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Standards, Standards, and More Standards

EDC Today is an independent publication on current information and issues in Electronic Clinical Systems (ECS) strategies and technologies for the Biotechnology and Pharmaceutical (Biopharma) industry. Each month we examine topics related to ECS theory, technology, practice, or implementation.

EDC Management has long been a promoter of the use of standards in processing Clinical Data, and is well versed in the benefits of as well as the difficulties involved with developing and using standards. From a strictly business point of view, processes should be both efficient and repetitive for optimal performance. From a practical point of view, repetitive processes can be stifling and lead to complacent job execution. However, it should be noted that good science that follows the scientific method should be repetitive, and certainly the results of a scientific endeavor must be repeatable.

In this issue, we explore some of the benefits of standards, mainly from a business point of view. Some of these benefits have been covered in past issues of EDC Today. We also describe some of the difficulties of managing the standards. Further we suggest that scientists embrace the notion of repeatability, and offer tips on how to prevent drudgery from occurring.

Introduction

In past issues of EDC Today, standards and CDISC have been discussed mainly from the perspective of data interchange. In this issue, standards are presented as useful and necessary business tools.

Recently, someone asked us, "How long should it take to set up a data entry system in EDC?" The real answer to this question depends upon a lot of factors such as the complexity of the study and the extent to which a previous data entry system has forms, database tables, derived fields, and edit checks that can be reused. It is critical from a planning and budgeting perspective to be able to answer this question as accurately as possible.

In the next issue of
EDC Today:

Off shoring Clinical Trials
and Clinical Data
Management

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We investigated this question and believe that on average the setup time can run from between 6 weeks (in the case of a simple protocol where a similar study has already been set up allowing a generous amount of reuse) to as long as 16 weeks (in the case of a complex protocol where all work is essentially ground breaking). However, these numbers should be taken with a grain of salt since different companies will have different staffing levels, different SOPs, and different requirements as to how much documentation must be produced.

Management faces questions of this nature, that is, planning and budgeting, on a regular basis. The process by which one answers a question of estimating time usually involves a comparison to a similar task or set of tasks previously performed.

There is a story about a mathematician who needs psychotherapy. The therapist decides to test the mathematician to see how his mind is working. First the therapist lights a fire in the metal waste can that is next to his desk. The mathematician gets up, gets a bucket of water, and douses the fire. The therapist is impressed. Next the therapist puts the can on top of his desk, puts more paper in it, and lights it again. The mathematician grabs the can and puts it back on the floor and sits down. The therapist is very puzzled and asked, “Aren’t you going to put out the fire?” The mathematician says, “No.” The therapist says, “Why not?” The mathematician replies, “Because I have reduced the problem to something I already know how to solve.”

Although clinical researchers cannot just stop once the reduction process occurs, it is an important skill to be able to break projects into manageable pieces, and hopefully many of those pieces have already been accomplished and to some extent refined.

In the case of setting up a data entry system, the project manager could conceivably review a protocol, decide on how similar to one or more previously implemented studies this new study is, and create a baseline estimate based on how long it took to set up the similar parts of the application that were set up in previous data entry systems. Having the baseline estimate, the manager would then more roughly estimate times for the new pieces that are needed. However, the estimates based on the new pieces will likely be just that, rough estimates.

In a perfect world all the pieces would have been done before, the pieces would only need to be “assembled” together, and the new data entry system would be ready to roll. Achieving this “perfection” is a worthy goal. This issue explores how one might attempt to exploit the benefits of standards.

The Business Case for Standards

One way to describe a successful business is to say that the business produces high quality products and services in an efficient and cost effective manner. One way to think about high quality products and services is “great stuff time after time”. A person would not continue to go to a restaurant if the food was fabulous one day and blah (or worse) the next day. Likewise, if one day you as the customer were treated like royalty and the next day you were totally ignored. At the same time, one could not justify repeatedly going to the restaurant if consistent quality or service was very expensive.

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For a business to deliver consistent, cost effective, quality goods and services, it needs consistent, efficient, and repetitive processes. From a business perspective, the processes need to be predictable. If a customer needs a product, the business needs to know it can deliver it and the length of time it will take to deliver it. A highly predictable process is one that has been done many times before and can easily be repeated or reused.

Customization introduces uncertainty. Whenever a product or service needs anything done that is different from the normal or typical product or service, the ability to predict the time requirements and the quality decline dramatically. As a result, the cost associated with producing a customized product or service rises to cover the risk and effort needed to insure quality output.

Standards are a tool for enabling repeatable and efficient processes. A standard object can be as small as one question on a CRF, to as large as an entire clinical visit. How much the standard object encompasses depends upon how much of a process can be repeated. The standard(s) will be more accurate as far as predicting how long a project will take if it encompasses a larger amount of the total effort.

Units of Standardization – Standard Objects

A standard can be thought of as a reusable portion of an overall process, product, or a software application that has been refined to cost effective optimal. For the example of the data entry application, there may be a standard demographics entry screen that has been developed that could be reused for many studies. Another example would be the SAS demographics listings. If the underlying SAS dataset comes from the same demographics data entry form (and underlying database table), the same SAS listings code can be used. Another example would be the template word document used for a protocol.

“Standards” then, might be thought to run the spectrum from “always do it the same way” to “use the template and fill in the same blanks”. Another standard might include the use of a “recycle bin” where anything that can be reused is, in order to save time. In this case a Standard Operating Procedure (SOP) that describes how and when to make use of items in the recycle bin actuates the standard. An example might be reusing metadata for demography items when creating a data entry system for a new clinical trial even if nothing else can be used in the new system.

Production versus Creativity/Research

Looking from the business point of view again, a good portion of a business evolves around production-oriented work. A much smaller portion of a business is creative work that would fall into the category of research and development. In our experience and from looking at several company annual reports to the percent of the funds allocated to research, perhaps as a rule of thumb, 20% would be creative work and 80% would be production work. In general, the production work contributes more directly to the bottom line of a business, and the creative work, while sustaining the business growth or future profitability, is often considered an overhead expense.

When it comes to clinical research, and in particular, clinical data management, “production” can be considered the work that follows the SOPs, executes the processes that are spelled out, and uses and reuses the building blocks that have been put together – the standard objects (screens, tables, documents, etc.).

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For Clinical Data Management, the creative aspect would of course involve creating anything that does not previously exist. However, much of that creative work is still a part of production. The creative work that is not part of production would involve the creation of new standard objects, the refinement of the standard objects, and the post mortem of the project/process just undertaken.

eClinical and Standard Objects

Table 1 shows the major steps followed by a clinical research department. Table 2 details the steps taken once the protocol is finalized. As one can see from these tables, there are a lot of places where standard objects can and should be developed to support the overall clinical research process.

Table 1. Major Steps in a Clinical Trial

Study Design and Management
Study Data Definition
Data Capture & Validation
Access and Reporting

Table 2. Steps after a protocol is finalized.

Case Report Form (CRF) or Workbook
Data Management Documentation
Management Plan
Entry Guidelines
Editing Guidelines
Data Entry System
Dictionary Additions and Updates
Codelists Additions and Updates
Data Items (metadata)
Forms
Entry validations (required fields, range checks, etc.)
Derived Items
Events/Study Periods
Edit Checks
Site Setup (User Accounts, training)
Portal Configuration
Reporting Database Definition
Generation
Analysis and Reports

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To start with, templates for each type of document created for every clinical trial should already have been created and be stored in an easy to find location. Templates should be managed and kept up to date. Creating a document should start with using the template. Copying a document from another trial should only be done in rare instances where the study similarity saves sufficient effort to make up for the added effort to eliminate “cut and paste” and other “copied from another source” errors. Standard templates should be created for the Protocol, the Management Plan, the Entry Guidelines, and the Editing Guidelines, along with any additional documents a sponsor deems necessary. It is possible that the templates can contain standard wording for different sections of the document.

Standard objects such as demographic questions (i.e., data items) or even the entire demographic page can make the development of the CRF (or the workbook if the study is performed using EDC) more of a process of routine assembly. Many pages could be similar from one study to another with the only necessary changes being the protocol number at the top of the page. However, efficacy pages will likely be different from study to study. If possible, individual questions can be stored in the software application that is used to produce the CRF to increase “recycling” possibilities.

The same concepts in the previous paragraph apply to the data entry application and reporting database. The only difference is that the entry application will have different support for the objects that can be reused.

The key concept is reuse. While the intent of standards is to promote REUSE without REDESIGN, there may be situations where no standard exists but an object exists that can be reused with little to no modification (usually from a very similar, recently conducted, clinical trial). To facilitate reuse of this sort, it is necessary to maintain some way of identifying, locating and copying these objects as discussed in more detail later.

Difficulties of Standards

There are a number of reasons why standards can be difficult to use. However, we at EDC Management believe there are two major reasons. First, time is not provided for clinical workers to build the appropriate libraries of standard objects since this effort is funded out of overhead, and the short-term view is that it takes time away from completing the required work for the clinical study being implemented. Second, employees cannot find or are unaware of, standards that can be used, or are using the wrong version of the standard.

The first difficulty requires a change in management attitudes. Management must be willing to allow for improvements to be seen in the future. It should be noted that many of the smaller biopharmas that are working on venture capital money often realize that they should be planning longer term, but are often forced by circumstances such as venture capital company oversight to focus on what it takes to get the first few products out the door. However, in many companies, it appears that many employees are not given incentives for making process improvements along with getting their current assignment completed.

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The second difficulty is sometimes organizationally challenging, and is often technologically challenging. Depending upon the type of standard object, finding the correct object to reuse might be difficult. The CRF authoring tool may not easily support saving reusable pages. One may have to save the pages on the files server, and the CRF authoring tool might not be able to search the files. File naming conventions can help, but if there are slight variations in the standard pages, the filenames could get long and unwieldy. For example, consider several standard demographics pages that are different only in that one page allows both genders, one page allows only male subjects. The filenames could be Demog.page and DemogMaleOnly.page. It is not too bad yet, but further permutations such as restrictions on race will only make the page names longer and more difficult. An indexing system is necessary.

Further difficulties are encountered when the standard objects are stored within the applications themselves. For example, the EDC application may support a library of pages. However, the application may or may not provide a search feature for finding objects. Also, many applications restrict the names of objects to a certain number of characters, some to as little as eight. In these cases, it is almost impossible to make the object names descriptive. Once again an indexing system is necessary.

Companies can and do provide guidelines on how to overcome some of these difficulties, and one such work around is for the developer to use the description field to describe the standard object. However, often the description fields are not searchable within the application, and furthermore, descriptions are often not as complete as they should be.

One area of difficulty that is not usually addressed is version control of standard objects. At most, a version number is built into an object name or a filename, but often it is difficult to tell what the latest version is. This often needs to be addressed through process or through documentation, which can be difficult to keep up to date.

Making Standards Easier

The most important contribution to making standards easier is making them searchable and accessible. If this step is not supported within the software application being used, then an appropriate means for accomplishing this must be provided through processes and documentation.

If the standard is a word template, then the templates should be stored in a directory structure with meaningful naming on a network server and should be described in the SOPs or Guidelines. Adequate naming conventions should be developed, and appropriate version control should be built into the name of the templates.

If the standard object library support is part of one of the applications used, then the first step would be to encourage the company that developed the application to provide search capabilities for library objects if it does not already have that capability. Again, object-naming conventions should be described in the SOPs or Guidelines. If however, the application still does not support searching capabilities, then an appropriate external method must be developed and employed.

One possibility is to develop a searchable database of standard objects that is maintained external to any of the existing software applications. This database could, for example, be in Microsoft Access or Oracle. It would then be up to the clinical professionals to update the database when a standard object is created or updated.

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It may make sense for a company to have someone who is in charge of maintaining the standards be part of every development effort, and this person can then show what standards should be used for each part of the effort. This may be a drastic step, but it may in the long run pay for itself. In the absence of doing this, a company should have periodic meetings where the latest standards are reviewed and presented to the clinical team. While this may be more costly, it may pay for itself due to better feedback and maintenance of the standard objects.

Avoiding a Rut

While promoting standard objects and their reuse, one must keep in mind that processes cannot just become rote. The processes and the standard objects associated with them must undergo periodic review and critical analysis. The critical review helps companies overcome employees who may become complacent and believe that things should be done a certain way because they have always been done that way.

EDC Management suggests that a post mortem process be part of every clinical research project. As part of this process, the use of standards should be discussed. Among many questions to ask the development team are the following:

1. Were the standards a good fit?
2. Were a number of standards used but modified?
3. Was the process detailed in the SOP followed completely?
4. Are any new developments candidates for standard objects?

The creative process of re-engineering the standard objects should prevent complacency, and should ensure that the company is always improving its processes and products.

What Standards Are Not

While standards are an enormous help with improving efficient development of the clinical trial program, there are things that standards do not do that should be kept in mind.

First, standards cannot make up for thorough thinking and thorough work. If things are not thought out, specified thoroughly, and implemented carefully, standards will not help eliminate rework cycles. However, to the extent that a standard object can be used, it can ensure that there should be less need to rework that part of the program.

A key concept is not starting a particular step until the prior step is finalized. EDC Management believes that most of the rework is caused by trying to get a jump on the process, and starting development before specifications are finalized. Using standard objects to enforce or restrict specifications is a viable path, however.

Finally, the time it takes to perform some steps is not going to budge much even if standard objects are used. One of these areas is overall system validation – one still needs to perform verification that all the parts are assembled even if a complete validation is not needed. In addition, folders and binder creation will still be needed.

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Conclusion

Standards and standard objects are powerful tools for management to effectively manage a clinical research project. As such, standards should be given priority by corporate management, and clinical workers should be given the time and money needed to create and manage standards to realize the potential benefits that they are capable of providing.

Those in the research arena should not look upon standards negatively. Research should be repeatable, and standards can assist in supporting the scientific method.

Corporate attitude should support standards by demanding their use and it should not just be lip service. Furthermore, the attitude should not layer standards in bureaucracy where their use is burdened in red tape and the efficiency benefits lost.

Standards should be searchable and accessible so that developers can make use of them appropriately. Thought should be given to creating a group responsible for maintaining the standards and overseeing their use.

Standards should be re-engineered periodically to make sure that employees do not get complacent about performing their job.

Resources

¹ *EDC Today*[™], Issue 8, “Data Transfer Standards: How to Leverage Your Investment in EDC”.

² *EDC Today*[™], Issue 28, “CDISC Update”.

³ *EDC Today*[™], Issue 34, “A CDISC Give and Take”.



Who's behind the research?

Our lead researcher, Kirk Mousley, PhD received BS and MS degrees in Electrical Engineering from MIT and a PhD in Computer Science from Lehigh University. He has been the President of Mousley Consulting, Inc. since its founding in 1993 and has directed the company's efforts in the areas of clinical database design, data editing/cleaning, document management, and submissions.

Karl Mousley received his BS in Mechanical Engineering from Rose-Hulman Institute of Technology and a MS in Computer Science from Villanova University. He has been a senior member of the technical staff at Mousley Consulting, Inc. since 1993. Among his significant accomplishments are the investigation, evaluation, and implementation of new computer technologies for clinical data management systems and developing strategic plans for integrating these technologies into current systems. He has extensive experience preparing Standard Operating Procedures (SOPs).



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