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A standard-driven approach for electronic submission to pharmaceutical regulatory authorities

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ABSTRACT

Objective: Using standards is not only useful for data interchange during the process of a clinical trial, but also useful for analyzing data in a review process. Any step, which speeds up approval of new drugs, may benefit patients. As a result, adopting standards for regulatory submission becomes mandatory in some countries. However, preparing standard-compliant documents, such as annotated case report form (aCRF), needs a great deal of knowledge and experience. The process is complex and labor-intensive. Therefore, there is a need to use information technology to facilitate this process.

Materials and methods: Instead of standardizing data after the completion of a clinical trial, this study proposed a standard-driven approach. This approach was achieved by implementing a computer-assisted "standard-driven pipeline (SDP)" in an existing clinical data management system. SDP used CDISC standards to drive all processes of a clinical trial, such as the design, data acquisition, tabulation, etc.

Results: A completed phase I/II trial was used to prove the concept and to evaluate the effects of this approach. By using the CDISC-compliant question library, aCRFs were generated automatically when the eCRFs were completed. For comparison purpose, the data collection process was simulated and the collected data was transformed by the SDP. This new approach reduced the missing data fields from sixty-two to eight and the controlled term mismatch field reduced from eight to zero during data tabulation.

Conclusion: This standard-driven approach accelerated CRF annotation and assured data tabulation integrity. The benefits of this approach include an improvement in the use of standards during the clinical trial and a reduction in missing and unexpected data during tabulation. The standard-driven approach is an advanced design idea that can be used for future clinical information system development.

1. Introduction

1.1. Background and significance

Under the reauthorization of Prescription Drug User Fee Act (PDUFA) V, use of data standards will become mandatory one year after the final guidance is issued for new drug applications and biological license applications [1]. Thus, the U.S. Food and Drug Administration (FDA) has been directed to develop data standards by FY2017. In addition, the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan has started a pilot project studying the feasibility of a submitted electronic data utilization system [2].

Standardizing the electronic formats used during clinical study submission will be able to shorten the review period, which will benefit patients because it will speed up approval of new drugs [3]. It will also facilitate the exchange of study data and metadata, thus helping with clinical research [4,5]. The Clinical Data Interchange Standards Consortium (CDISC) standards are now being adopted globally and have been mandated by the U.S. FDA [6]. CDISC standards cover different purposes and have the aim of supporting clinical research starting at protocol design, reaching through data collection and data analysis and then on to data tabulation. For example, the Clinical Data Acquisition Standards Harmonization (CDASH) describes the basic recommended data collection fields and the best practice recommended question text for the case report form (CRF) design [7], while the Study Data Tabulation Model (SDTM) provides a structure and format for the tabulation of clinical data [8].

Some pilot studies have shown that the increased use of CDISC standards is able to reduce significantly the time required for this activity during the entire study by 50–80%, including study start-up, study conduct and submission; in addition, it also improves overall approval rates, [9,10]. This is because CDISC standards incorporate the

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essence of the different guidelines. For example, the CDISC protocol representation model (PRM) harmonizes the International Conference on Harmonization (ICH) guidance (E3, E6, and E9) and the requirements for registration of studies at WHO and clinicaltrials.gov [11].

The case report forms are an important tools used during the collection of clinical research data and thus they are also a medium appropriate for the adoption of data standards [12]. The data standard mainly consist of standard variable and controlled terminology, it is able to not only standardize data collection, but also facilitates follow-up comparisons of results across multiple studies [13]. At present, most study groups design CRFs on the basis of their own codebook. Establishing the relation between private variable names to standard variable, such as CDASH/SDTM or common data elements [14], is both the first step and a critical requirement in the move towards data integration. In the other hand, the controlled terminology is a set of standard-developed or standard-adopted expressions. For an instance, CDISC is collaborating with the National Cancer Institute's Enterprise Vocabulary Services (EVS) [15] to develop test code/test name codelist and parameter code/parameter name codelist [16]. The controlled terminology can be used to standardize the field value in order to facilitate the data integration.

1.2. Preparing standard-compliant documents

When preparing standard-compliant documents for submission, applicants have to follow the Study Data Technical Conformance Guide [17] and the Guidance for Industry [18]. These documents provide specifications, recommendations, and general considerations on how to submit standardized study data with FDA-supported data standards. In general, the submission documents need to include protocol administration data, clinical data, results of analysis, and annotated CRFs (aCRFs). Annotated CRFs, which are essential documents for FDA regulatory submission, map the data collection fields to CDASH/SDTM variables by writing the annotations next to the questions (Fig. 1). The aCRF provides a traceable transparent description of the data, which helps the reviewers or statisticians of regulatory agency to locate the origin of the various data variables [19]. Usually, aCRF is manually generated by a person who is familiar with the standards being used. A CRF annotator firstly identifies the domain concept of each question field and then looks up different CDISC standard specification documents for annotating the clinical question with the most appropriate standard variables. In addition, annotator has to ensure all standard -required questions (i.e. subject identifier field) are presented on the CRF and each question's option matched controlled terminology (i.e. options for gender should be male and female instead of man and woman). This manual process is indeed a tedious and time-consuming process [20].

In addition to aCRF preparation, applicants also need to categorize the clinical study data into standard domains for tabulation by referring to the standard specifications. A study domain is defined as a collection of logically related observations on a common topic and is represented by a single dataset. The CDASH/SDTM standards currently focusing on the most commonly domains in every kind of clinical trial such as demographics, adverse event or trial summary. For the specific requirements of study, the study data tabulation model implementation guide (SDTMIG) [21] provides principles and overall process for the custom domain creation. As shown by Fig. 1, there may be more than one domain present in an aCRF and therefore data classification and integration needs to be conducted before regular submission. The dataset should be vertical data structures (normalized) to comply with the regulations. Furthermore, the data items, the format and the responses also need to be standardized.

In summary, preparing standard-compliant documents consists of a series of complex and labor intensive tasks. The manual process lacks a well mechanism to ensure data integrity and standard adoption. It will further affects the quality and efficiency of flowing data tabulation.

1.3. Aims of this study

To increase the efficiency and quality of standard-compliant document preparation, a "standard-driven approach" was proposed. The standard-driven approach involves using standards to drive the design and conduct of clinical data acquisition and tabulation. The essence of this approach is to follow standards from the initiation of the whole process. In particular, this approach attempts to collect all required data fields and uses controlled terminology as well as validation rules to ensure compliance with the applied standards.

A novel architecture and processing flow were developed to integrate the CDISC standards into an existing clinical study information system. In addition, this study evaluated the impact and issues raised

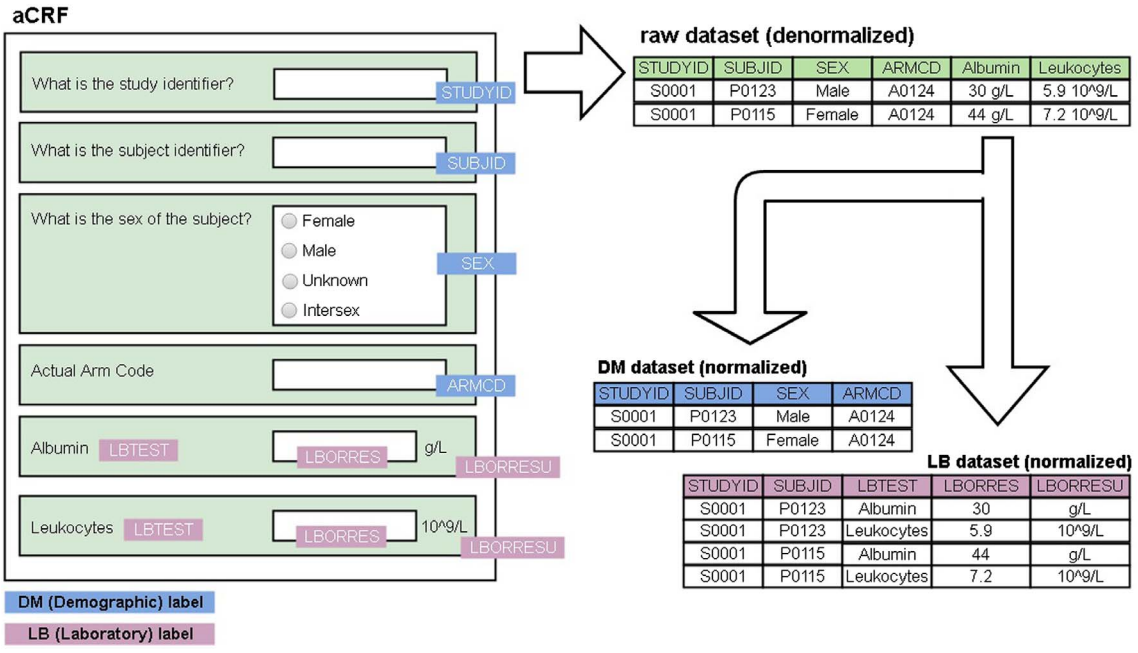

Fig. 1. aCRF and standard datasets.

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