Digitizing Therapeutic Areas: Increasing Standardization and Reusability

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History of Therapeutic Area User Guides

• First one published in 2011 – Alzheimer's Therapeutic Area User Guide v1.0

• CFAST is Launched in 2012

• Original plan: 55 TA Standards in 5 years, today 44 TA Standards in 8 years
Today we are here

CDISC Standards in the Clinical Research Process

PRE-CLINICAL

ORGANIZE

SEND

ORGANIZE

PLAN

COLLECT

DATA EXCHANGE
ODM-XML
SDM-XML

CDASH

DATA EXCHANGE
ODM-XML

SDTM

DATA EXCHANGE
Define - XML
Dataset - XML

ADaM

SUBMIT PUBLISH REPORT

TAUGS

BRIDG, CONTROLLED TERMINOLOGY AND GLOSSARY
Therapeutic Area (TA) Standards extend the Foundational Standards to represent data that pertains to specific disease areas. TA Standards include disease-specific metadata, examples and guidance on implementing CDISC standards for a variety of uses, including global regulatory submission.

Autoimmune
- Psoriasis
- Rheumatoid Arthritis

Cardiovascular
- Cardiovascular
- Heart Failure
- QT Studies
- Traditional Chinese Medicine - Coronary Artery Disease

Angina

Endocrine
- Acute Kidney Injury
- Diabetes
- Diabetes - Type 1
- Diabetic Kidney Disease
- Dyslipidemia
- Kidney Transplant
- Polycystic Kidney Disease

Gastrointestinal
- CDAD
- Crohn’s Disease

Infectious
- COVID-19
- Ebola
- Hepatitis C
- HIV
- Influenza
- Malaria
- Tuberculosis
- Virology

Mental Health
- Major Depressive Disorder
- Post Traumatic Stress Disorder
- Schizophrenia

Neurology
- Alzheimer’s
- Huntington’s Disease
- Multiple Sclerosis
- Parkinson’s Disease
- Traumatic Brain Injury

Oncology
- Breast Cancer
- Colorectal Cancer
- Lung Cancer
- Pancreatic Cancer
- Prostate Cancer

Other
- Nutrition
- Traditional Chinese Medicine - Acupuncture

Rare Diseases
- Duchenne Muscular Dystrophy

Respiratory
- Asthma
- COPD
- COVID-19

Treatments
- Pain
- Vaccines

https://www.cdisc.org/standards/therapeutic-areas/disease-area
CDISC Standards Development Process
Concept Map (scoping)

• Provides scope and extent of TA User Guide

• Facilitates communication between scientists and data standards experts
Annotated Case Report Forms and Datasets

Example CRF: Hypoglycemia

CRF annotated to show mapping SDTM variables as red. CDC/ARV changes differ from SDTM the CDC/ARV variable is in blue.
3.3 Hypoglycemic Episodes Summary Dataset

The analysis dataset ADHYPO is used for the statistical analysis of the hypoglycemic events and for the detailed summary of frequency of hypoglycemic episodes (see Table 3.3.1). The dataset includes one observation per combination of subject, analysis parameter, time window and indicator (i.e., treatment emergent flag). Each record is a summary of the type of hypoglycemic episode described by the parameter, per subject. For each combination of parameter and the main variable, ADHYPT records are created even if no hypoglycemic episodes occurred. The statistical model presented below is based on the actual treatment received (TREAT) and adjusted for subject-level values of covariates. Therefore, these variables are included in ADHYPT from ADHYPO to support marginal estimates. The duration exposure (TREXPURG) is added to the dataset in order to facilitate exposure adjusted incidence rates. For overall summaries the records which have “cumulative frequency count” within the text (PARAM) and ADHYPT and “End of treatment” can be selected. In this example, parameter for each of the low ADR classification values are defined, along with a derived parameter that represents a grouping of two of the classification values (documented symptomatic or severe hypoglycemia). Most data for this summary dataset is provided below in Table 3.3.1, yet this small data shows only a subset of the possible values of analysis parameters. The examples below do not attempt to derive all the data needed fully to validate the relationship between ADHYPO and ADHYPT for a given subject; the volume of required such data would be large. Hypoglycemia, however, the counts derived in ADHYPT for a given subject could be completely reconciled to the counts of individual events for that subject found in the source ADHYPO dataset.

<table>
<thead>
<tr>
<th>Table 3.3.1: ADHYPT Analysis Dataset</th>
<th>PARAM</th>
<th>ADHYPO</th>
<th>ADHYPT</th>
<th>ADHYPT</th>
<th>ADHYPT</th>
<th>ADHYPT</th>
<th>ADHYPT</th>
<th>ADHYPT</th>
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<tr>
<td>1</td>
<td>122</td>
<td>18008</td>
<td>ADHYPO</td>
<td>Asymptomatic Hypoglycemia</td>
<td>Time</td>
<td>56</td>
<td>17</td>
<td>1</td>
</tr>
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<td>Time</td>
<td>56</td>
<td>17</td>
<td>1</td>
</tr>
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<td>18008</td>
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<td>1</td>
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<td>122</td>
<td>18008</td>
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<td>Asymptomatic Hypoglycemia</td>
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<td>1</td>
</tr>
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<td>56</td>
<td>17</td>
<td>1</td>
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<td>Time</td>
<td>56</td>
<td>17</td>
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<td>17</td>
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<td>122</td>
<td>18008</td>
<td>ADHYPT</td>
<td>Asymptomatic Hypoglycemia</td>
<td>Time</td>
<td>56</td>
<td>17</td>
<td>1</td>
</tr>
</tbody>
</table>

3.4 Hypoglycemic Episodes Summary Analysis Results

The summary statistics in Table 3.4.1 are presented for all hypoglycemic episodes as well as by ADA classification group. The statistics presented in the current examples are number of subjects experiencing an event, the number of events, and the raw event rate. To estimate and present the results of information, exposure time is needed. Table 3.4.1 is based on the ADHYPO dataset.

<table>
<thead>
<tr>
<th>Table 3.4.1: Summary of Hypoglycemic Episodes by Classification</th>
<th>TREAT</th>
<th>Summary</th>
<th>Safety Analysis Set</th>
<th>Drug A</th>
<th>Drug B</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Total events</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

Figure 3.4.1: Mean Cumulative Function Plot of Documented and Severe Symptomatic Hypoglycemic Episodes

Documented and Severe Symptomatic Hypoglycemic Episodes - Treatment Emergent - Mean Cumulative Function - Safety Analysis Set

Figure 3.4.1: Mean Cumulative Function Plot of Documented and Severe Symptomatic Hypoglycemic Episodes

Documented and Severe Symptomatic Hypoglycemic Episodes - Treatment Emergent - Mean Cumulative Function - Safety Analysis Set
Biomedical Concepts

The CDISC 360 Project: Adding a conceptual layer to standards

- Create and store standards as concepts which create meaning between data
- Electronically publish data standards as linked metadata
- Add derivation and transformation metadata to avoid unnecessary variability

→ CDISC 360 will develop concept-based standard definitions, and test and demonstrate end-to-end automation of study specification, data processing, and analysis
Standardize implementation
Linked derivations & transformations
What Follows?

• Create biomedical and analysis concepts
  • Establish semantic link between end to end implementation
  • Standardize derivation and transformation metadata

• Evolve Therapeutic Area standards
  • Analog documents to electronic metadata
  • End to End: from collection through analysis

• CDASH eCRF Library
  • Will cover Therapeutic Area content

• Analysis Results Metadata
  • Standardize most common analysis