Classifying Adverse Events From Clinical Trials

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Abstract
The use of adverse event data from investigator-initiated clinical trials, outside of the study event itself, has not been practical because of the absence of uniform data collection. The release of CTCAE 3.0 provided a controlled vocabulary for several components of adverse event data, but was difficult to use in a research setting. We have created a web-based application that combines data from clinical trials and the CTCAE classification information into a queryable database.

Introduction
The pharmaceutical and device research community has been actively involved in collecting, classifying and reporting adverse events (AEs) since the advent of efforts to improve human subject protection.[1,2] Within this domain there has been acceptance of terminology standards for AEs. However, investigator initiated clinical research makes up the majority of clinical research conducted within the United States[3] and within this domain use of standard terminology and classification is not a common practice.

Initial and follow-up reporting of AEs during clinical trials is primarily driven by the regulatory process, which is determined by the requirements of the sponsor, the Food and Drug Administration[4] (FDA) and the Office of Human Research Protection[5] (OHRP). The data collected are used to determine if the AE is serious, if the AE affects the enrollment status of the study participant, and whether the AE is related to the study drug, device or procedure. Once this process is complete, formal classification of the adverse event is required for reports to data and safety monitoring committees and as part of the statistical analysis plan.

We have created a straightforward, browser-based application to provide domain experts enough information to classify AEs using the National Cancer Institute Common Terminology Criteria for Adverse Events[6] (CTCAE), which is an initial step in the process of designing an ontology for clinical research AEs.

Background
Investigator-initiated clinical research in the United States that involves human participants routinely includes processes for identifying AEs and collecting data about the event. Frequently the person(s) collecting these data are clinical coordinators or study nurses and not the principal investigator. When AEs are considered to be serious, a mandatory reporting process is usually started. This process notifies various regulatory entities (IRB, DSMB, sponsor, FDA)[7,8,9] with a

minimum data set of information that fulfills the short-term requirements for reporting, but does not provide enough metadata about the event to be useful outside the context of the initial report. AEs that are determined to be non-serious may not receive any further evaluation other than their frequency.

Classifying AEs in a standardized way (system organ class, term, definition, grade and severity) requires someone with domain knowledge of the clinical presentation, the study protocol and the classification standard. Correlating and evaluating all of these data is time consuming, requiring simultaneous review of multiple data sources.

Objective

Our objective was to create a web-based application that could import AE data from a clinical or device study and display that data, related study data and a search window of CTCAE data within a single browser page. This display allows a domain expert to quickly evaluate the AE data, determine the correct CTCAE classification and then, with a few mouse clicks, link these data and store them in a new AE classification table which is associated with the study meta data.

Methods

Since the application is database driven, we needed a data model that could import research data with a minimum of extraction-transpose-load (ETL) effort. Only meta data about the study and a subset of the AE data are imported into two tables (Figure 1). This is currently a manual process using a formatted text export file or a direct SQL query of the study database.

The published NCI CTCAE data are loaded into multiple tables by a similar process; however, since this is a known structure, the process is straightforward and required only when CTCAE data are updated. The CTCAE data are loaded into three tables in a relational database, PostgreSQL,[10] to enable faster searching by the person evaluating the AEs (Figure 2).

The application interface allows the user to select a study that filters the display of AE data. As each AE is displayed, the user can select a System Organ Class (SOC), filtering the number of AE terms displayed, or an AE term directly. Once the Preferred Term has been selected, the corresponding Grades are displayed. Once the Grade has been chosen, all of the data from both data sources are ready to be inserted into the Evaluated AE table (Figure 3).

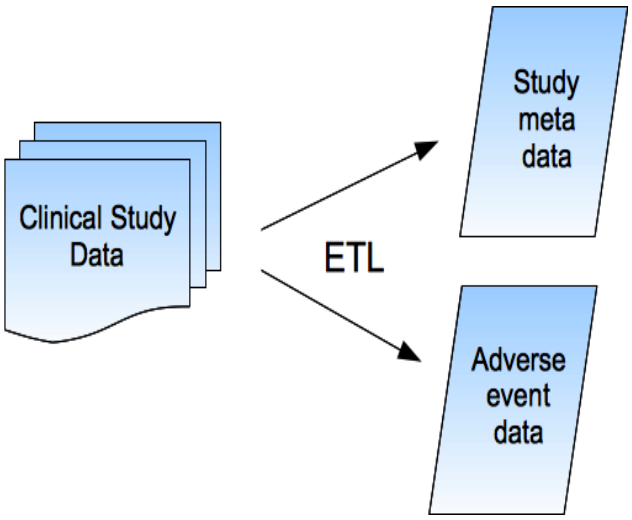

Figure 1 depicts the loading of clinical study data to be classified into the application database tables. Only data relevant to classifying the AE are loaded.

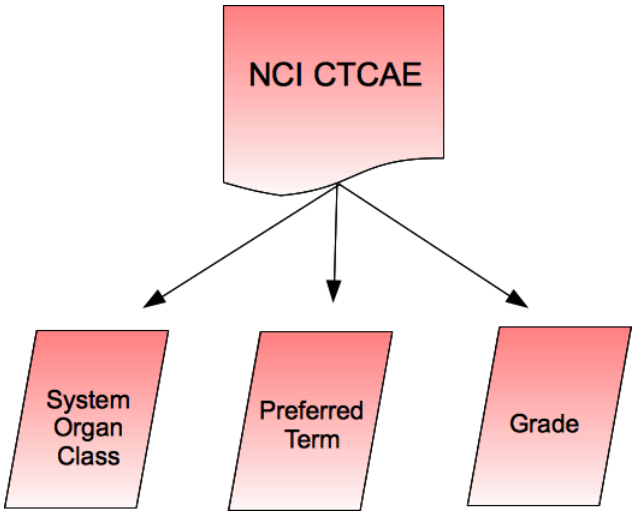

Figure 2 shows the reorganization of CTCAE data into relational tables. Each System Organ Class contains the AE preferred terms within the class and each term has several possible Grades.

Results

The application allows users to view AEs in a browser interface within a single device screen. Users have the ability to view only AEs that require classification, filtered by study. A search engine allows users to reduce the focus of data being displayed by selecting either the SOC or the term relevant to the AE being classified. Once the user has determined the correct classification, she then selects the correct grade. The associated classification data and AE data from the study are automatically populated into a data table. Previously classified AEs can be reviewed and edited within the same interface. Meta data about the study are assigned a unique identification number that is associated with each classified AE. This allows comparison of AEs within a single trial or across trials when appropriate.

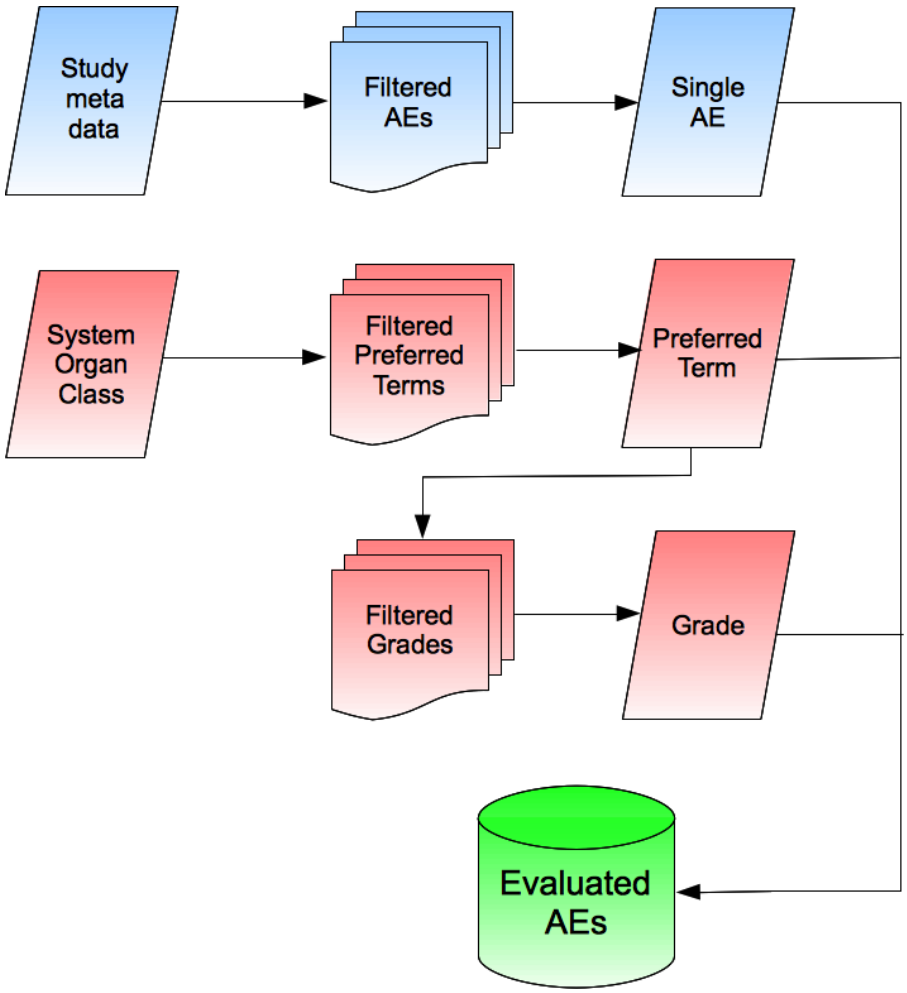

Figure 3 shows the process flow 1) Selecting a study and a single AE from the subset of AEs filtered by the study ID; 2) Selecting the SOC and a single preferred term filtered by the SOC; 3) Selecting a grade from the grades associated with the preferred term. The data from these three steps are merged and stored.

Conclusion

Individual research sites and data centers will use a variety of data models and data sources when collecting clinical research data. We have created an application that simplifies importing AE data though the use of mapping tables during the ETL process. By using an existing classification standard (CTCAE) and a standard results table, we can standardize the AEs from multiple trials once they are classified. The resulting data can now form the basis for discussions about whether CTCAE is the most appropriate classification system, whether the meta data collected are sufficient to compare AEs across trials, and how this could contribute to the creation of an ontology for AEs.

The classifying and reuse of adverse event data can be a significant contribution to patient safety, and is critical to orphan disease clinical research, particularly within pediatric populations. Standardized vocabularies and concepts of AEs may allow

investigators to reuse safety data from previous clinical research, which would significantly reduce the cost and length of clinical research trials.

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