JumpStarting the Regulatory Review Process: The Review Perspective

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Office of Translational Science
CDER
Transforming the Regulatory Review Process

Policy
eStudy Guidance and Technical Conformance Guide

Standards
Electronic Standardized Study Data

Tools and Services
JumpStart and Janus Clinical Trials Repository

Improved Access to Study Data to Support Regulatory Decision-Making
Office of Computational Science

Our Mission
To support CDER in continually improving the drug evaluation and review processes across the drug lifecycle through innovation, supporting the submission and use of high quality data, and providing access to high-end analytical tools and technologies.

Our Vision
To enable advanced scientific review across the lifecycle of regulated projects.
Intersection of data, tools and technology

Standardized Data

Data Warehouse

Data Marts

Data & Analysis Support Services

Tools & Technology Support Services

Training & Customer Support Services

Computational Science Center (CSC) Reviewer Services
CSC Reviewer Services

DATA & ANALYSIS SUPPORT SERVICES
- Data Validation and Quality Assessments
- Support Data Standardization
- Script Development & Sharing to Support Analysis

TOOLS & TECHNOLOGY SUPPORT SERVICES
- Analytic and Visualization Tool Support
- JumpStart Service
- Regulatory Review Services

TRAINING & CUSTOMER SUPPORT SERVICES
- Analytic Tool Training
- Data Standards Training
- Clinical Reviewer Portal

INNOVATION
High quality data is the key to enabling regulatory reviewers to fully utilize the Computational Science Center’s tools and services to support decision making.
Interaction with Sponsor (Phase 1, 2, 3)

Sponsor submits standardized study data to CDER

CDER runs data quality checks and loads into CTR

Data are accessed through CTR User Interface

Technology

Analysis Tools

Standard Analysis Panels

Search Download

The Vision

JumpStart
Regulatory Review

Applying the Right Tools at the Right Time for the Right Audience

JumpStart Video at FDA.gov

http://www.fda.gov/Drugs/ResourcesForYou/Consumers/
**Follow Up Activities**

**Purpose**
- After the sessions, reviewers need to be able to access and understand the outputs and findings.

**When**
- Occurs after the sessions.

**How**
- Provide reference documentation.
- Work with reviewers to draft technical language and explanations to support information requests.

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**Data Fitness Session**

**Purpose:**
- Assist in determining whether data is fit for review.
- Figure out the impact on review from deficiencies.

**When:**
- 2 weeks after acceptance.

**How:**
- Use data standard validation tools.
- Use results to drive human exploration of data.

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**Exploratory Analysis Session**

**Purpose**
- Improves the efficiency of review by setting up tools and common analyses.
- Points out ways to explore safety signals in more depth.

**When**
- 4 weeks after acceptance.

**How**
- Utilizes a suite of analyses that rely on standardized data.
- Compare results with sponsor’s clinical study report.
SDTM enables JumpStart to quickly analyze the data submission.

- Efficient Review of Data Quality
- Standard Analysis of the Study Population
- Repeatable Safety Analyses
Navigating the data fitness findings

Data Fitness Findings Discussion Flow

SDRG/Define File → Supplemental Info → Controlled Terminology

Deaths → Missing Data → CDER Common Issues → Duplicates

Term Matching → Standard Units → Safety Population → Race/Ethnicity
Review Questions:
We will walk through each finding and point out questions you may have that can be answered using the highlighted findings group.

Findings:
We will then outline how the data fitness findings may impact your analyses and ultimately your review.

JumpStart has analyzed 10 submissions in FY2015 so far. All statistics around findings in this presentation are based on this set of 10 submissions.
Review Questions:

SDRG
- Were the SDTM datasets used as sources for the analysis datasets?
- If there are issues with the data, why did the sponsor choose not to fix them?
- What version of MedDRA/WHODRUG did the sponsor use?
- Where is the efficacy data located?

Define File
- How does the information in the annotated CRFs map to the datasets?
- Does the sponsor provide an explanation of the codes used?
Supplemental Information

Review Questions:
- What information is available in the supplemental domains?
- How does the information contained in these domains map to the parent domains?
- What information from the supplemental domains could be useful for analysis?

FY2015 Findings:
For every application that goes through JumpStart, the team analyses the content of the Supplemental domains to highlight useful information as well as uncover inconsistencies.
Controlled Terminology

Review Questions:

- How does the sponsor’s terminology map to controlled terminology?
- Which domains do not use controlled terminology?
- Did a lack of controlled terminology cause ambiguity in the data?

FY2015 Findings:
60% of applications have had issues with controlled terminology.
Controlled Terminology Findings and Impact

Findings
- Adverse Event Action Taken (AEACN) is not populated with controlled terminology

Impact
- Actual values provided in the data may be difficult to interpret and cause uncertainty during review

Illustrative Example:

<table>
<thead>
<tr>
<th>USUBJ</th>
<th>AEEDCOD</th>
<th>AEACN</th>
</tr>
</thead>
<tbody>
<tr>
<td>001-123-456</td>
<td>Palpitations</td>
<td>DOSE ALTERED OR WITHHELD</td>
</tr>
<tr>
<td>001-123-456</td>
<td>Nausea</td>
<td>DOSE ALTERED OR WITHHELD</td>
</tr>
</tbody>
</table>

Examples from AEACN Codelist

<table>
<thead>
<tr>
<th>DOSE INCREASED</th>
<th>DOSE NOT CHANGED</th>
<th>DRUG WITHDRAWN</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOSE REDUCED</td>
<td>DRUG INTERRUPTED</td>
<td>UNKNOWN</td>
</tr>
</tbody>
</table>
Deaths

Review Questions:

- How many deaths occurred during the study?
- Where is information about deaths located?
- Was the death information represented consistently across domains?

FY2015 Findings:
100% of studies that go through JumpStart are provided a summary of death information. The summary highlights issues such as:

- DM death flags are not consistent with DS and AE records
- Potential death information located only in the CO domain
Death Findings and Impact

Findings
- Death information not represented consistently across DM, AE, DS, and CO domains.

Impact
- You may miss pertinent death information if relying on certain flags or indicators

Illustrative Example:

<table>
<thead>
<tr>
<th>USUBJID</th>
<th>DM Death Flag</th>
<th>DM Death Date</th>
<th>DSDECOD</th>
<th>DSSTDTC</th>
<th>FATAL AE</th>
<th>FATAL AE End Date</th>
<th>Death Info in Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>001-123-456</td>
<td>Y</td>
<td>2011-12-21</td>
<td>DEATH</td>
<td>2011-12-21</td>
<td>Acute Renal Failure</td>
<td>2011-12-21</td>
<td>N</td>
</tr>
<tr>
<td>001-123-678</td>
<td>Y</td>
<td>2010-06-05</td>
<td>DEATH</td>
<td>2010-06-05</td>
<td>Cardiac Arrest</td>
<td>2010-06-03</td>
<td>N</td>
</tr>
<tr>
<td>001-123-912</td>
<td></td>
<td></td>
<td>ADVERSE EVENT</td>
<td>2010-04-15</td>
<td>Cerebral Haemorrhage</td>
<td>2010-04-15</td>
<td>Y</td>
</tr>
<tr>
<td>001-123-345</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Y</td>
</tr>
</tbody>
</table>
Missing Data

Review Questions:
- What data is missing?
- How will the missing data impact analyses?
- Are there other variables that can be used in lieu of the missing data?

FY2015 Findings:
60% of applications are missing AE Seriousness Criteria or have inconsistencies between AE Serious Flag and Seriousness Criteria
Missing Data Findings and Impact

Findings
- A portion of Serious AEs are missing AE Seriousness Criteria

Impact
- Cannot independently verify whether an adverse event was serious or not

Illustrative Example:

| DOMAIN | USUBJID | AEDECOD       | AEBODSYS                                | AESER | AESCONG | AESDISAB | AESDTH | AESHOSP | AESLIFE | AESMIE |
|---------|---------|---------------|-----------------------------------------|-------|---------|----------|--------|---------|---------|--------|-------|
| AE      | 123101  | Headache      | Nervous system disorders                 | N     |         |          |        |         |         |        |       |
| AE      | 123101  | Neutropenia   | Blood and lymphatic system disorders     | Y     |         |          |        |         |         |        |       |
| AE      | 123101  | Pulmonary embolism | Vascular disorders                | Y     |         |          |        | Y       |         |        |       |
| AE      | 123101  | Stroke        | Nervous system disorders                 | N     |         |          |        |         |         | Y      |       |
| AE      | 123101  | Chest Pain    | General Disorders and Administrative Site Conditions | N     |         |          |        |         |         |        |       |
CDER Common Issues

Review Questions:

- Does the DM domain include start and end dates, an actual arm variable, a death flag, and a date of death variable?
- Are domains missing the EPOCH variable?
- Did the sponsor include the trial summary domains?
- Does the AE domain include a treatment emergent flag?

FY2015 Findings:

- EPOCH variable was missing from key domains (AE, LB, CM, EX, VS, DS) in 90% of applications
- TS domain missing in 30% of applications

Review Questions:
- Do any of the datasets contain potential duplicate records?
- How will these duplicates impact analyses?

FY2015 Findings:
Potential duplicate issues found in 40% of applications
Duplicates Findings and Impact

**Findings**
- There are contradictory duplicate records present in the EG and LB domains

**Impact**
- Manipulations may have to be made to ensure results are not double counted for particular subjects. In some cases, it will be difficult to tell which record is correct

**Illustrative Examples:**

<table>
<thead>
<tr>
<th>USUBJID</th>
<th>EBTEST</th>
<th>EBSTRESC</th>
<th>EBDTC</th>
</tr>
</thead>
<tbody>
<tr>
<td>001-123-1234</td>
<td>ECG Interpretation</td>
<td>NORMAL</td>
<td>2011-06-22T08:53</td>
</tr>
<tr>
<td>001-123-1234</td>
<td>ECG Interpretation</td>
<td>ABNORMAL</td>
<td>2011-06-22T08:53</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>USUBJID</th>
<th>EBTEST</th>
<th>EBORRES</th>
<th>EBORRESU</th>
<th>EBORN RLO</th>
<th>EBORN RHI</th>
<th>EBFAST</th>
<th>EBDTC</th>
</tr>
</thead>
<tbody>
<tr>
<td>001-123-5678</td>
<td>GLUCOSE</td>
<td>3.9</td>
<td>mmol/L</td>
<td>4.6</td>
<td>6.4</td>
<td>Y</td>
<td>2011-04-13T10:45</td>
</tr>
<tr>
<td>001-123-5678</td>
<td>GLUCOSE</td>
<td>3.9</td>
<td>mmol/L</td>
<td>3.6</td>
<td>7.7</td>
<td>N</td>
<td>2011-04-13T10:45</td>
</tr>
</tbody>
</table>
Review Questions:
- How can you efficiently review coding quality?
- Was an adverse event mapped to the appropriate dictionary term?
- Was the disposition term reported using the appropriate dictionary term?
- Did the sponsor use the term “Other” appropriately?

FY2015 Findings:
Potential coding issues found in 40% of applications
Term Matching Findings and Impact

Findings
- AEDECOD is missing for AETERMS
- DSDECOD of “Other” could have been coded more appropriately

Impact
- These events will not be included in analyses unless they are manually coded
- Clinically relevant disposition events could be lost from analysis

Illustrative Example:

<table>
<thead>
<tr>
<th>USUBJID</th>
<th>DSDECOD</th>
<th>DSTERM</th>
</tr>
</thead>
<tbody>
<tr>
<td>001-123-1231</td>
<td>OTHER</td>
<td>SUBJECT WITHDREW DUE TO WORSENING PAIN</td>
</tr>
<tr>
<td>001-123-1232</td>
<td>OTHER</td>
<td>LESION CONTINUED TO GROW</td>
</tr>
<tr>
<td>001-123-1233</td>
<td>OTHER</td>
<td>SUBJECT DECEASED</td>
</tr>
</tbody>
</table>
Standard Units

Review Questions:
- Did the sponsor use standard units?
- Did the sponsor use the same units for each type of test?
- Did the list of standard units submitted by the sponsor match the data?

FY2015 Findings:
30% of applications have inconsistent units or missing standard units when original units are given.

- Term Matching
- Safety Population
- Race/Ethnicity
**Safety Population**

**Review Questions:**
- Are there population inconsistencies between the SDTM data and the study report?
- Are there any subjects who were randomized but not treated?
- Are there any subjects who received a treatment that was different from their planned treatment?

**FY2015 Findings:**
For every application that goes through JumpStart, the team searches for inconsistencies between DM, EX, and the clinical study report to determine the appropriate Safety Population to use in analyses.
Race and Ethnicity

Review Questions:
- How does the sponsor indicate race/ethnicity?
- Where is detailed information about race/ethnicity located?
- Are there any subjects who are missing race or ethnicity data?

FY2015 Findings:
80% of applications have had race/ethnicity issues
Purpose:
- Set up tools, run common analyses, and point out ways to explore safety signals in more depth

“(I’m) very satisfied overall – (JumpStart) gives reviewers more time to focus on actual signals vs. matching numbers with the sponsor data.” – DOPII Reviewer

“For analyses that I already knew how to perform, it served as confirmatory; it allowed me to explore signals that I did not know how to look for; it enabled me to be more efficient.”
– DOPII Reviewer
JumpStart analyses and outputs support specific sections within the clinical review

<table>
<thead>
<tr>
<th>Clinical Review Sections</th>
<th>7.3.5 Submission Specific Primary Safety Concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.1.2 Demographics</td>
<td>7.4 Supportive Safety Results</td>
</tr>
<tr>
<td>6.1.3 Subject Disposition</td>
<td>7.4.1 Common Adverse Events</td>
</tr>
<tr>
<td>7. Review of Safety</td>
<td>7.4.2 Laboratory Findings</td>
</tr>
<tr>
<td>7.3 Major Safety Results</td>
<td>7.4.3 Vital Signs</td>
</tr>
<tr>
<td>7.3.1 Deaths</td>
<td>7.4.4 Electrocardiograms (ECGs)</td>
</tr>
<tr>
<td>7.3.2 Nonfatal Serious Adverse Events</td>
<td>7.4.5 Special Safety Studies/Clinical Trials</td>
</tr>
<tr>
<td>7.3.3 Dropouts and/or Discontinuations</td>
<td>7.4.6 Immunogenicity</td>
</tr>
<tr>
<td>7.3.4 Significant Adverse Events</td>
<td></td>
</tr>
</tbody>
</table>

*Bold, red font* indicates sections covered during JumpStart presentations
Delivering Data to Reviewers

CTR Tools

Analysis-Ready Views

CTR Reporting for JumpStart Service

Standard AE Analyses

Standard Safety Analysis Reports

Regulatory Review

Analysis-Ready Views

Additional Views to Support Regulatory Review & Data Integration

SAS
JMP
R
JReview
CTR Tools

Standard Reports using JReview
JumpStart delivered to 41 applications since FY13

Applications Receiving JumpStart

- FY13 (Pilot)
  - Performed: 0
  - Planned: 0
- FY14
  - Performed: 15
  - Planned: 0
- FY15
  - Performed: 20
  - Planned: 15

Applications by Division (FY14 & FY15)

- DAIP
- DAPII
- DCRP
- DAVP
- DMEP
- DHP
- DAAAP
- DDDDP
- DTOP
- DGIEP
- OHOP
- DNP

Number of Applications

- 0 to 5
- 10 to 15
- 20 to 25
- 30 to 35
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JumpStart

Interaction with Sponsor (Phase 1, 2, 3)