



Clinical Teams and Tools: New Approaches for Smarter Clinical Trials

Doing things the same way, and expecting different results. Most of us are familiar with this particular definition of insanity. Keeping this in mind, improving the Clinical Trial process requires that we find new ways to work more efficiently and effectively. In short we need to work smarter.

Improved collaboration and the better utilization of technology are areas that hold promise for improving the Clinical Trial process. In both cases, doing things the same way we always have just won't result in the outcomes we are hoping for. Instead, we need to break the mold and find new ways to leverage the tools and talents that are available.

The Power of EDC

Electronic Data Capture systems are cost effective when they help sponsors move to filing more efficiently, in effect by "keeping the end in mind". If teams think ahead about study reports and filings as they are developing an EDC system, only information that is really needed is collected and cleaned. In addition to the efficiencies this brings to the data collection process, it also eliminates the risk of getting to the end of the study and realizing essential information is missing. Modern EDC technologies have the potential to help clinical research teams collect data in a much more precise, rapid and accurate way, which in turn results in high quality data ready for analysis sooner.

Implementation of EDC has caused changes in roles for various members of the clinical team. The teamwork of statisticians, data manager and other team members in the set up of EDC trials is essential to success. Wise planning in the use of EDC technologies allows for cleaner data to be entered into the clinical trial; accuracy, completeness and timeliness criteria are met.

Changing role of data managers

Traditionally in clinical trials, data has been collected on paper-based case report forms (CRFs). After the CRFs are completed, batched and transmitted, the data managers perform edit checks to make sure there are no obvious mistakes and all the required fields have been completed. The CRFs are then entered into the database manually or scanned by text-recognition device such as OCR. Again, the data in the database needs to be compared against the original documents to make sure that no errors have been introduced during the digitalization process (1).

Some data managers see EDC as a threat to their job, because EDC systems automate much of the work that used to be done by data management personnel. Information is entered directly into the database. No comparison against the paper-based CRF is needed. Such jobs as visual (or manual) edit checking will need minimum human interference after EDC is implemented and the query process is greatly streamlined.

It is true that EDC eliminates some of the low level clean-up jobs, but in the long run, EDC will emancipate data managers to do jobs with greater added-value to their organization. Traditionally, data managers begin their work after the data are collected. With the primary objective, assuring high data quality for each project, data managers have to carefully balance their expected functionality in the organization and the resources they have. The data management procedure is time-consuming and cost ineffective if it is done without assistance of available computer technologies. The higher the quality expectation, the more time and resources are needed. Moreover, in some scenarios, no matter how careful you are, some errors cannot be detected at the site level, i.e. a visit time violation or a misinterpretation of the CRF.



Adoption of EDC offers data managers the opportunity to change their role from an emergency-based fireman to a real manager who uses his/her time to plan and to deal with exceptions. EDC also offers clinical trial research teams the ability to re-engineer the operational process and make it more efficient. With the implementation of EDC, data managers should be proactive and involve themselves with the team well before any information is collected.

Data managers apply their expertise as early as eCRF design to ensure data are collected in a standardized and manageable way. They are responsible for controlling user access to the system so that only qualified people can complete eCRFs and no changes can be made to the eCRF without involvement of the original author. By working with statisticians and site monitors, data managers set specifications for validation and edit checks prior to data collection. The data collection personnel get dynamic feedback from EDC system as to the acceptability of data (with range, date, type, etc.) at the point of entry. Problems get resolved at an early stage. More, errors that used to be undetectable at site level can be discovered upon initial data entry, which is another productive result from the strategic thinking (2).

Changing role of statisticians

Statistical analysis on clinical trial is based on the work of data management personnel. Sometimes statisticians find data quality to be unacceptably poor, and they have to do data clean-up before any substantial analysis can be performed. The lack of confidence in data quality causes statisticians to conduct extensive data examines which, in their eyes, should be the data manager's job.

Statisticians have different perspectives on data than data managers do. They focus more on the data values. They discover questionable combinations of data values with their analyzing tools, which may look perfectly fine to data managers when they examine the data. The more outliers found in the dataset, the less confidence statisticians have in the study results, because outliers and missing data will enlarge the variance of the observed measure of interest and make the result less precise. Statisticians under such circumstances could either return the data sets to the data managers and insist that additional data queries be sent to the investigatory sites or use computation methods to constrict the variation. Neither of these two choices is too appealing because the first approach is very expensive and time-consuming and the latter approach is likely to engender debate about the methodologies. The best scenario is to have as few outliers and missing values as possible at data lock. This requires statisticians to get involved more in the process of form design, data collection, and data cleaning.

EDC enables the research team to design more sophisticated way of data collection and more detailed and logically complex validation rules that cannot be checked manually. Statisticians in the EDC age will no longer sit back waiting for analyzable data but contribute their knowledge in the whole data management process: what data will be collected, how data is collected, how to validate it, etc. A sound data collection plan will only collect data that is necessary for the analysis.

This change requires the statistician think through the reporting requirements before the eCRF is designed. The team members then map the fields in the planned eCRF to the study report. Since it is costly to collect and clean information, this process assures that all necessary study information is collected and only necessary study information is collected. The edit checking library is developed and applied before the data are entered. Unblinded statisticians can monitor data collection and do analysis to find pitfalls that may lead to low quality data. The team may come up with new validation rules during the data collection process, and those rules can be quickly implemented in EDC (3).



Teamwork and planning

Teamwork among statisticians, data managers and other members of the project team is the "Symbiosis that we must seek" (4) to quote Hill in 1902 ... although he was referring to the teamwork between the physician and the statistician. To achieve this symbiosis, both the statistician and the data manager need to be aware of the expectations they each have of each other. As Andrew Grieve, past president of the Royal Statistical Society, stated in his Presidential address "It is essential that each side has an understanding of the language and concepts of the other and an acknowledgement that although it may not always be an equal partnership, it is a partnership none-the-less" (5).

The expectations that the data manager has of the statistician include:

- *Clear concepts.* Clinical data managers would expect statisticians to have clear concepts of what is to be measured, why and when it is measured. Those concepts are expected to be communicated before the development of CRF/eCRF.
- *Mapping from report to CRF and vice versa.* Statisticians should be able to map from the intended study report to the CRF and to map from the CRF to intended study report.
- *Edit checking plan review.* Data managers want statisticians to review the edit checking plan very carefully.
- *Sense of economy.* Data managers also expect statisticians to bear in mind that collecting, cleaning and maintaining data is costly.
- *Professional integrity.* Statisticians are expected to adhere to sound statistical principles including professional ethics and confidentiality of research findings.

The expectations that the statistician has of the data manager include:

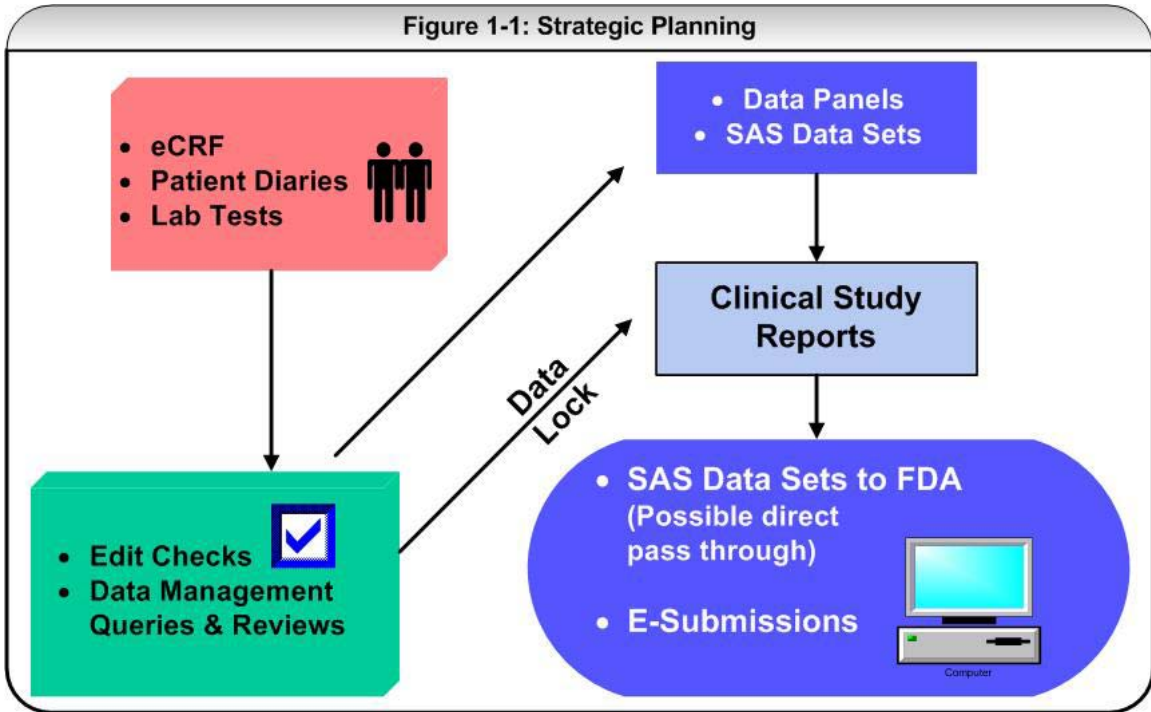
- *Clear concepts.* Similarly, data managers are expected to have a clear concept of what is to be measured, knowing why and when it is measured.
- *Edit checking plan preparation.* Data managers are supposed to prepare the edit checking plan after CRFs are developed. If the study is a part of a series for a product or within a therapeutic area, the data managers should be drawing upon a company library of edit checks in a thoughtful way.
- *Data of high quality.* When working toward database lock, data managers are expected to emphasize the accuracy, completeness and timeliness of the data.
- *Professional integrity.* Statisticians expect data managers to adhere to sound data management principles, including guarding the confidentiality of patient information and study findings.
- *Statistical skill.* Data managers are also expected to be able to examine patterns in the data, look for heaping the distribution, and observe study outliers, etc.

Those expectations are only realized by consistent communication and cordial partnership. Training, informal talks, routine team meetings are effective ways to build good relationships between the two professions.

Besides teamwork, strategic planning is another vital factor for acquiring high quality data. All team members should meet to plan for the project well in advance, within the context of the overall program for the product and/or the therapeutic area. An optimal process collects only necessary data and ensures that all essential information is obtained. The statistician teams with the clinical data managers through statistical planning and by visualizing the end of the project before development begins. The best way to ensure the appropriate mapping of data elements into the eCRFs is for the clinical trial statistician to have considered the design of the study report



in terms of definitions, derived data sets, tables, and listings before the eCRF is designed. The eCRF is then designed with the envisioned study report mock-up in mind. This results in an efficient and reliable process that achieves the initial goal of compiling all essential information without gathering unnecessary data.



To further enhance the process, hard and soft edit checks are developed. Hard edit checks display error messages in the pop-up window and users are not allowed to proceed unless they fix the current mistake; soft edit checks only warn users by highlighting errors, and users can continue without fixing the issue. Hard and soft edit checks govern the screens upon which investigatory sites enter information. This results in much cleaner information from the start. Standard edit checks, therapeutic area edit checks and study specific edit checks govern the data entry.



File View Status Tools Help

Login Info Subject Viewer eCRF Message Center Reports

Initials:PAM Subject #:5292 Screening #:2 Visits:ALL VISITS Form:AE 2 Copy:2 Audit#: 0

Adverse Events Visit Date: New Visit

AE Description

Start Date - - dd-MMM-yyyy

Year value for Start Date is required.

OK

Association to Drug

Countermeasures-None

Countermeasures-Study drug discontinued permanently

Countermeasures-Study drug dose reduced

Countermeasures-Study drug interrupted (stopped/delayed)

Countermeasures-Treatment

Outcome

Show Subject Viewer Show Form Verification Audit Trail Comments Form Help

Finally, clinical data managers can use frequency reports (usually weekly) to facilitate monitoring of metrics and timely decision-making. Reports can also be designed to support the Clinical Research Associate or study monitor during site visits. These processes ensure that missing data is minimized before data lock which minimizes or eliminates the need for imputation techniques. SAS data sets are prepared which are CDISC compatible. These SAS data sets are available to the clinical data manager regularly and can be used for routine reporting and special queries and tabulations.

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eCRF Summary Report

Client ID: Client Name:
 Study ID: Study Name:
 Study Status: Active
 User ID: Date/Time: 04/18/2006 12:24:49 PM

Site ID	Site Name	Initials	Screening	Subject ID	Visit Name	Visit Date	Form Name	Copy	Locked	SDV	Monitor Reviewed	DM Reviewed	Signed
Flex001	Flex001	BCD	1112	1112			SUBJECT	n/a	No	No	No	No	No
							Registration_Part_1	n/a	No	No	No	No	No
							Registration_Part_2	1	No	No	No	No	No
							Special_Flags	n/a	No	No	No	No	No
Xpress002	Xpress002	AAA	1111	1111			SUBJECT	n/a	No	No	No	No	No
							Registration_Part_1	n/a	No	No	No	No	No
							Registration_Part_2	1	No	No	No	No	No
							Special_Flags	n/a	No	No	No	No	No

Teamwork and planning are keys to improving the quality of clinical study information. The yield is improvements in the accuracy, completeness and timeliness of the study data.

Discussion

Making effective improvements to Clinical Trials processes requires a solid understanding of existing roles and processes, a working knowledge of available technology and a willingness to “think outside the box”. In the right combination, these essential elements can result in new ideas about team synergies and tool utilization that further the goals of time and quality improvements while maintaining the integrity of the overall process.

Clinical data has its own life cycle; such cycles should be clearly defined and carefully studied. Teaming with statisticians, data managers can conduct multiple research projects to systematically study the quality issues during data collection and processing and to develop tools and methodologies to enhance data quality. There are several potential projects proposed by Data Quality Research Institute (DQRI) which are visionary in reforming the role of the data manager given EDC technology. These projects involve redefining interdisciplinary clinical data standards for the entire data life cycle, studying the role of manual data review to ensure clinical data quality, to identify risk factors in instrument design, data collection and analysis, to develop quality assessment tools for existing databases, with applications to transferred databases and regulatory submissions, to define and measure error rates for primary and secondary safety and efficacy data, etc. (6)

EDC technologies help clinical research teams locate clean-up processes and some validation at the investigatory sites which saves time as well as other resources. Data quality is greatly. The



implementation of EDC system is a re-engineering process for the organizations. Strategic planning can help everyone gets prepared for the changes that may occur within the organization as a result of EDC deployment. Research team members are motivated to redefine their roles under the new environment. Some new skills may be required in order to match the new roles, and they may need to be acquired quickly. Teamwork not only helps team members to share their expertise with colleagues but also provides opportunities for them to have a deeper understanding of the other parties.

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