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

Ingeborg Holt[2], Joseph Tonning[1], Frank Pucino[1], David Fram[2], Channing Russell[2] , Geoff Gordon[2], Ana Szarfman[1]

[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.

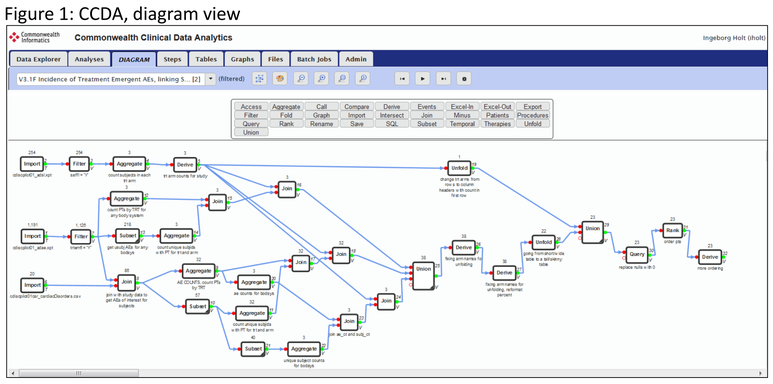
We used Commonwealth Clinical Data Analytics application to analyze submission data sets, but the work is being presented here uses the CDISC Pilot study to avoid disclosing proprietary data . CCDA is available to the FDA through a 2 year Research Collaboration Agreement (RCA). The focus of this agreement 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 analyses in the CSR. This study was a prospective, randomized, multi-center, double-blind, placebo-controlled, parallel-group study that evaluated the efficacy and safety of 2 doses and placebo.

In the first confirmatory CCDA analysis developed, the CDISC Pilot ADaM datasets were used to verify the incidence of treatment-emergent adverse events (AEs) by treatment group for events in the MedDRA System Organ Class "Cardiac Disorders". Data was downloaded from the CDISC website as SAS transport files and read into the CCDA. The analysis was then created in the application which allows the user to load, access and manipulate data in a relational database. An analysis consists of a series of connected steps, each performing a transformation on the data. The steps are translated into Structured Query Language (SQL) supported by relational database (Postgres). The steps for this analysis included specifying the ADaM treatment-emergent flag (TRTEMFL) = 'Y' and manipulating the data to count all adverse event occurrences, count unique subjects experiencing one or more AEs in the specified MedDRA System Organ Class by treatment group and calculate the percent of those subjects relative to the total number of patients randomized to the treatment group.

Figure 1: CCDA, diagram view



The CSR for the Xanomeline trial concluded that "a statistically significantly higher proportion of subjects in the active treatment groups withdrew prematurely from the study as compared to the placebo group" and attributed this to "the higher proportion of subjects in the active treatment groups experiencing a dermatologic event". This was thought to hinder the study's ability to demonstrate efficacy. The report included a Survival curve showing time to dermatological event or end of study if no such event occurred. We developed a second confirmatory analysis to confirm the numbers that supported this conclusion.

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. The DESI were then joined with the previously loaded SDTM AE table restricting the join query to only select AEs where the study day was greater than 0, excluding any AEs that were found prior to study start. We then selected the minimum onset date for the DESI using AESTDY. For those subjects who did not have a DESI, the Disposition (DS) table was used to find each subject's end of study day. The 2 datasets were combined and used to produce a survival-like graph showing the time to first dermatological event or end of study. We also created a summary table of the counts of subjects with the event and those censored.

.

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: Premarketing 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 for more than 2 weeks*
3. *ALT or AST >3xULN and (total bilirubin [TBL] >2xULN or INR >1.5)*
4. *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 requires joining 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 .

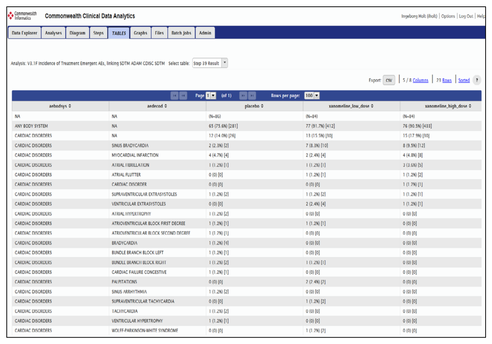
Figure 2: Comparison of CSR Table 14-5.01 , Incidence of Treatment-Emergent Adverse Events by Treatment Group (left) and CCDA generated table (right)

Protocol: CDISCPILOT01 *Page 1 of 16*
Population: Safety

Table 14-5.01
Incidence of Treatment Emergent Adverse Events by Treatment Group

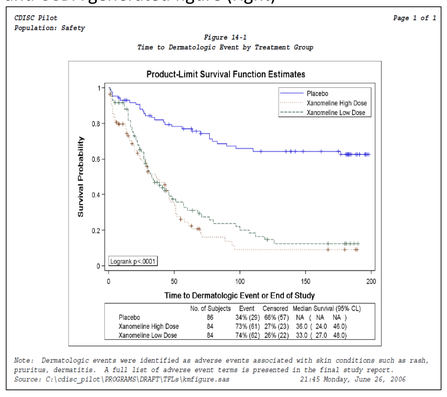
System Organ Class/ Preferred Term	Placebo (N=86) n(%)	[AEs]	Xanomeline Low (N=84) n(%)	[AEs]	Xanomeline High (N=84) n(%)	[AEs]	Fisher's Exact p-values Placebo vs. Low Dose	Placebo vs. High Dose
ANY BODY SYSTEM	65 (75.6%)	[281]	77 (91.7%)	[412]	76 (90.5%)	[433]	0.007*	0.014*
CARDIAC DISORDERS	12 (14.0%)	[26]	13 (15.5%)	[30]	15 (17.9%)	[30]	0.831	0.534
SINUS BRADYCARDIA	2 (2.3%)	[2]	7 (8.3%)	[10]	8 (9.5%)	[12]	0.097*	0.056*
MYOCARDIAL INFARCTION	4 (4.7%)	[4]	2 (2.4%)	[4]	4 (4.8%)	[8]	0.682	>0.99
ATRIAL FIBRILLATION	1 (1.2%)	[1]	1 (1.2%)	[1]	3 (3.6%)	[5]	>0.99	0.365
ATRIAL FLUTTER	0		1 (1.2%)	[1]	1 (1.2%)	[2]	0.494	0.494
CARDIAC DISORDER	0		0		1 (1.2%)	[1]		0.494
SUPRAVENTRICULAR EXTRASYSTOLES	1 (1.2%)	[2]	1 (1.2%)	[2]	1 (1.2%)	[1]	>0.99	>0.99
VENTRICULAR EXTRASYSTOLES	0		2 (2.4%)	[4]	1 (1.2%)	[1]	0.243	0.494
ATRIAL HYPERTROPHY	1 (1.2%)	[2]	0		0		>0.99	>0.99
ATRIOVENTRICULAR BLOCK FIRST DEGREE	1 (1.2%)	[1]	1 (1.2%)	[1]	0		>0.99	>0.99
ATRIOVENTRICULAR BLOCK SECOND DEGREE	1 (1.2%)	[1]	0		0		>0.99	>0.99
BRADYCARDIA	1 (1.2%)	[4]	0		0		>0.99	>0.99
BUNDLE BRANCH BLOCK LEFT	1 (1.2%)	[1]	0		0		>0.99	>0.99
BUNDLE BRANCH BLOCK RIGHT	1 (1.2%)	[2]	1 (1.2%)	[1]	0		>0.99	>0.99

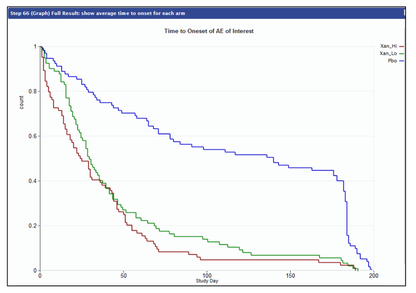
Note: Treatment emergent events are defined as events which start on or after the start of treatment.
Note: Adverse events are coded using MedDRA.
Note: Percentages are based on the number of subjects in the safety population within each treatment group.

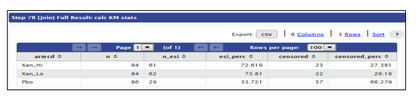


In the second analysis looking at DESI and End of Study, the numbers of subjects experiencing an adverse event were matched exactly and the CCDA survival-like graph was similar to the Time to Dermatologic Event by Treatment Group shown in the CSR. However, the CCDA graph displays the count of subjects as they complete or withdraw from the study, without the statistics used to for standard survival curves and thus the graphs differ, most notably at the end of the study.

Figure 3: Comparison of CSR Figure 14-1 Time to Dermatologic Event or End of Study by Treatment Group (left) and CCDA generated figure (right)







In the third, exploratory analysis using the FDA DILI criteria, one subject was identified who met all of the criteria in one of the 4 specifications. This analysis was done as proof of concept and we expect to build more robust analyses going forward.

Conclusion:

The participants in the project concluded that the CCDA tool enables the development of novel, re-usable analyses and visualizations that enhance the comprehension of clinical trial information. The application is optimized to work with clinical trial data, but can handle a variety of data sources allowing customized analyses and the ability to reproduce results in specific areas addressed by clinical study reports. In addition, the interactive nature of the analysis makes it possible for a non-technical user to create an analysis or edit values within an analysis, such as a reference lab range, with inherent traceability.