Development of Novel Analyses and Visualizations for Clinical Trial Review that Enhance Comprehension of Information

Ingeborg Holt, Joseph Tonning, Frank Pucino, David Fram, Channing Russell, Geoff Gordon, Ana Szarfman

1 Center for Drug Evaluation & Research, Food and Drug Administration, DHHS, Silver Spring, MD
2 Commonwealth Informatics, Waltham, MA

Background: A goal for submission of clinical trial (CT) data to FDA is to enable effective review and verification of efficacy and safety findings and identify relevant patient demographics and clinical characteristics contributing to research outcomes. This understanding combined with proficiency with Clinical Data Interchange Standards Consortium (CDISC) data standards and use of interactive, auditable analytical tools, gives reviewers the ability to perform focused, custom analyses supporting efficient communication with team members and stakeholders. We used Commonwealth Clinical Data Analytics application to analyze submission data sets, but the work is being presented here uses the CDISC Pilot study to avoid disclosing proprietary data. CCDA is available to the FDA through a 2 year Research Collaboration Agreement (RCA). The focus of this agreement is to enhance the application platform for analyzing drug safety data.

Methods: CDISC Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) submission data and supporting data were imported into Commonwealth Clinical Data Analytics (CCDA), a web-based application that can access and transform a variety of data formats. We used CCDA to develop both confirmatory and exploratory safety analyses with full traceability on clinical trial data submitted to the FDA. Once created for standardized data, these analyses can be reused on data adhering to the same data standards. Analyses were created to confirm tables, figures and listings from Clinical Study Reports (CSRs). We used data from the CDISC Pilot Project, a Phase 2 trial investigating the safety and efficacy of the Xanomeline Transdermal Therapeutic System (TTS) in patients with mild to moderate Alzheimer’s Disease, to verify two exploratory safety analyses with full traceability on clinical trial data submitted to the FDA. We first used Excel to create a list of dermatological events of special interest (DESI) using the list provided in the CSR, and loaded the custom list into the CCDA.

A third, exploratory analysis was conducted in a synthetic data set to look for Drug-Induced Liver Injury (DILI) as defined by the FDA’s Guidance for Industry Drug-Induced Liver Injury: Premarking Clinical Evaluation (2009). We evaluated subjects using criteria listed in the Guidance stating that: Discontinuation of treatment should be considered if:

1. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >8x upper limit of normal (ULN)
2. ALT or AST >5xULN and (total bilirubin (TBL) >2xULN or INR >1.5)
3. ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

A list of relevant adverse events was created and uploaded into CCDA. The terms were then mapped to MedDRA’s Preferred Terms and matched with SDTM formatted AE data. The LB data set was then queried for subjects that matched the laboratory criteria. In the fourth set of criteria, the analysis requiring the laboratory data with the adverse event data using usubjid and also specifying a range of days with in which you can expect the AE and lab results to be related; here we chose 7 days.

Results: In the first analysis, we were able to use CCDA to replicate Table 14-5.01 Incidence of Treatment-Emergent Adverse Events by Treatment Group exactly. We were also able to reuse this analysis for other MedDRA System Organ Classes.