it clearly states that SAEs must be captured beginning at IC, I'd be grateful. I was unable to locate any such statement, but my sources are primarily US regulation and guidances, ICH guidances, ISO standards, and some European regulations and guidances.)

The Question

The original question was whether SAEs occurring after randomization but before treatment must be reported. Because of the range of responses from the LinkedIn Group, I have also expanded the question to "Must all AEs and/or SAEs occurring on study be reported?"

There are two elements to consider here.

- The first is the meaning of "reported." Does it mean that AE/SAEs must be *reported on a CRF*? Or does it mean that AEs/SAEs must be *reported to regulatory authorities under the expedited reporting rules*? Or does it mean that AEs/SAEs must be reported in the study report? Each of these is a valid question, and the answers depend upon a number of factors, some of which are discussed below.
- The second is the meaning of "on study." Is it when IC is signed, or at randomization, or the beginning of baseline, or something else? One could use the term "enrolled" instead, but it turns out that neither term is clearly defined. It does imply that timing plays a role, and this is explored later in this article.

What Do the Regulations/Guidances/Etc. Say?

As mentioned above, I did not find any regulations or guidances that defined when to start capturing AEs/SAEs beyond those potentially associated with study treatment. Here is what I did find that relates to this discussion.

ICH E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting

- Focuses on the requirements for expedited reporting, rather than on determining the timing of what should be captured
- Lists the minimal information necessary to send a report, which includes a treatment having a plausible causal relationship with the event
- States that there are circumstances where certain SAEs may be exempt from routine reporting, such as when the SAE may be the primary outcome and expected. *(KH: This indicates that there is no absolute rule that all SAEs must follow expedited reporting, although this does not speak to whether they are captured.)*

Definition: Adverse Event (from ICH E2A):

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease ***temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product****. (emphasis mine)*

Different regulations/guidances have slightly different wording, but all require a potential association with treatment, so if the event occurred prior to treatment it cannot, by definition, be an AE. Thus, a sponsor could capture only those AEs beginning with study treatment and be technically completely compliant.

Definition: Serious Adverse Event (from ICH E2A):

During clinical investigations, adverse events may occur which, if suspected to be medicinal product-related (adverse drug reactions), might be significant enough to lead to important changes in the way the medicinal product is developed (e.g., change in dose, population, needed monitoring, consent forms). This is particularly true for reactions which, in their most severe forms, threaten life or function.

This is part of the definition of an SAE, and indicates some reasons why expedited reported should happen for SAEs. As SAEs are, by definition, a kind of AE, they too cannot occur prior to treatment initiation. In reality, there are times when treatment may not be the only factor to consider, especially with respect to SAEs.

ICH E3 Structure and Content of a Clinical Study Report

- *5.3 PATIENT INFORMATION AND CONSENT: How and when informed consent was obtained in relation to patient en-*

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rolment, (e.g., at allocation, pre-screening) should be described.

- *10.1 DISPOSITION OF PATIENTS: (…) It may also be relevant to provide the number of patients screened for inclusion and a breakdown of the reasons for excluding patients during screening, (…)*

Item 5.3 suggests that IC and enrollment are not necessarily the same time point, and 10.1 reminds us that subjects can be excluded during screening, prior to treatment.

ICH E6 Consolidated Good Clinical Practices

- In section 6.9.2, it states that the clinical trial protocol should include *The number of subjects planned to be enrolled. In multicentre trials, the numbers of enrolled subjects projected for each trial site should be specified. Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.*

This implies that enrollment refers to the subjects needed for analysis, not those screened.

21 CFR Part 312.62

(b)Case histories. An investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. (…) The case history for each individual shall document that informed consent was obtained prior to participation in the study.

The regulation does not define what "participation" means, but since signing IC means agreeing to participate in the study, anything that happens after IC is, by definition, participating in the study. It's a bit circular, but there it is!

ISO 14155.2 Clinical Investigation of Medical Devices for Human Subject – Good Clinical Practice

Definition 3.32: Point of Enrollment - time at which, following recruitment, a subject signs and dates the informed consent form

This brings up an interesting point:

1. Patients sign IC prior to participating in the study, meaning prior to any study procedures being performed (including those for screening)
2. Screening procedures are performed both to determine eligibility and, when appropriate, establish baseline values
3. If eligible, the subject continues. It is only at this point that the subject can be considered to be "on study." Prior to this, eligibility has not been established, and so the subject must not be in the study, as GCP does state that ineligible subjects should not be included! (ICH E6 4.5.1 & 6.5.1)
4. Randomization may or may not occur at this point, depending upon the study design (there may be washout, baseline observation or other periods prior to randomization)
5. All of which means that the ISO definition of enrollment does not follow the same logic as the other regulations and guidances.

Even here it's not completely clear, because later in the same standard, the Monitoring requirements state that the monitor should verify that:

f) signed and dated informed consent forms have been obtained from each subject at the point of enrollment and/or before any clinical investigation-related procedures are undertaken,

g) only eligible subjects as defined in the CIP are enrolled in the clinical investigation,

If only eligible subjects are enrolled, and enrollment happens at the time of IC, then all subjects who provided IC must be eligible, which cannot be true because screening procedures have not yet begun!

FDA's Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use, April 2006

5.1.1.2 Other safety issues requiring expedited reporting. Other safety issues also qualify for expedited reporting where they might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the trial, for instance: (…)

c) new events related to the conduct of the trial or the development of the investigational medicinal products and likely to affect the safety of the subjects, such as: - a serious adverse event which could be associated with the trial procedures and which could modify the conduct of the trial, - a significant hazard to the subject population such as lack of efficacy of an investigational medicinal products used for the treatment of a life-threatening disease, (…)

5.1.2 What should not be reported? Expedited reporting is not usually required: - for reactions which are serious but expected, - for non-serious adverse reactions whether expected or not. It is generally not necessary to report events that are considered unrelated to the investigational medicinal product.

This last part speaks particularly to the distinction between capturing the SAEs and doing the expedited reporting. Section c. above brings in the point that study procedures may also cause SAEs, and although SAEs by definition must occur during treatment, study procedures happening during pre-treatment periods may also be important.

The take-home message is that one has to think about the context of the definitions, the spirit of the regulations/guidances/etc., and the specifics of the trial in order to determine the best course.

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The Importance of Context

Why do we capture AEs and SAEs in a trial? We are trying to determine if the treatment causes undesirable effects that outweigh its benefits. We want to tease out the relevant events from the "background noise." If randomization has happened appropriately, and there are no other sources of treatment assignment bias, and the investigators understand how to identify treatment emergent AEs, then the incidence of any given non-treatment-related AE in each treatment group should be the same, as should the incidence of the AE in the pre- and during-treatment periods. This suggests that, absent any additional risk factors or protocol design requirements, it should be unnecessary to capture AEs prior to treatment.

The question then becomes what to capture and/or what should follow expedited reporting rules. The following are other factors to consider.

- *Screening procedures*: if the screening procedures are invasive or otherwise risky, capturing AEs/SAEs prior to randomization may be desirable, as it may influence the conduct of the trial, and/or the requirements for patient monitoring after the product is approved. Whether they should be subject to expedited reporting would depend upon an assessment of the other factors below.
- *Indication/population*: how severe is the indication? If the subject population is quite ill, and SAEs are expected, then it may be appropriate to capture the SAEs, but not do expedited reporting. This should be defined a priori in the protocol after discussion with regulatory authorities, the company's regulatory affairs and clinical colleagues.
- *Time frame:* If the decision is to capture SAEs for subjects who were randomized but never receive treatment, what time frame should be used? Should they be captured only for subjects who didn't receive treatment because of the SAE? Should the subjects be monitored for the same follow-up duration as treated subjects? Should the SAEs be subject to expedited reporting, considering that it is known the subject was not on treatment?
- *How much is known*? If very little is known about the indication, treatment, study population and/or expected SAEs, then it would be appropriate to capture and report more information, as it is more likely that an event would be unexpected. As noted above in the FDA's AE reporting guidance Section 5.1.2, if certain SAEs are already known to occur and this is documented in the Investigator's Brochure, expedited reporting may be unnecessary, even if they are still "reported" on the CRF.
- *Geographic location:* where is the study being conducted? The regulatory authorities in different regions may have different requirements or preferences for how much should be captured/reported.
- *Study design:* randomization does not necessarily happen when the subject is enrolled, meaning that IC is signed and all eligibility criteria are met, and the subject is cleared to continue in the study. There can be washout periods, baseline observation periods, or other epochs that occur prior to randomization, and collecting AEs and/or SAEs may or may not be necessary. Much depends on the procedures performed and whether there is interest in comparing AE/SAE incidence before and after treatment.

Consequences of Reporting and Not Reporting

There are other, perhaps less obvious, consequences to these decisions.

- *Capturing SAEs:* capturing SAEs requires providing considerably more information than is necessary for AEs. This is an additional burden on the site. It can also be a burden and expense for the sponsor, as it requires additional attention at each stage from data entry to data management to analysis and report writing.
- *Reporting SAEs:* The burden is even greater when the expedited reporting processes are followed, as this requires completing additional forms, informing the sponsor and also the Institutional Review Board (IRB)/Ethics Committee (EC). The IRB/EC can be swamped with reports of routine events, which reduces their effectiveness. Finally, the receiving regulatory authorities have to distinguish between important events and those that are reported because the site/sponsor/etc. is being ultra conservative. This impairs their ability to respond to the critical events.
- *Analyzing the data:* analysis and study reporting happen using the data that are captured. Whether SAES from randomized-but-not-treated subjects are included in the general intent-to-treat analyses or are put in a separate table is the choice of the biostatisticians, medical writers and clinicians responsible for the study report.

Bottom Line

I don't think it's possible to answer the overall question with an absolute statement of yes or no.

- It is usually appropriate to capture SAEs for subjects who have been randomized but not treated, but they generally don't need to follow expedited reporting.
- It's also usually unnecessary to follow expedited reporting for SAEs for subjects who have signed IC but have not been randomized (assuming randomization is when they are enrolled), but whether to capture them is more ambiguous.
- Generally, it's not required to capture AEs for subjects who signed IC but weren't randomized.

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The caveat is that there are exceptions to every one of these cases, as suggested by the earlier discussions. Like so much of what we do, the decision requires judgment. Regardless of your decision, it is good practice to define clearly in the protocol what is meant by "enrolled," "on study" and any other similarly unclear term.

In order to make the right decision,

- Educate yourself on the variables involved, and read the regulations
- Gather the relevant questions and information
- Talk to the other functional areas – this decision cannot be made in a silo, because other perspectives and knowledge bases are required to ensure that all angles are covered

Your regulatory affairs group may have already spoken with the regulatory agencies about this; a good time to bring it up is at the early Phase II or end of Phase II meeting with the regulators. Whatever decision is made, be sure that it is documented fully, including the rationale for each element, because you may need that documentation later to justify the decision. There are few absolutes in our business, and nowhere is that more true than when dealing with regulations. ■

Many thanks to those who posed and responded to the question on LinkedIn. The thread was accessed on 6 December 2009 at http://www.linkedin.com/groupAnswers?viewQuestionAndAnswers=&discussionID=10132121&gid=77402&commentID=8843270&goback=.anh_77402&trk=NUS_DISC_Q-subject#commentID_8843270

Disclaimer: The author does not work for a regulatory authority, and the material in this article is based on reading the regulations/guidances and applying her own experience and observations. Each company should confer with their internal experts and the appropriate authorities to determine the best approach for their situation.

Will the Roles of CRAs and Data Managers Ever Merge?

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biotechnology companies. In this evolving era of modern technology, whichever role one fits in, continuous learning and innovative approach are the key aspects that can drive you and your company home safe. ■

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EDC Advantage: Shrinking LPO-DBL Timelines in an EDC Study

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Few industries are considered to be as cutting-edge as the life sciences industries. The advancements in drug development and biomedical devices are often astonishing and can sometimes seem like something straight out of a science fiction movie. But the reality is that some of the underlying technologies and business processes are more like old silent motion pictures.

Optimizing the trial process has become an urgent priority for the clinical research industry. With pharmaceutical R&D budgets falling and patent expiries looming, the imperative to streamline the drug development process has become increasingly important. One report states that the cost of developing a new drug is over $1.1 billion, while another indicates declining industry productivity is affecting the introduction of new drug compounds.[1,2]

The industry estimates that only one out of every 5,000-10,000 drug candidates makes it to human trials. Eighty-nine percent of drugs fail from Phase I to U.S. Food and Drug Administration submission. Even with 20-year patent protection, some companies are unable to get their drug to market before the patent's expiration date. The *Wall Street Journal*[11] reports that between 2007-2012, generic competition will cut $67 billion in annual sales from the top pharmaceutical companies as more than three dozen drugs lose patent protection.

Clearly, time is not on the side of the drug industry. It's no surprise that pharmaceutical companies and the CROs which serve as their principal R&D outsourcing arm, are seeking to reduce costs and time-to-market without compromising the legal requirements critical for developing safe drugs.

With these challenging bottom-line realities, the industry is examining alternative approaches for bringing new drug products to market that rely on real-time technologies, such as EDC which has developed over the past 20 years. And while EDC is not a new concept, it is taking a long time to become widely adopted in the pharmaceutical industry. However, organizations are beginning to recognize the value in using EDC. A savings of 25% to 30% is realized by using EDC just from decreasing traditional monitoring/double data entry budgets. It was predicted by Banick[3] that with EDC, time to database lock could be reduced by 43% and queries by 86%.

An attempt has been made in this paper to explain how last patient out to database lock (LPO-DBL) timelines can be reduced for an EDC study.

Number Facts About EDC Advantages Over Paper

- Forrester Research estimates that EDC can deliver operational savings of more than $300,000 for a Phase II trial and more than $6 million for a Phase III trial.[4]
- Novartis, for example, claims that it has saved roughly $100 million a year using EDC; while Pfizer revealed that over a five-year period it saved $85 million.[5]
- According to Pricewaterhouse Coopers (PWC), the shift from paper-based to Internet-enabled clinical trials will bring a 30% to 50% reduction in development time and cost.[6]
- On-site monitoring costs are significantly reduced (up to 75%) by reduction in frequency and duration of monitoring.
- EDC and electronic trials management systems could save life sciences and pharmaceutical firms up to $15 million a year in mailing and protocol distribution costs alone.[7]
- Around 43% of time to lock database could be reduced by EDC as compared to paper.[9]
- Cost savings alone with EDC vs. paper methodologies was calculated to be greater than $60 million per drug.[10]
- Novartis Pharmaceuticals has documented actual savings of $65 million in 2002 by substituting EDC for outsourced paper methodologies.[10]
- Overall EDC provides better data accuracy, data standardization, centralized workflow and management, real-time study results and lower operational costs.

EDC Advantage

Testing new drug candidates is an increasingly complex, lengthy and expensive process. Clinical testing alone currently costs more than $100 million, with large-scale Phase III studies typically costing $2 million to $30 million each. Each day's delay in getting to market is estimated to cost $1 million in lost revenue[12].

In paper-based studies, the time to DBL from LPLV is typically eight to 10 weeks. This milestone is dependent on three processes: retrieval of the last CRF from sites; entry of the final data; and resolution of the last outstanding query. EDC technology improves the efficiency of each these processes, thus significantly reducing this critical time period.[12]

It is the combination of three elements (i.e. People, Process & Technology) which help achieve an earlier DBL from LPO. (Figure-1)

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EDC Advantage: Shrinking LPO-DBL Timelines in an EDC Study

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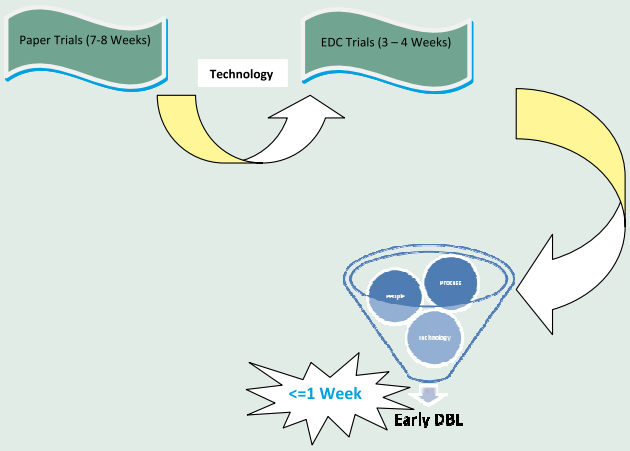

Figure-1: Process Flow for Early DBL

Advantages of Early Database Lock

Database lock is considered as one of the most important and significant milestones in the entire CDM cycle. Adequate efforts are made from the beginning of the project in planning and execution ensure that there is no delay in database lock date, since the cost associated with the delayed DBL is enormous. Some advantages/benefits of an early database lock are highlighted below:

- Significant revenue savings for a customer due to early DBL.
- The expedited database lock in the short-term can influence both the submission of NDAs and in long-term can maximize the patent life of a new drug.[8]
- Creating competitive market position.
- Significant impact on revenue earnings from early market launch.

Factors Affecting Database Lock in an EDC Study

- SDV (source data verification): Delay in SDV of eCRFs during the study can result in creating a huge backlog for site monitors, which going forward can cause potential bottlenecks for any upcoming milestones/deliverables.
- Response to queries (clinical and DM): It is very important to have a quick TAT (turn around time) for resolution of queries by both clinical and DM to avoid a backlog.
- PI (principal investigator) signatures: Not obtaining PI signatures on the case record books as the data are cleaned, SDV'd, frozen and locked will result in a backlog for investigator signatures.
- Data issues identified by biostatistics after the final transfer: Failing to have any interim data transfers done by biostatistics during the course of study will lead to high risk of issues being found near the DBL milestone.
- Resolution of pending issues sent for clarification to respective stakeholders: Delay in resolution of pending issues sent for clarification will have a significant impact on critical milestones such as DBL.

Strategy for Achieving Early Database Lock

One of the strategies for early DBL for an EDC studies can be achieved by implementing the "lock as you go" principle. The core activities that support this principle are:

Operations

- Good understanding about the study protocol and CRF.
- Being current on all activities from the start-up phase.
- Data cleaning, SDV (source data verification), freezing and locking of patients on an ongoing activity rather than done at the end of study.
- Escalation of issues in a timely manner.

Project Management

- Detailed project plan for all phases of study. (i.e. startup, ongoing and closeout).
- Regular transfers to biostatistics to check for any data-related issues and early feedback to data management.
- Identification/Anticipation of risks and having a mitigation plan in place.

Communication

- Effective communication with respective stakeholders both internal and external.
- The above-mentioned points discussed in this strategy are demonstrated in a case study discussed below:

Case Study

The DBL for a Phase II EDC study was achieved within five days from LPO. Some of the facts about the study are as follows:

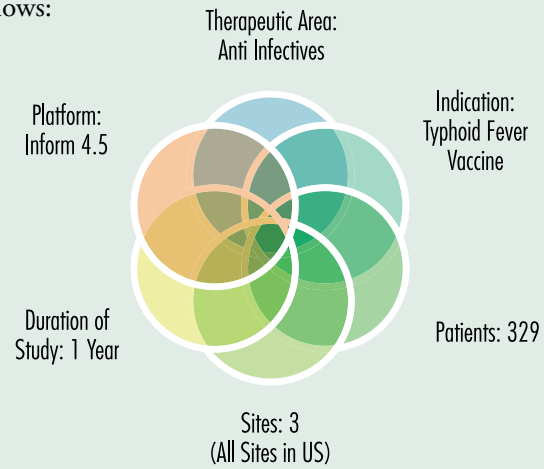

Figure-2: Snapshot of Study.

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EDC Advantage: Shrinking LPO-DBL Timelines in an EDC Study

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The achievement of early DBL was attributed to some of the best practices that were adopted by the project team during the entire cycle of study (i.e. start-up, ongoing and closeout).

Operations

- Excellent coordination and regular follow-ups with concerned stakeholders.
- Weekly teleconferences with project manager, sponsor, programming and data management team members.
- Being current with all data management activities.
- Regular transfers to biostatistics to check for any data-related issues and early feedback to data management.
- Closely monitoring the timelines for milestones and deliverables.
- Passion: From the very beginning of the study, the project team had the passion to set benchmarks.
- Positive Attitude: Despite numerous challenges faced during the study, the team was very positive in taking challenges head on.

Communications

Free flow of communication: We created a project mailing ID to which all team members had access. All project-related e-mails were copied to this e-mail ID so the team was aware of the developments/communications happening on the project.

People Management

- Regular team meetings to discuss the progress of the project and to discuss issues and appropriate action plans.
- Involvement of all functional groups (i.e., programming, biostatistics and data management) during decision making.
- Team was open for suggestions to perform the task in a better/faster way.
- Efficient planning and execution at startup, ongoing and closeout phase.
- Identifying risks in the project and putting risk mitigation plan in place.

Metrics/Turn Around Time

- Quick TAT for resolution of the queries / issues.
- Weekly status reports to respective stakeholders.
- Daily monitoring of key metrics which could become potential bottlenecks for the DBL.
- Cycle time for actioning of queries (i.e., auto and manual) by the clinical sites and data management was very short. This short cycle time for actioning of queries was achieved by sharing the metrics to respective stakeholders (i.e., sites) and following up regularly with those sites until those were inline with the agreed-upon metrics set at the start of the study.

Advantages of Best Practice

Some of the advantages of above-mentioned best practices are:

- Minimal post-production changes
- No risk when nearing any critical milestone
- Delivery of all milestones without any delay
- Early database lock against the expected /target date

Conclusion

Implementation of EDC technology in a study helps us in many ways such as real-time data access, clean data at any given point of time, immediate resolution to queries, locking patient data when clean. Additionally, the LPLV-DBL timelines can be significantly reduced (i.e.) from conventional eight to 10 weeks for paper studies to three to four weeks for an EDC.

These three to four weeks can further be reduced to a week or even less than that by adopting one of the strategies, such as "Lock As You Go" as has been discussed in this paper.

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Effective CDM Training in the 21st Century

Ruizhe (Luther) Zhao, Sr. Supervisor of Data Management, Pfizer; Ling (Linda) Ling, Technical Supervisor of Data Management, Pfizer; Zhenghua (Mary) Wang, Sr. Supervisor of Data Management, Pfizer; Juan (Joan) Huang, Sr. Supervisor of Data Management, Pfizer

On May 9, 2005, two data managers and two data processing associates joined Pfizer China R&D center (Shanghai), as a pilot group of Global Clinical Data Services (GCDS). From the subsequent first big batch of new employees in December 2006 until now, a remarkable expansion formed a department with close to a hundred colleagues working on Pfizer global clinical trials, phases I through IV.

This is a path many organizations may experience; it largely occurred decades ago in Western countries, it is happening now in the BRIC countries (Brazil, Russia, India and China), and most likely such expansions will continue in the future in other rising countries around the world. No matter how the pharmaceutical landscape differs, we hope by sharing our challenges and innovative training program, we can inspire discussion and improvement in each CDM organization.

We are setting and continuously refining a training program which is efficient, reusable, smart and measurable. This is expected to meet the requirements of the rapidly-changing operation environment and deliver long-term values.

It was not an easy path. The expansion was keeping the pace of the industry's development environment in China, as well as the company strategy. At the same time, the technological and legal demands were changing rapidly to keep pace with healthcare requirements. Additionally, one of the biggest challenges has been that experienced data managers in China are a very limited resource. As a result, newly graduated students were included in the hiring plan.

In the past three years, we've had four batches of new employees come onboard with a big percentage of candidates without previous data management experience. Our training capability has had to grow along with the organizational expansion. The training program is repeated evidence of the efficiency and is continuously improved. Now, both the trainers and the materials are a treasured asset of this young organization.

To meet the training needs, the program is formed with four key elements.

Web-Based Training for Pfizer SOPs and Processes

Web-based training is mandatory for Pfizer. It is a series of courses on ICH GCP, regulations, Pfizer SOPs, processes, and systems. It is easy for supervisors to track and monitor employee progress. Also the material and online evaluation is available any time for review. A method of "see it, try it, do it" is used in the Web-based courses, which are very interactive and efficient.

11-Week Interactive Orientation Training on DM Technology Including Periodic Evaluation

The 11-week course is designed to teach the basic technologies of data management and is divided into protocol understanding, database and CRF development, data processing, dictionary coding, discrepancy management, and data listing review.

Methods used during the 11-week session include presentation, group learning and discussion and off-line practice using dummy data. It is a stretch to cover everything in the training program within the 11-week timeframe, but the key to being efficient is setting up clear goals for each section.

Let's take data processing for example. After training and practice are completed for this portion, the goal is for trainees to be able to perform the data entry work with minor assistance from their mentors. An evaluation session is held base on a planned agenda.

This program has proved to be successful and very productive. Experience shows trainees were able to take over new assignments of basic data management work every other week, which fulfilled their passions and involvement in the department.

Long-term (9-12 months) Mentoring Plan

People might ask, "Will the 11-week plan really be enough to create a completely qualified data manager?" Definitely not. In addition to the 11 weeks of intensive training, a 9-12 month mentoring plan is set up for everyone to ensure all required knowledge and skills are captured. It includes clinical trial and drug development foundations, data management skills in different clinical trial stages (study set up, conduct, and close-out) and soft skills.

The plan can be customized for each individual based on her developing progress and project assignment. An experienced mentor or supervisor plays an important role with the trainee during this period.

As part of this plan, DM will join departmental or center-wide group training sessions. for the continuous improvement of technical skills as well as training in such areas as communication skills, decision making and time management.

- **Advanced Training for Lead Data Manger Role**

Included in the long-term mentoring plan, there is advanced training focused on project management, oversight and resource planning. This portion is open for experienced data managers who are ready to take the leading role in a study team.

In general, this training program provides support to ensure our colleagues are capable and qualified to deliver high-quality project work as well as supporting their individual development plans. They are excited and dedicated to their work, getting positive feedback globally for the fast learning and quality deliv-

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Effective CDM Training in the 21st Century

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ery. However, there are still challenges we need to face every day and conquer as fast as we can, such as how to enhance the knowledge of clinical trial and industry standards; how to build up work experience especially in an international company with diverse cultural environment; how to improve colleagues' soft skills.

To support further development, we realized SCDM is a huge training and technical connection resource. About 30 colleagues with more than two years of data management experience are supported to join the SCDM membership and encouraged to pursue the certification. Thus far, we have three Certified Clinical Data Managers and anticipate more. Also, we are getting more and more participation in SCDM training and other activities, such as off-site training sessions and annual conferences. Some small study groups are set up voluntarily by colleagues for the CCDM certification exam. Each member is rotated on each study session weekly. These not only result in more in-depth understanding of data management processes but also a wider vision of clinical trials.

We also provide inter-company short-term opportunities to work with other Pfizer R&D sites. Colleagues can work with global peers face-to-face. This has not only helped on technical skills improvement, but more importantly to understand different cultures.

Considering China's market situation, we have limited talent resources for experienced data managers but a large need for qualified professionals to support clinical research. To enlarge the DM pool, we start one step ahead of university. A three- to four-month intern program was initiated in 2008. Post graduate students from pharmaceutical universities were recruited as interns to prepare DM candidates. In 2009, Pfizer and FuDan University set up a partnership to establish a graduate program in Shanghai. It is a three year Masters Degree program in Clinical Data Management and Statistical Programming.

All in all, we have gained in-progress success from what has been done and the vision for what needs to be done. This experience could benefit other rising organizations and create new ideas for training. There will be different challenges along the way, and these challenges will affect other functions served in the same study team. In Shanghai Center (not only CDM roles but other functions) and also in China Market, we see the same growth pattern. Sharing across teams, supporting each other's training programs and modifying the plan are other important efforts of 'long-term values'.

For everyone's take home message:

- Identify the problems before setting up the plan
- Identify short-term goals and long-term goals for this plan
- The training plan should be smart and reusable
- Always evaluate the progress ■

Ruizhe (Luther) Zhao, ssenior supervisor of data management, Bachelor of Pharmacology, has eight years experience in data management. Ling (Linda) Ling, technical supervisor of data management, Bachelor, has spent nine years in clinical research including three years experience of data management. Zhenghua (Mary) Wang, senior supervisor of data management, Bachelor of Pharmacology, has more than eight years in clinical R&D including more than six years experience of data management. Juan (Joan) Huang, senior supervisor of data management, Bachelor of Biochemistry, has more than 15 years in pharmaceutical industry including six years experience of data management.

Patient Reported Outcomes: Data Collection Using Digital Pen Technology

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within two minutes of transfer.

- Final cleaning by data management is simple and quick.
- The whole process requires minimal time and cost, therefore allowing for a quick database lock and satisfied sponsors. ■

Ellen Loonan Goldberg has more than 20 years of experience in the clinical data management field for three New Jersey CROs and is currently director, electronic clinical data systems, at writeresult, LLC. She started her career as a programmer, and then expanded her skills performing all aspects of clinical data management including developing data management plans, coding, EDC, OCR, creating SOPs, designing reports, edit checks, leading client audits, staff development, working directly with clients and statisticians, and numerous leadership activities. Goldberg has either worked on, or led data management activities for five NDAs and hundreds of studies across numerous therapeutic areas for both small and large pharmaceutical clients.

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