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Clinical Data Acquisition Standards Harmonization (CDASH)

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Every time a research site conducts a study, it must work with a new case report form (CRF). Every CRF has its own way of asking questions and its own expectations for suitable answers. As a result, research sites waste substantial time learning (and remembering) how to use each CRF. Errors are more common than necessary and interpretation of the data by study sponsors and FDA more difficult and time-consuming.

In 2006, FDA published a list of opportunities to implement its Critical Path Initiative.[1] Opportunity #45 is intended to relieve the "plight of the site," wherein investigative sites must deal with this multiplicity of CRFs. It states:

> **Consensus on Standards for Case Report Forms.** Clinical trial data collection, analysis, and submission can be inefficient and unnecessarily expensive. A wide array of different forms and formats are used to collect clinical trial information, and most data are submitted to the FDA on paper. Differences in case report forms across sponsors and trials creates opportunities for confusion and error. Standardization of the look and feel of case report forms could reduce these inefficiencies and also help accelerate progress toward electronic data capture and submission.

CDISC

Clinical Data Interchange Standards Consortium (CDISC) is a non-profit organization with the mission to develop data standards in support of clinical research. To date, it has developed standards that span the research spectrum from preclinical through post-marketing studies, including regulatory submission. These standards primarily focus on definitions of electronic data, the mechanisms for transmitting them, and, to a limited degree, related documents, such as the protocol. CDISC has released the following standards, and others are in development:

- Submission Data Tabulation Model (SDTM)
- Operational Data Modeling (ODM)
- Analysis Dataset Model (ADaM)
- Laboratory Standards (LAB)
- Standard for Exchange of Non-clinical Data (SEND)
- Clinical Data Acquisition Standards Harmonization (CDASH)
- Case Report Tabulation Data Definition Specification (CRT-DDS)
- Controlled Terminology (Terminology)

CDASH

The newest CDISC standard, and the one that will have the most visible impact on investigative sites and data managers, is Clinical Data Acquisition Standards Harmonization (CDASH). As its name suggests, CDASH defines the data in paper and electronic CRFs. Although it is compatible with CDISC's standard for regulatory submission (SDTM), CDASH is optimized for data captured from subject visits, so some mapping between the standards is required. In addition to standardizing questions, CDASH also references CDISC's

Controlled Terminology standard, a compilation of code lists that allows answers to be standardized as well.

The CDASH development team assessed the relevance of questions in a wide variety of existing CRFs. The standard includes questions that meet four criteria: (a) they are used in most of the CRFs reviewed; (b) they have some regulatory or other compelling basis for inclusion; (c) they cannot be answered in any other way (for example, by calculation from other data); and (d) there is a consensus about how to ask and answer the question. Excluded questions are listed in a separate file that will be made available as part of the Implementation Guide, expected to be published by the end of 2009. It should be noted that CDASH allows flexibility in implementation depending upon study requirements. It does not set standards for CRF formatting, electronic data capture (EDC) systems, and other aspects of data capture beyond the questions, related answers, completion instructions and database field names.

Examples

The CDASH standard requires a question about the severity of an adverse event (AE) because the data are essential for determining safety. The question asks about "Severity" and not "Intensity," as it is sometimes known, and notes that it is not the same as "Seriousness," which is a different CDASH question. The CDASH standard references the expected response levels of "Mild," "Moderate" and "Severe" in CDISC's Controlled Terminology list "AESEV." It also specifies a database variable name of AESEV. The sponsor may assign specific meanings to each level if appropriate for the study. The standard includes CRF completion instructions. The instructions indicate that the investigator should use his or her medical judgment in assigning the appropriate severity level. Together, this information allows the sponsor and the site to arrive at a common understanding of the term and its intent.

On the other hand, CDASH excludes questions about the duration of an AE. These data can be calculated from the start and end dates of the AE. Since AEs happen during the study, the dates should be available, and computers are more reliable than people in performing the calculation.

CDASH does not, and cannot, resolve all data capture issues. A typical example is the question "Was the AE related to study treatment?" There are three schools of thought with respect to capturing this information, particularly in blinded trials:

- A range of responses should be provided, such as "Definitely," "Probably," "Possibly," "Unlikely" and "Definitely Not," in order to provide maximum insight into the investigator's judgment of relatedness.
- Only "Yes" and "No" responses should be provided, since the responses above are generally collapsed into these two categories for summarization purposes in the New Drug Application (NDA) or Biologic License Application (BLA).
- The question is irrelevant for most blinded placebo-controlled trials because the investigator cannot know the subject's treatment group and therefore cannot assess the relatedness to study treatment. In any case, particularly for pre-registration studies, whether or not an event is related to study treatment is not determined on the basis of the investigator's opinion but rather on comparing the incidence and severity of the events between treatment groups.

ICH E2B guidelines[2] and the European Clinical Trials Directive[3] require relatedness information for expedited reporting of serious AEs, which represent a very small percentage of AEs. Relatedness information can be included on the appropriate forms, which are outside

the scope of CDASH. The standard therefore allows all three choices, leaving the decision up to the study sponsor.

Related CDISC Standards

CDISC's Study Data Tabulation Model (SDTM) is a set of data definitions that describes how electronic subject data from clinical trials are to be submitted to the FDA in NDAs and BLAs. This standard gives the FDA a predictable data structure so it can use its own tools to view and analyze the data, thereby enabling much faster and more efficient review of submissions. SDTM and CDASH are both referenced in the FDA's PDUFA IV Information Technology Plan[4], which states that SDTM will be mandatory in the near future. While it currently covers only drugs and biologics, CDISC and the FDA Center for Devices and Radiological Health (CDRH) are collaborating to create a version for devices as well. Although only the FDA has stated that it will require SDTM, other regulatory authorities will, in time, probably follow suit.

CDISC, in collaboration with Health Level Seven (HL7), is developing standards for expressing protocol design in a way that can be electronically understood and manipulated. Perhaps most exciting, there is an intensive effort underway to leverage CDISC standards together with an electronic data capture interface developed by CDISC and the Integrating the Healthcare Enterprise consortium (IHE) to link electronic healthcare records (EHR) systems to clinical trial data capture systems. This integration will permit EHR data to be transferred to EDC systems without manual rekeying, while still respecting HIPAA requirements.

Conclusion

Adopting CDASH will require significant effort by study sponsors. Any change in study data collection creates significant risks. People have expertise and other vested interests in current systems. Nevertheless, CDASH offers huge efficiencies in a business environment that increasingly penalizes wasteful methods.

References

1. "Critical Path Opportunities List," Food and Drug Administration, March 2006
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