Managing Clinical Data For Worldwide Acceptance

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Manufacturers conducting clinical studies to support medical device safety and performance claims need to ensure that clinical study data are appropriately managed. Not doing so can risk the success of the project related to the clinical study. This article discusses a guideline that can assist in this effort.

Importance of data management

Medical device clinical studies are conducted to generate data regarding the safety and performance of a device. Often, these data are needed for marketing authorisations in countries that have varying regulatory requirements such as the United States (US), Europe and Japan. Unless these data are properly managed, valid conclusions on the results of a clinical study cannot be reached. Clinical studies are also expensive and resource-intensive activities that involve a series of steps that need to be clearly understood and planned before the study is initiated.

For any clinical study, a clinical strategy should be determined, clinical investigation plans or protocols developed based on a valid statistical rationale, and case report forms (CRFs) designed. In addition, sites should be evaluated and qualified, and agreements made with investigators and clinical-study sites. After identifying and meeting regulatory requirements, regulatory notifications or submissions should be made and Ethics Committee approval obtained. Investigators and site personnel should be trained in the requirements of the study so that subjects are recruited and enrolled into the study in accordance with inclusion and exclusion criteria, and treated as specified by the protocol. Finally, planning is required for management and monitoring of the study, including requirements for recording adverse events, and management of the data generated during the study. These steps should be conducted in accordance with documented procedures.

Data management encompasses a number of activities related to the manner in which the data are collected, recorded and analysed. This includes the development and management of CRFs, the design and creation of a clinical study database, data entry, recording and resolving queries, and data analysis. In spite of the importance of data management in relation to the success of a clinical study project, some companies fail to adequately understand the activities related to this critical task or plan the proper conduct of these activities at the beginning of the project. The guideline discussed below can help prevent these serious omissions.

Good clinical data management practices

There are no European or US guidelines that have been specifically issued on the design of CRFs or data-management practices. However, a useful guideline, Good Clinical Data Management Practices, has been developed by the Society for Clinical Data Management Inc. (SCDM, www.scdm.org), which is a nonprofitmaking professional organisation founded to advance the discipline of clinical data management.

It should be noted that the principles and practices on which the guideline is based generally originate from pharmaceutical good clinical practices. Nevertheless, the guideline addresses data management issues and activities concerning pharmaceutical, biotechnology and medical device clinical studies. The guideline must be purchased from the Society for approximately €40, which was the

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physician, pathologist and pharmacist with 25 years' regulatory experience, worked with the US FDA before becoming President of Donawa Consulting, an international consultancy firm, which provides clinical research, quality management system, regulatory affairs, and European Authorised Representative services to medical technology companies.

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amount paid for the document reviewed for this article. Additional information on the Society and the purchase of the current version of the guideline (version 4, October 2005) can be accessed from its website.

Readers should note that the guideline states that it constitutes neither consensus nor endorsement by regulatory agencies, pharmaceutical or biotech companies, contract research organisations or the academic community, but rather reflects the views of SCDM membership. The guideline also states that none of its recommendations supersede regulations or regulatory guidelines, which should always be consulted prospectively to ensure compliance. Furthermore, it states that it should not be considered an exhaustive list of topics.

Nonetheless, the guideline is a useful document, whose purpose is to provide guidance on accepted practices for the various aspects of clinical data management that are not covered by existing regulations and guidance documents. The guideline was developed to serve the needs of data managers, data processors, statisticians, site personnel, clinical professionals, compliance auditors, regulatory affairs personnel and all clinical research professionals and to assist them in making decisions regarding or using clinical study data.

The guideline addresses the clinical data management areas of responsibility in twenty sections, each providing minimum standards and best practices (Table I). The minimum standards are those that ensure that data are complete, reliable and processed correctly, otherwise known as data integrity. The best practices are those that offer higher efficiency, quality and function and lower risk, in addition to ensuring data integrity. The body of each section provides the rationale for the minimum standards and best practices, technical detail and often discussion of alternate or common practices. In addition, each section includes a list of recommended standard operating procedures (SOPs) and references. A detailed discussion of each area is beyond the scope of this article; however, important advice provided by the guideline on data acquisition and CRF printing and vendor selection will be discussed.

Data acquisition

The guideline points out that, with the exception of the clinical protocol, no document related to the conduct of a clinical study is more important than the one used to acquire clinical study data. The document employed to acquire clinical study data is usually referred to as a CRF, which may consist of paper forms completed at a clinical study site, electronic data capture systems, file transfers, central web-based systems or other systems for acquiring clinical study data. The recommendations made in the section on data acquisition are intended to assist in the design, development and quality assurance of the CRF so that the data collected will meet the highest standards. For example, the minimum standards for these activities are to

- design the CRF to collect the data specified by the protocol
- document the process for CRF design, development, approval and version control
- make the CRF available at the clinical site prior to enrollment of a subject
- document training of clinical site personnel on the protocol, CRF completion instructions, and data submittal procedures prior to enrolment of a subject.

The guideline lists several best practices, one of which is to design the CRF and the clinical protocol concurrently to ensure that the data collected are only those that the protocol specifies. Too often, CRFs are developed after the protocol has been approved and in a hasty manner. This can lead to an identification of data points that are recognised as undesirable or unattainable. This may then require an amendment to correct a clinical protocol that has already been submitted to an Ethics Committee or regulatory authority. Significant delays and increased costs may result.

Another best practice is to keep questions, prompts and instructions related to the completion of CRFs clear and concise. The guideline states that this will ensure that complete and comparable data are obtained across the various populations using the CRFs. It is suggested that instructions and definitions for completion of CRFs are provided for data items that are not directly measured. The guideline provides the example, "Did the subject have hypertension?" Additional information accompanying this question should include the blood-pressure range, the →

Table I: The 20 areas of responsibility of clinical data management covered by the guideline.

- Data acquisition
- Data privacy
- Electronic data capture principles
- CRF printing and vendor selection
- Preparation and preservation of CRF completion guidelines
- CDM presentation at investigator meetings
- Data storage
- Database validation, programming and standards
- Data entry and data processing
- Laboratory and other external data
- Dictionary management
- Safety data management and reporting
- Serious adverse event data reconciliation
- Measuring data quality
- Assuring data quality
- Database closure
- Clinical data archiving
- Training
- Vendor management
- Metrics for clinical trials.

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→ length of time that the blood pressure was sustained or details of the specific intervention that was required for the condition. Advice is also provided on the manner in which questions should be phrased, which is in the positive and not the negative voice.

The guideline further advises the use of consistent formatting, which takes into account the intended use of the CRF when designing the layout. For example, the guideline points out that CRFs completed by site personnel can look different from those completed by subjects. Other best practices are discussed such as the need to design the CRF with the primary safety and efficacy endpoints as the main goal of data collection. Readers need to consult the guideline for a full discussion of these points.

The guideline also provides practical advice on production aspects of the CRF once it is ready for printing.

The recommended SOPs include CRF design, CRF development, CRF quality assurance, CRF approval process, CRF version control process, and applicable training of site personnel on CRF use.

CRF printing and vendor selection

The guideline not only discusses the development of the CRF, but also provides practical advice on the production aspects of the CRF once the CRF is ready for printing by a print vendor. This guidance is difficult to find elsewhere.

Several minimum standards for CRF printing and vendor selection are listed in the guidance. For example, specifications outlining CRF printing and distribution requirements should be established and should include a complete list of items to be included in the CRF binder, the total number of each item to be printed, the type of paper, and other relevant information. Practical advice is also given regarding the determination of the total number of CRFs, diaries or other required pages to be printed. That is, the number should be based on the number of subjects to be evaluated as specified by the protocol and the expected dropout/replacement rate, as well as a back-up supply. It is suggested that the back-up supply should 10–15% of the total number of patients enrolled.

Other minimum standards include the need to

- provide packaging instructions to the printer
- submit new printing specifications including printing and shipping timetables to the printer each time significant modifications are made to the CRF or any item outlined in the specifications
- obtain approval by appropriate team members of the final print-ready CRF, CRF printing specifications, and the shipping/distribution timetable before the final printing specifications are submitted to the printer.

Best practices include

- the establishment of a vendor qualification programme for selecting the print vendor
- the printing of other study materials such as pocket cards, study schedule posters, preprinted return envelopes and study contact information to complement the CRF and associated materials
- the provision by the printer of a prototype of the CRF book including all pages, tabs, spine label and cover for review and approval before the final print run
- the establishment of a vendor evaluation programme, which should used throughout the vendor relationship.

It is interesting that the guideline also covers areas that are often overlooked or inadequately considered. These include the need to decide on paper specifications including the type of paper, colour, page weight, hole punch, perforation and gum for each page or section. For example, it is mentioned that conventional three-part, no carbon required (NCR) paper comes in many colours and weights and that many organisations use a white, yellow, pink combination or a white, yellow, heavy card stock combination. It also mentions that traditionally, white is the original copy, yellow the data management copy and pink the study site copy. Other important points are made concerning the use of NCR paper and the need to consider the copy quality on the second or third ply, the usefulness of tabs when using the CRF during the clinical study, and the need to specify the type of binding, binder colour, width, number of inside pockets, cover text or art and spine label of the CRF binder.

The activities that are recommended for being addressed in SOPs include CRF design, CRF production guidelines, CRF printing specifications, and vendor selection.

Need for additional guidance

The SCDM should be commended for developing guidance on data management where none existed previously. This work can be especially valuable to companies marketing their products worldwide because it can facilitate acceptance of clinical data under varying regulatory systems. However, considering the critical role of data management in clinical studies and the importance that these same regulatory agencies place on this activity, additional guidance documents should be developed under a consensus process, preferably with the participation of regulatory agencies. mdt

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