ABSTRACT

Despite advances in computer technology, the management of clinical trials data has remained a challenging task. The competitive nature of our industry, combined with the quantity and variety of information collected, creates a need to enter data in a way that facilitates subsequent retrieval, review, and analysis. Enhancements found in SAS® Version 6.06 and higher provide the requirements for a database and review system suitable to the pharmaceutical industry's needs. With these considerations in mind, Genelabs decided to license the ClinAccess™ clinical trials system, a third-party system built with SAS/AF® software. ClinAccess takes advantage of the recent enhancements in SAS software to simplify the data entry, review and analysis processes and thereby enhances our progress towards regulatory submission. ClinAccess also provides the ability to review data which facilitates in-house review by the clinical staff. It can also support the development of a computer-assisted New Drug Application or Product License Application (CDRA or CAPLA), an added advantage with the FDA's approaching 1995 deadline to computerize regulatory submissions. This paper discusses our experience in using SAS software and the ClinAccess clinical trials system and how they have effectively resolved the issue of clinical data management and data review for our company.

BACKGROUND

Over the last eight years, I have been intimately involved in the development and regulatory submission process for several drugs at both a large, established pharmaceutical company and a small, start-up biotechnology company. Regardless of company size, the lengthy process of developing a drug followed by exhaustive data review by the FDA prior to drug approval, creates a powerful incentive to shorten the process wherever possible. Seven to twelve years are typically needed to move a newly discovered drug through the research and development process and demonstrate that it is safe and effective for human use. It is during the clinical phase of development that we collect information from many patients to demonstrate the safety and efficacy of the drug. To do this, patients are given the drug and their progress is monitored. Information about the patient, including disease status, dosing experience, adverse events and laboratory changes is recorded on Case Report Forms. Patients are followed for many weeks, so the numbers of forms filled out and the volume of data collected can quickly become unmanageable. Despite this, we needed not only to manage the data, but quickly enter it, validate it and move it into analysis.

Given the magnitude of the information that must be collected, tracked, validated and analyzed, computer systems have become a critical part of the drug development process. As an emerging company in the biopharmaceutical industry, Genelabs chose to license the ClinAccess clinical trials system, a system developed with SAS/AF software by MAJARO® InfoSystems, Inc. to meet our clinical data management requirements. As a small, PC-based company, we wanted a system that was affordable, easily implemented, flexible and expandable. In choosing ClinAccess, we knew that we would have a user-friendly menu-driven data entry system with a double-entry capability, that our SAS programmers could provide the needed database management support without the immediate need for additional personnel, that we would have data security and that we could easily access the data for statistical analysis with SAS software or review the data through the ClinAccess review capability.

DATA ENTRY/VALIDATION

The most basic requirement from a clinical trials system is to get the data entered accurately, consistently and quickly. The developers of ClinAccess have taken advantage of the SAS Systems's applications development ability to create a double-entry system within a point-and-click menu-driven shell. In the double data entry system, each case report form is entered twice. Those entries that match the first entry exactly are moved to the Master database, while those that do not match go to a file for resolution (verification) in a separate on-line procedure. In addition to the functionality of ClinAccess, we have put data entry standards in place to maintain data consistency. These standards deal with questions improperly answered or not answered, insufficient space for data entry (usually in a comment field) and standardized entry of fields that will be linked to a dictionary or thesaurus (e.g. COSTART coding of adverse event data). As a further validation step, one person writes SAS data checks and puts them in a SAS catalogue that ClinAccess runs from a menu. This allows others in the group to run these as batch validation checks and assist in the data validation process.

DATABASE MANAGEMENT

Database management is another essential part of a clinical trials system. Data sets and data entry screens must be created and data security must be in place to allow only certain users access to the data. Within ClinAccess, we use SAS/FS® to create data entry screens that resemble the case report forms that we use. By using relatively standard case report forms, we have reduced the process of creating data entry screens to copying screens from previous studies or other forms within the same study, and making minor modifications. In copying data entry screens, we also copy the same variables for the same question. The use of standard data entry screens and standard variables (questions) improves the efficiency of data entry and facilitates summarization across studies later (for example, for the FDA required annual safety reporting). The security provided by ClinAccess limits access to particular functions in the database, which permits data entry or data changes to be controlled and meets FDA requirements for strict data integrity. The audit trail also provides information about what has been done (additions, deletions, changes) and by whom, and provides a way to backup to a particular time point in the database.

Another important benefit of our SAS-based database is the flexibility provided by using only one programming language for both database management and data analysis. Since all programming is done in SAS, programmers can readily be reassigned in response to acute needs in particular areas. In contrast to systems that use SQL or other programming languages to maintain and access the database, ClinAccess allows us to operate all data management in a single language.

Facilitating Clinical Data Management and Regulatory Review In the Pharmaceutical Industry: A Manager's Perspective

By Randi Olsen McFarland, Genelabs Technologies, Inc.
DATA ANALYSIS AND REVIEW

Data analysis and review is also enhanced by our SAS-based system. Since we use SAS software to do our data analysis, it is very easy for us to "extract" the data from the database, by just copying it to a working directory, a more tedious and time-consuming process with other databases whose data formats may require conversion. Saving a copy of the data, separate from the database, is necessary for the reproducibility of any data analyses or reports, especially those sent to the FDA. Additionally, the ClinAccess menu provides options to run some simple statistical analyses, though we have not taken much advantage of this feature.

The review capability is a very important to us, however. Currently the medical staff uses Macintosh computers. However, the ClinAccess application is easy enough that even they can use it to review data, especially for adverse events review and COSTART coding. The initial COSTART coding of adverse events is performed during data validation through a computerized "lookup" against an online COSTART thesaurus or against similar events that have been coded. If there is no match, the COSTART field is left blank or the COSTART code from a similar event is selected. The clinical staff must then validate every COSTART code that was selected by data management, and code those events that were not automatically coded. This is done within ClinAccess by viewing the adverse event data, requesting not yet validated or missing COSTART codes and deliberately validating each record with a keystroke. With SAS analysis data sets created for data analysis, we can create data entry (SAS/FSP®) screens for internal review of these data sets, as well as facilitate the creation of a computer-assisted NDA (CANDA). Whether we use a third-party CANDA system or develop our own, the major task of creating data sets in the correct format for a CANDA will be mostly complete.

CONCLUSION

Using a SAS-based system for clinical data management has provided us with many tools as well as flexibility. We are able to meet our data entry and validation needs, which include quick and accurate entry of the data, enhanced by the double data entry system and a method for users to run and review batch validation checks. Our database management requirements are met with the capabilities to control and monitor data access, and use standardized variables for data entry fields, which encourages data entry screen standardization. The SAS-based database gives us additional flexibility in meeting our data management and analysis deadlines. Our data analysis and review process has been enhanced through the use of a SAS-based database and the use of SAS/FSP data viewing screens. As a small, PC-based company, we have been pleased with the capabilities that our SAS-based system has given us as well as the small initial investment and ease of expandability as our department grows.

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