Advancing the Development and Implementation of Analysis Data Standards: Key Challenges and Opportunities

Tommy Douglas Conference Center
June 12, 2019
Welcome and Overview
Opening Remarks
Session I: FDA Efforts to Support Analysis Data Standards for Product Development and Review
Data Standards and FDA’s Review Process: Submission Considerations

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Office of Biostatistics, CDER

Advancing the Development and Implementation of Analysis Data Standards: Key Challenges and Opportunities
June 12, 2019
FDASIA Act authorizes electronic submissions

“FDASIA Umbrella” Implementation Guidance

eCTD Guidance requires e-submission to be in eCTD format

eStudy Data Guidance requires studies be compliant with standards outlined in the FDA Data Standards Catalog

For details, see https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources
FDASIA Implementation Guidance

Providing Regulatory Submissions in Electronic Format — Submissions Under Section 745A(a) of the Federal Food, Drug, and Cosmetic Act

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

December 2014
Electronic Submissions

- Implement 24 Months after Final Guidance publication
- Individual Guidance specifies format and timetable for implementation
- **Binding Guidance**
Standardized Study Data Guidance

Providing Regulatory Submissions In Electronic Format — Standardized Study Data

Guidance for Industry

NDAs, BLAs, ANDAs

Studies that start after December 17, 2016, must use the standards in the Data Standard Catalog

Commercial INDs

Studies that start after December 17, 2017, must use the standards in the Data Standard Catalog

Binding Guidance

For details, see: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/providing-regulatory-submissions-electronic-format-standardized-study-data
FDA Data Standards Strategic Goals

For details, see https://www.fda.gov/media/124313/download
FDA Data Standards Strategic Goals

Goal 1: Incorporate data standards to support more efficient, science-based pre-market review of medical products.

Goal 4: Promote innovation in the development and use of data standards.

Goal 6: Improve the management and usability of the volume of information through data standards.

Goal 5: Ensure effective communication and collaboration with stakeholders on data standards.
FDA Data Standards Strategic Goals

Goal 1: Incorporate data standards to support more efficient, science-based pre-market review of medical products.

Goal 2: Implement common data standards to improve the quality and integrity of marketed medical products.

Goal 3: Ensure effective communication and collaboration with stakeholders on data standards.

Goal 4: Promote innovation in the development and use of data standards.
Key Milestones in NDA/BLA Review Process

For details, see https://www.fda.gov/media/78941/download
Where do Submissions Go?

- Electronic Submissions Gateway (ESG)
  - portal for accepting regulatory submissions
  - does not review submissions, but routes them to proper FDA Center.
- High Level Technical Validation
- eCTD Validation Criteria

For details, see: https://www.fda.gov/industry/electronic-submissions-gateway
Formation of Review Teams

- Clinical
- Biostatistics
- Clinical Pharmacology
- Pharmacology/Toxicology
- Clinical Microbiology
- Other disciplines
Filing Review

- Is there sufficient evidence to complete a substantive review?
- Are there serious deficiencies in the application?
  - FDA can refuse to file if study data do not conform to the required standards.
- Is the submission fileable?

For details, see https://www.fda.gov/media/109758/download
NDA/BLA Submission Review

Legacy Data

Standardized Study Data
Define.xml  ADaM  SDTM
ADRG  cSDRG
Benefits of Standardized Study Data

• Reviewers able to work with data more effectively and efficiently with less preparation time.
  – easier to complete standard analyses and use standardized tools
  – allows integration of data from multiple studies within a submission
  – allows for additional “think time” during their review
• It provides for better transparency.
• It facilitates understanding diseases and potential cures.
Take Official Action

Do the benefits outweigh the known risks?

FDA determines if a drug can be approved
  • Approval letter, action package, labeling

Or if additional information is needed
  • Complete Response letter (CR) to Sponsor
FDA Study Data Standards Resources

• Data Standards Catalog
• Guidance for Industry
• Technical Specifications
• Business and Validator Rules
• Position Statements

For study data standards questions, email eData Team:
CDER: cdar-edata@fda.hhs.gov
CBER: cber.cdsc@fda.hhs.gov

For details, see: https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources
Session I: FDA Efforts to Support Analysis Data Standards for Product Development and Review
FDA Analyses Data standards

Vaishali Popat MD, MPH
Associate Director of Biomedical Informatics and Regulatory Review Science
Office of New Drugs
Begin With the End in Mind: Regulatory Perspective

Clinical Reviewers and their role

• Most are physicians

• Responsible for reviewing all clinical data

• Examine all submission types – preINDs, INDs, NDAs, meeting requests, safety reports, etc.

www.fda.gov
What Do I Do with the Data?

- Understand what is in the datasets – walk through (eyeball) for general orientation
- Check coding, data integrity, traceability
- Verify definitions (e.g., TEAE)
- Look for answers to review questions or issues that arise
- Confirm analyses or conduct them differently
- Look for outlier sites to advise inspectors for site selection
Data Without Standards
Obscure Datasets

File Edit Tables Rows Cols DOE Analyze Graph Tools View Window Help

ADVERSE

Notes Advers

Columns (3/4)

DAI_ORD PSETNO AGE

1 2 • 53
2 2 • 53
3 • • 50
4 1 • 50
5 2 • 54
6 • • 54
Impact of Standardized Data on Overall Review

Makes it easier to complete my review

- Strongly agree: 39
- Agree: 8
- Neutral: 4
- Disagree: 1
- Strongly disagree: 1

Avg Rating: 4.57

Total = 53

Improves my review experience

- Strongly agree: 38
- Agree: 9
- Neutral: 4
- Disagree: 1
- Strongly disagree: 1

Avg Rating: 4.55

Total = 53

Requires less support (e.g., training and support tools) to aid in my review

- Strongly agree: 24
- Agree: 12
- Neutral: 10
- Disagree: 6
- Strongly disagree: 0

Avg Rating: 4.04

Total = 52*

Note: *1 respondent answered N/A. 27 primary reviewers did not answer these questions. Average rating obtained from assigning values of 1-5 for strongly disagree to strongly agree responses.

Source: FDA/FAA Electronic Review Assessment Survey
Impact of Standardized Data on Review Time and Analyses

- Makes it easier to set up and conduct standard analyses
  - Strongly agree: 29
  - Agree: 17
  - Neutral: 5
  - Disagree: 0
  - Strongly disagree: 0
  - Total: 51
  - Avg Rating: 4.47

- Decreases time spent preparing data
  - Strongly agree: 26
  - Agree: 19
  - Neutral: 4
  - Disagree: 1
  - Strongly disagree: 1
  - Total: 51
  - Avg Rating: 4.33

- Allows me to perform analyses for my review more efficiently
  - Strongly agree: 29
  - Agree: 17
  - Neutral: 4
  - Disagree: 2
  - Strongly disagree: 0
  - Total: 52
  - Avg Rating: 4.4

- Allows me more time to conduct additional non-standard analyses that utilize my specialized expertise
  - Strongly agree: 19
  - Agree: 18
  - Neutral: 13
  - Disagree: 0
  - Strongly disagree: 1
  - Total: 52
  - Avg Rating: 4.05

Note: *27 primary reviewers did not answer the question; 1-1 reviewers responded N/A to each response. Average rating obtained from assigning values of 1-5 for strongly disagree to strongly agree responses.

Source: FDA/FA Electronic Review Assessment Survey
### Variability in the ‘Standard’ Datasets

**AEREL= Adverse event, related- 329 ways to report (in standardized datasets)!!!!**

**ADAЕ.xpt from >4000 clinical trials**

<table>
<thead>
<tr>
<th></th>
<th>CDISC IG: AEREL= Causality Char, * Perm, AE.AEREL</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td></td>
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<tr>
<td>Alternate Etiology</td>
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<td>CANNOT BE CLASSIFIED</td>
<td>CD</td>
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<td>CONDITIONAL / UNCLASSIFIED</td>
<td>CONTRAST MEDIA</td>
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<td>Definite</td>
</tr>
<tr>
<td>DEFINITE RELATION</td>
<td>DEFINITE/CERTAIN</td>
</tr>
<tr>
<td>DEFINITELY NOT CAUSED</td>
<td>DEFINITELY NOT RELATED</td>
</tr>
</tbody>
</table>
Pre-market Safety Assessment Working Group

Data in non-standard format, no standardization of processes for NDA/BLA safety review; wide variations across divisions

**Objective:** perform detailed assessment of the NDA/BLA safety review process and develop an efficient, effective, standardized process – adaptable to different needs across teams/applications
Safety Analytics Initiatives

Pre Market Safety Workgroup

• FDA Queries Project
• Standard Tables and Figures
• Type C meeting for data request
• Pre-NDA data request list
• Data Integrity Assessment
• Safety Signal Tracker
The FDA Queries Project

In their analyses of adverse events, Applicants code/translate verbatim terms to some 23,000 standard MedDRA Preferred Terms.

When related Preferred Terms are not grouped, it is possible to miss important safety signals.

By standardizing groupings of related Preferred Terms, Reviewers will be better able to detect safety signals, and labeling can be standardized.
Example: Drug X and Suicidal Ideation

Generate an adverse event table with a 2% cut-off, “Suicidal Ideation” doesn’t make the cut:

<table>
<thead>
<tr>
<th></th>
<th>Drug X</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suicidal Ideation Percent of Patients</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Slide Curtesy: Dr. Ellis Unger
Example: Drug X and Suicidal Ideation

But group these Preferred Terms, and the signal emerges at the 2% cut-off (no patient counted twice):
Goal and Methods

Goal:
Develop FDA standard queries for detecting and summarizing safety signals from clinical trial adverse event datasets

Methods:
• Several prior efforts in this area were evaluated
• Develop FQs based on most frequently labelled terms found in >38,000 labels using natural language processing.
• Establish “ground rules,” apply medical judgment to develop logical groupings (queries).
Phase 1: Most frequently labelled terms and WG proposals. Similar preferred terms/single medical concept (54).

Phase 2: Division requests (18).

Phase 3: Algorithmic queries to detect syndromes, complex conditions (e.g., Hypersensitivity, Opportunistic infections).
Standard Tables and Figures for Premarket Safety Review

- Standardized data makes uniform strategy for data presentation possible. These tables/figures:
  - Reflect formatting standards used in major medical journals
  - Instructions are provided with each table/figure
  - Modifiable as appropriate

- Standardized data make generating analyses easier with the use of review tools:
  - Can be loaded relatively easily in a review tool
  - Data management activities-easier
  - Generating standardized analyses-easier

- Make interpretation of analyses easier:
  - Templates for commonly appearing tables in clinical reviews
Exciting Times

• We are at a tipping point-
  – Requirements for the standardized data
  – Newer tools for analyses (review tools)
  – Biomedical informatics tools and technologies (NLP, algorithms)
  – Health IT and real word data revolution

• Policy, data standards and new software tools are coming together.

• Non-standard data analysis requires the skills of a programmer, but with the standardized study data and new software tools, it is possible to set up standard analyses for efficient reviews.
Resources

• The Final Binding eCTD Guidance
• The eCTD Website
• Study Data Standards Resources
• eSUB@fda.hhs.gov – General eSUB questions
• eDATA@fda.hhs.gov – Clinical / non-clinical data questions
• Study Data Technical Conformance Guide v. 4.1 (PDF - 581 KB) (March 2018)

http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm
References

- eCTD Web Page:

- Electronic Submissions Gateway:
  http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm

- Electronic Submissions Presentations:

- Questions about submitting electronically to CDER: ESUB@fda.hhs.gov
HIV Data Specifications

- Pre-NDA meeting comments
- 31 pages of data specification
- The purpose of these additional data specification request was to aid statistical and clinical reviewers in their review of HIV drug applications by applying standard dataset configurations
- Attachment to the Guidance? not flexible enough to house data specifications, which may need to change with changing endpoints and indications.
Three Areas of Considerations

**Adverse Events**
CDISC standard variables could be used to meet the specification.

**Laboratory analysis**
There were seven dataset requests that were aligned to CDISC standards.
Straightforward because updates were mostly variable naming conventions.

**Efficacy and other data elements**
Over 200 variables related to demographics, treatment variables, exposure, disposition, genotypic, phenotypic data, and efficacy outcomes.
Needed extensive discussions.
## Lessons Learned

1. This can be a resource intensive process
2. Aligned safety (AE, LB and DM domains) related dataset specifications to current CDISC foundational standards
3. Realized that there are no standards that were related to HIV specific safety and efficacy analyses
4. Collaboration with External stakeholders is crucial
5. Technical Conformance Guide/Level 2 guidance process
Session I: FDA Efforts to Support Analysis Data Standards for Product Development and Review
Break
Session II: Industry Experience with Data Standards During Product Development and Review
FDA Workshop on Analysis Data Standards
Convened by Duke-Margolis

Session II: Industry Experience with Data Standards During Product Development and Review

June 12, 2019
Presenters

**Patti Compton**  
VP, Statistical Programming & Analysis  
Pfizer

**Stephen Hamburg**  
Manager, Programming Standards & Efficiencies  
GSK
Objectives

Potential difficulties sponsors face using standards such as the Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) to develop analysis data files.

Improving the traceability of data as it’s transformed and mapped to SDTM and ADaM standards for electronically submitted results.

Opportunities to reduce the variation of how SDTM and ADaM standards are implemented to improve consistency and quality of submissions for review as well as support better data integration of submitted results within a therapeutic area or class of products.
Developing Analysis Data Standards

<table>
<thead>
<tr>
<th>Opportunities</th>
<th>Challenges / Questions</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Harmonizing FDA, CDISC Guidance Documentation and Pinnacle 21 Checks (e.g., one source of truth)</td>
<td>• Naming Conventions for Reviewers Guides vary by Agency</td>
</tr>
<tr>
<td>• Opportunity to version and publish Technical Conformance Guide with advance notice</td>
<td>• Derived variables in SDTM</td>
</tr>
<tr>
<td>• Potential expansion of the ability to apply Real Time Oncology Review (RTOR) to other divisions</td>
<td>• SUPPQUAL</td>
</tr>
<tr>
<td>• Continuing to conduct targeted workshops to explore industry lessons-learned</td>
<td>• Optimal representation of Controlled Terminology (CT)</td>
</tr>
<tr>
<td></td>
<td>• Sponsor burden to maintain and update multiple sources of guidance</td>
</tr>
<tr>
<td></td>
<td>• SDTM 3.1.3 &gt; 3.2 &gt; 3.3; Quarterly CDISC NCI CT release</td>
</tr>
<tr>
<td></td>
<td>• Ongoing studies</td>
</tr>
</tbody>
</table>
## Improving the Traceability of Data

<table>
<thead>
<tr>
<th>Opportunities</th>
<th>Challenges / Questions</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Consolidate the SDTM and ADaM Define.xml and Reviewers Guides</td>
<td>• Continue to reduce the need for listings</td>
</tr>
<tr>
<td>• Industry support to improve traceability</td>
<td>• Listings can be made available upon request</td>
</tr>
<tr>
<td>• Understanding FDA reviewers challenges</td>
<td>• Clarify role of listings, if any, in traceability</td>
</tr>
<tr>
<td>• Documentation (e.g., Define.xml, Data Reviewers Guides)</td>
<td>• Sponsor traceability starts at data collection</td>
</tr>
<tr>
<td>• Explicit guidance of split SDTM domains based on category vs. aggregate</td>
<td>• FDA position on the use of CDASH standards</td>
</tr>
<tr>
<td>domains</td>
<td>• CDASH awareness is currently limited to safety</td>
</tr>
<tr>
<td></td>
<td>• Impact of release frequency of TAUGs</td>
</tr>
</tbody>
</table>
# Improving Consistency and Quality of Submissions

## Opportunities

- Harmonization of regulatory approaches across FDA, global health authorities, and CDISC
- Potential forum to share CDISC best practices (e.g., domain allocation)
- CDISC library to increase support of efficacy standards
- Eliminate Historical Practices

## Challenges / Questions

- Impact on global health authorities
- Interplay with General Data Protection Regulation (GDPR)
- Managing the volume of industry standard materials and decisions
- Subjective debate regarding SDTM domain allocation
- Requirements for use of TAUGs
- Aligning the Study Data Standardization Plan (SDSP) between CDER and CBER
Thank You!

• Opportunities to enhance the consistency and quality of submissions:
  • Improve the adoption and usability of data standards
  • Further collaboration and harmonization
    • Document best practices, additional forums, and FAQs
    • Agreement within, and amongst, regulatory authorities and consortia
  • Continue to ensure efficient and predictable regulatory structures
Session II: Industry Experience with Data Standards During Product Development and Review
Outline

• ViiV experience with HIV tec spec & datasets

• Challenges

• Opportunities

• Summary
ViiV Experience with HIV Tec Specs

- Different projects spanning 2012 to present
- Includes NCEs as well as fixed dose combinations of approved compounds
- Broad HIV populations:
  - Treatment-naïve
  - Treatment-experienced and virologically suppressed
  - Highly Treatment-Experienced (HTE)
- Different modes of administration (oral, intramuscular)
- Older submissions according to previous datasets guidance
- Current submission according to Mar 2018 Tec spec

• Recently issued HIV guidance (Mar 2018)
• Builds upon prior guidance documents:
  • HIV drug development
    o Original: Oct 2002
    o Updated: Nov 2015
    o Attachment: Feb 2016
  • Role of resistance testing (Oct 2007)
  • Virology study resistance data (Feb 2014)
• Specs for content & format of datasets
  • General eSub dataset standards (Dec 2014)
  • Dataset conformance guide (Oct 2018)
## HIV Tec Specifications – Content and Structure

<table>
<thead>
<tr>
<th>Dataset Name</th>
<th>Content (key variables)</th>
<th>Structure</th>
</tr>
</thead>
</table>
| ADEFFOUT     | • Demographics<br>• Baseline disease characteristics<br>• Baseline resistance<br>• Treatment & exposure<br>• Primary efficacy parameter<br>• Major secondary efficacy outcomes | One record per subject (means many variables) |}
| ADAE*        | Adverse Events (AEs)                                                                   | One record per AE per subject            |
| ADLB*        | Laboratory assessments                                                                | One record per lab test, collection date and subject |

*Denotes separate FDA datasets from original ADAE and ADLB ADaM datasets"
FDA Dataset Development – Dataset Flow

Raw → SDTM → Standard ADaMs → TLFs (CSR)

Study Data Standardisation Plan (SDSP)

Some data in SDTM not needed for TLFs mapped directly to FDA datasets

FDA datasets

Note that FDA datasets are not on critical path to TLFs

CRTs (Standard ADaMs+FDA)

+Associated documentation such as define.XML, RG

ADEFFOUT
ADAE*
ADLB*
Challenges - Conceptual

• Other secondary or “exploratory” parameters
  • Exploratory biomarkers; even those as transformations of original variables
  • Plasma HIV-1 RNA < BLQ and TND; VL “blips”; inflammation markers; etc…
  • Including data not “carried through” from raw/SDTM/ADaM datasets
    • Select mutations especially for new targets (eg, gp160)
    • Original viral sequences (not vs reference or consensus sequences)
  • Studies and work packages in scope
    • Ph 1 in HIV+; Ph 2a; Integrations (ISE/ISS)?
  • Traceability
    • Variables often derived from intermediate ADaM dataset (eg, ADSNAP)
Challenges - Operational

- **Circular, iterative, or recursive logic**
  - Changes introduced in producing FDA datasets may cause change to ADaMs
  - Eg, multiple changes in optimized background therapy for HTE studies
- **Timing of development including feedback from FDA**
  - Often “encroaches” on submission timelines
- **Considerable resources for producing and documenting datasets**
  - Adds to volume and complexity of submissions
  - Must ensure consistency with prior/other datasets
- **Harmonisation with other Health Authorities and other bodies**
  - PMDA, Health Technology Assessment
Challenges - ADEFFOUT

• Variability in study design to dataset production
  • Naïve vs suppressed switch vs HTE
• Visit-level information
  • Windowing, values, intermediate/unscheduled visits, etc…
• Confirmation visit information after landmark analysis milestone(s)
  • Week 52 for 48 week milestone; Week 100 vs Week 96 milestone
• Primary and major secondary HIV-1 RNA endpoint variable(s)
  • Binary response indicator and composite outcome category
  • Modified snapshot analysis (may be more common in RAPID treatment era)
Opportunities – Further Guidance

• Guidance for other domains
  • Medical history (especially related to HIV-related illnesses)
  • Concomitant medications (especially those specific to HIV)

• Long term extension, rollover trials, and companion/sister trials
  • What static data to carry forward to current trial? ADSL of prior trial?
  • Concatenation of current trial data and prior trial data?

• Paediatric/Pregnancy studies
  • Outcomes of both mother (Associated Person) and infant

• Collaborative studies for registration – flexibility in approaches?
• Real World Data for pivotal (or supportive) registrational studies?
  • What is applicable? How can it be customized to RWD setting?
Summary

- Current HIV dataset technical specifications build upon prior guidance documents, previous guidance and correspondence with sponsors
- Further updates and extensions are needed to:
  - Continue to improve quality and consistency of HIV submission reviews
    - Key datasets “one proc” or “one script away” from analysis results
    - Helpful for both FDA technical reviewers as well as sponsors
  - Support more efficient integration of submitted results across submissions
  - Allow for other settings such as novel small molecules development for new targets, HIV prevention, long-acting therapies and different modes of administration, biologics, remission & cure, and vaccines
- Further continued public open forum collaborations with industry, academic and collaborative research groups and FDA needed
Acknowledgements

- Meeting sponsors and organizers
  - Duke Margolis Center for Health Policy
- Past and current colleagues
- ViiV Healthcare
  - Amy Cutrell
  - Qiming Liao
- GlaxoSmithKline
  - David Izard
  - Ken Chow
  - Fangfang Du
  - Mark Hopton
Backup
<table>
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<tr>
<th>Generic Name(s)</th>
<th>Brand Name</th>
<th>Indication(s)</th>
<th>NDA Filing Year</th>
<th>Tec Spec Used?</th>
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<tr>
<td>Dolutegravir</td>
<td>Tivacay</td>
<td>ARV-Naïve, TEP</td>
<td>2012</td>
<td>Precursor</td>
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<td>2019</td>
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<td>TBD</td>
<td>Highly Trt Exp’d</td>
<td>2019</td>
<td>Tec Spec</td>
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About ViiV Healthcare

• Fully integrated independent, global specialist HIV company
• Combined HIV expertise parent companies GSK, Pfizer, and Shionogi
  • Extensive expertise in biostatistics and data management expertise
• Focused on HIV treatment, prevention and care
• More than 1,000 employees and offices in 15 countries
  • GSK support in 50 other markets = presence in >65 countries.
• Broad portfolio of marketed ARVs across multiple drug classes
• Robust R&D pipeline of new medicines and treatment regimens
  • Recent/current innovations in 2DR, long-acting therapies, and HTE
  • Other programs focused on remission and cure, biologics, paediatrics
  • Extensive collaborations with outside networks (eg, NIAID/DAIDS)
Challenges – ADAE* and ADLB*

• Straight forward as many variables mapped from ADAE and ADLB

• LB broken in to smaller domains for size or ease of review
  • Liver, Renal, lipids, etc…

• Maximum laboratory toxicity grade and adverse event severity grade mapped through from ADAE and ADLB to ADAE* and ADLB*

*Denotes separate FDA datasets from original ADAE and ADLB ADaM datasets
Session II: Industry Experience with Data Standards During Product Development and Review
Lunch
Session III: Additional Applications and Impact of Data Standards on Clinical Research and Development Outside of Industry
Biomedical Translational Research Informatics System (BTRIS)

- Enabling platform supporting clinical research and patient care
- 53% active clinical protocols actively utilize BTRIS services
  - Self-serve clinical data warehouse
  - BTRIS assisted custom data search
  - BTRIS assisted custom data analytics support
  - Research and hospital / administrative QA / QC
Use of Data Standards in Research

When are Standards Applied?

- Time of collection / generation
  - Large percentage of clinical data is collected in ambiguous text
  - EMR = ”e”lectronic Medical Record - still largely a paper representation

- Post collection - secondary data curation
  - BTRIS
  - EDC
BTRIS - Application of Standards

- Data comes to BTRIS relatively free of standard annotations
- Research Entities Dictionary
  - High specificity - very granular representation of clinical research data
  - Poor sensitivity - difficult for researchers to extract meaningful data
- Moving to standards metadata approach
Use of Standards

- Leverage healthcare industry standards to
  - Improve ability for researchers to find data using clinically meaningful terms and hierarchies
  - Improve interoperability
  - Improve machine readability, including use of NLP to standard terms from documents
- Rely on Standard Development Organizations (SDOs)
  - SDOs have the authority and resources to support the development of standards
  - Standards are kept up-to-date
Challenges

- Receive clinical data from several NIH sources/systems without consistent or no standardization.
- Receive several clinical data types including Labs, diagnosis, procedures, meds, images, genetic data
- For a single clinical data type each source may represent it using a different standard
  - Example: Diagnosis/Procedure received with ICD9, ICD10, or MedDRA depending on source/system
Standards - UMLS backed

DTS

- SNOMED
- LOINC
- MONDO
- ICD-10-CM
- HPO
- Orphanet
- DOID
- OMIM
- MedDRA

Custom Ontology e.g., UFO

Other..

UMLS

BTRIS Terms

BTRIS EXT

Export

Export

BTRIS

BTRIS UMLS & EXT Data

BTRIS Clinical Data
Tagged with multiple UMLS and/or BTRIS EXT codes

Example: Lab result tagged with UMLS for analyte and UMLS for specimen type

Clinical data tagged with multiple UMLS and/or BTRIS EXT. Search parameters driven by standard or custom ontology.
 HOW STANDARDS PROLIFERATE:
(SEE: A/C CHARGERS, CHARACTER ENCODINGS, INSTANT MESSAGING, ETC)

SITUATION: THERE ARE 14 COMPETING STANDARDS.

14?! RIDICULOUS! WE NEED TO DEVELOP ONE UNIVERSAL STANDARD THAT COVERS EVERYONE'S USE CASES. YEAH!

SITUATION: THERE ARE 15 COMPETING STANDARDS.

https://imgs.xkcd.com/comics/standards.png
BTRIS Data - What’s Missing?
What’s Missing?
Protocols Information

- Still written as a manuscript
  - Data elements are not defined in the protocol
  - Schedule of events are not defined in a machine readable format
  - Expected adverse events nor defined in a standard manner
What’s Missing?

CTMS

- Protocols are compiled / built within in each CTMS system independently
- Common Data Elements
  - Difficult to utilize and implement
  - At the discretion of the PI
Where are we Succeeding

NCI Cancer Research Data Commons (CRDC)

- Data Access
  - The Cancer Genome Atlas (TCGA)
  - Therapeutically Applicable Research to Generate Effective Treatments (TARGET)
  - The Clinical Proteomics Tumor Analysis Consortium (CPTAC)

- Standards
  - The Global Alliance for Genomics and Health (GA4GH)
  - Digital Imaging and Communications in Medicine (DICOM)
  - Clinical Data Interchange Standards Consortium (CDISC)
Session III: Additional Applications and Impact of Data Standards on Clinical Research and Development Outside of Industry
Session III: Additional Applications and Impact of Data Standards on Clinical Research and Development Outside of Industry

Advancing the Development and Implementation of Analysis Data Standards: Key Challenges and Opportunities

June 12, 2019

Jackson Burton, PhD
Associate Program Director, Quantitative Medicine
Who: The Critical Path Institute

- Form pre-competitive, area-specific consortia with participants from industry, academia, advocacy groups, and regulators to address unmet medical needs

  - Regulatory qualification of preclinical and clinical biomarkers for use in safety, efficacy, and trial enrichment
  - Development of quantitative modeling and simulation tools
  - Regulatory acceptance of nonclinical tools for medical product development
  - Development and qualification of clinical outcome assessment tools
  - Impact on regulatory science
  - Forming and managing large international consortia
  - Data acquisition, management, curation, and integration
  - Clinical data standards development support
What: Data Acquisition and Management

Clinical data contributed to C-Path

- Huntington's Disease
- Friedreich's Ataxia
- Type 1 Diabetes
- Duchenne Muscular Dystrophy
- Healthy Kidney Study
- Polycystic kidney disease
- Multiple sclerosis
- Tuberculosis
- Parkinson's disease
- Alzheimer's disease
Creating solutions for bottlenecks in drug development through Model-Informed Drug Development (MIDD)

ALZHEIMER DISEASE
Regulatory endorsed clinical trial simulation tool for mild to moderate Alzheimer disease (completed)
Clinical trial simulation tool for pre-dementia (in progress)

PARKINSON DISEASE
Regulatory endorsed model-based dopamine imaging biomarker for early motor Parkinson disease (completed)
Clinical trial simulation tool for early motor Parkinson disease (in progress)

HUNTINGTON DISEASE
Clinical trial simulation tool for early stage Huntington disease (in progress)

DUCHENNE MUSCULAR DYSTROPHY
Clinical trial simulation tool for various disease stages of Duchenne Muscular Dystrophy (in progress)

TYPE 1 DIABETES
Clinical trial simulation tool to predict T1D diagnosis informed by islet level autoantibody dynamics (in progress)

TRANSPLANT THERAPEUTICS
Clinical trial simulation tool to predict kidney graft failure (in progress)

TUBERCULOSIS
Model-based tool based on the In vitro Hollow Fiber System for use in optimization of drug regimens and dose selection in TB
Case study: Considerations of ADS in Parkinson’s disease

• The Critical Path for Parkinson’s (CPP) in a consortium for the advancement of therapies in Parkinson’s Disease (PD)

• A key deliverable is to use patient-level data from legacy studies to build a clinical trial simulation tool to enable efficient design of clinical efficacy studies

What are some key considerations for ADS in this context?
1. Early introduction of CDISC standards and structure to relevant team members
2. ‘Atypical’ FDA review pathways → Qualification program & Fit-for-Purpose Initiative for the review and endorsement of drug development tools
3. Practicality of standard data terminology vs. standard data structure for analysis
Early introduction of CDISC standards for PD Data

**PD Clinical Trials**

<table>
<thead>
<tr>
<th>STUDY NAME</th>
<th>CONTRIBUTOR</th>
<th># OF SUBJECTS</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>START UP</td>
<td>Roche</td>
<td>201 untreated PD</td>
<td><em>Annals of Neurol</em> 1993, 33: 350-356</td>
</tr>
<tr>
<td>SP513: Ropinirole</td>
<td>UCB</td>
<td>561 early stage PD</td>
<td><em>Mov Dis</em> 2007; 22(18):2398-404</td>
</tr>
<tr>
<td>SP512: Rotigotine</td>
<td>UCB</td>
<td>273 early stage PD</td>
<td><em>J Park Dis</em> 2016, 6(2): 401-11</td>
</tr>
<tr>
<td>SURE PD PhII</td>
<td>Michael J Fox Fdn/ M. 75</td>
<td></td>
<td><em>JAMA Neurol.</em> 2014 7(2):141-50</td>
</tr>
<tr>
<td>(inosine)</td>
<td>Schwarzchild/ Indiana Jniv</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CONFIDENT-PD</td>
<td>Michael J Fox Fdn/Junaxo</td>
<td>425</td>
<td><em>NCT0160878 (CT.gov)</em></td>
</tr>
<tr>
<td>PRECEPT</td>
<td>Teva</td>
<td>806 early PD</td>
<td><em>Neural</em> 20:82; 1791-7; 2014</td>
</tr>
<tr>
<td>ADAGIO</td>
<td>Teva</td>
<td>1,176 early PD</td>
<td><em>Lancet Neurol.</em> 2011; 10: 415-23</td>
</tr>
<tr>
<td>DATATOP</td>
<td>NINDS</td>
<td>800 early PD</td>
<td><em>Neural</em> 1999; 40: 1529-34</td>
</tr>
<tr>
<td>FS-1</td>
<td>Univ Rochester/NINC5</td>
<td>200 early PD</td>
<td><em>Clin Neuropharmacol.</em> 2008 31(3):141-50</td>
</tr>
</tbody>
</table>

**PD Observational Cohorts**

<table>
<thead>
<tr>
<th>STUDY NAME</th>
<th>CONTRIBUTOR</th>
<th># OF SUBJECTS</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marker Initiative PPMI</td>
<td>Foundation</td>
<td>controls, 64 SWEDD, 65 prodomal</td>
<td></td>
</tr>
<tr>
<td>Biomarker Study</td>
<td></td>
<td>1,223 genetic registry participants</td>
<td></td>
</tr>
<tr>
<td>ICICLE</td>
<td>Newcastle University, UK</td>
<td>160</td>
<td><em>Neurology</em> 2014 82: 308-18</td>
</tr>
<tr>
<td>Tracking</td>
<td>University of Glasgow, UK</td>
<td>3,000 (2,000 patients within 3</td>
<td><em>J Park Dis</em> 2015 5: 947-59</td>
</tr>
<tr>
<td>Parkinson’s/ProBaND</td>
<td></td>
<td>years of diagnosis; 240 young</td>
<td></td>
</tr>
<tr>
<td>study</td>
<td></td>
<td>onset and 760 relatives)</td>
<td></td>
</tr>
<tr>
<td>OPDC Discovery cohort</td>
<td>University of Oxford, UK</td>
<td>1,630 (1,086 PD patients within 3</td>
<td><em>J Park Dis</em> 2015 5: 269-79</td>
</tr>
<tr>
<td></td>
<td></td>
<td>years of diagnosis; 111 first degree PD relative; 133 PSG-confirmed RBD; 300 control</td>
<td></td>
</tr>
</tbody>
</table>

- 16 studies from industry and academics
- > 8,100 patients, 41K observations
- CDISC standard terminology for PD and SDTM were adopted early on to ensure interoperability of future acquired datasets

FDA Review Pathways for Drug Development Tools

- Focus on reviewing tools for drug development → low throughput pathways
- Often require more time from FDA scientists from multiple divisions
- Some submissions are extremely analysis heavy and fall outside of ‘typical’ statistical analysis for studies
- CDISC standards / ADaM are not officially required, but are preferred for efficient review

FDA: Qualification Program

FDA: Fit-for-purpose Initiative

https://www.fda.gov/drugs/development-approval-process-drugs/drug-development-tool-qualification-programs

Standard Terminology vs. Standard Structure

- CDISC terminology is helpful for efficient review across multiple divisions
- Official ADaM structure, however, is more complicated to implement in terms of ‘Analysis Readiness’

Ex)

<table>
<thead>
<tr>
<th>STUDYID</th>
<th>US1STUDYID</th>
<th>SUBJID</th>
<th>AGE</th>
<th>SEX</th>
<th>FOLLOW_UP_TIME_IN_DAYS</th>
<th>MDS_UPDRS</th>
<th>END_POINT</th>
<th>S_UPDRS_III_TOTAL</th>
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<tbody>
<tr>
<td>PD-1000</td>
<td>PD-PD-1000</td>
<td>PD-1000/03000</td>
<td>69</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>MDS_UPDRS_III_TOTAL</td>
<td>4</td>
</tr>
<tr>
<td>PD-1000</td>
<td>PD-PD-1000</td>
<td>PD-1000/03000</td>
<td>69</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>MDS_UPDRS_II_TOTAL</td>
<td>1</td>
</tr>
<tr>
<td>PD-1000</td>
<td>PD-PD-1000</td>
<td>PD-1000/03000</td>
<td>69</td>
<td>1</td>
<td>365</td>
<td>1</td>
<td>MDS_UPDRS_III_TOTAL</td>
<td>4</td>
</tr>
<tr>
<td>PD-1000</td>
<td>PD-PD-1000</td>
<td>PD-1000/03000</td>
<td>69</td>
<td>1</td>
<td>365</td>
<td>0</td>
<td>MDS_UPDRS_II_TOTAL</td>
<td>2</td>
</tr>
<tr>
<td>PD-1000</td>
<td>PD-PD-1000</td>
<td>PD-1000/03000</td>
<td>69</td>
<td>1</td>
<td>731</td>
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<td>19</td>
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<tr>
<td>PD-1000</td>
<td>PD-PD-1000</td>
<td>PD-1000/03000</td>
<td>69</td>
<td>1</td>
<td>1096</td>
<td>2</td>
<td>MDS_UPDRS_III_TOTAL</td>
<td></td>
</tr>
<tr>
<td>PD-1000</td>
<td>PD-PD-1000</td>
<td>PD-1000/03000</td>
<td>69</td>
<td>1</td>
<td>1096</td>
<td>0</td>
<td>MDS_UPDRS_II_TOTAL</td>
<td></td>
</tr>
<tr>
<td>PD-1000</td>
<td>PD-PD-1000</td>
<td>PD-1000/03000</td>
<td>69</td>
<td>1</td>
<td>1461</td>
<td>19</td>
<td>MDS_UPDRS_III_TOTAL</td>
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<td>PD-1000</td>
<td>PD-PD-1000</td>
<td>PD-1000/03000</td>
<td>69</td>
<td>1</td>
<td>1461</td>
<td>0</td>
<td>MDS_UPDRS_II_TOTAL</td>
<td></td>
</tr>
</tbody>
</table>

- One record per time point
- Structure dependent on the analysis: Best structure for use of NONMEM analysis
- Neither are officially ADaM (although similar to ADaM BDS) but both are fully ‘analysis ready’ ➔ No further transformations needed before input into analysis software.
Summary: The Role of ADS at C-Path

• Translating data into actionable knowledge through regulatory pathways is critically dependent on ADS principles

• Key points to consider:
  • The early introduction of standards and training of data managers
  • The distinction between standard terminology and standard structure
  • The type of analyses that will be performed using ‘analysis ready’ datasets
C-Path’s impact in MIDD, thanks to ADS principles

- Alzheimer’s disease
- Parkinson’s disease
- Duchenne muscular dystrophy
- Huntington’s disease
- Kidney transplant
- Type 1 diabetes
- Polycystic kidney disease
- Tuberculosis
Thank you!
Backup slides
Developing a Clinical Trial Simulator: Data as a Foundation

$$\mu_{TMS,ij}(t_{ij}) = (f_{bl}(X) + a_{bl} + a_{bl,ij}) + (f_r(X) + a_r + a_r,t_{ij}) + \varepsilon_{TMS,ij}$$

$$P(Y_{TFC,ij} = k) = P(\tau_{k-1} < Y^* < \tau_k | X)$$

$$Y^* = X\beta + Za + \epsilon$$

$${Y}_{TFC} = \begin{cases} 6, & Y^* \leq \tau_1 \\ 7, & \tau_1 < Y^* \leq \tau_2 \\ 12, & \tau_7 < Y^* \leq \tau_B \\ 13, & \tau_B \leq Y^* \end{cases}$$
Session III: Additional Applications and Impact of Data Standards on Clinical Research and Development Outside of Industry
Break
Session IV: Key Opportunities to Improve the Implementation of Analysis Data Standards
Session IV: Key Opportunities to improve the implementation of ADS

Analysis Data Standards Public Workshop
June 12, 2019

Weiya Zhang, PhD, CDER Office of Biostatistics
CDER Statistical Reviewer’s Suggestions on Data Submission

• Datasets
  – Analysis datasets should be able to accommodate primary, secondary, and sensitivity analyses specified in the statistical analysis plan
  – Submit datasets used to generate tables, figures, and listings for study reports
  – Submit intermediate datasets (if applicable) to support traceability

• Documentation
  – Complete descriptions and logic in data define files
  – Complete and concise reviewer’s guide

• Software programs
  – Follow Technical Conformance Guide and communicate with Review Division
  – Follow good programming practice
  – Provide software versions and build identification
Session IV: Key Opportunities to Improve the Implementation of Analysis Data Standards
Session IV: Key Opportunities to improve the implementation of ADS

Analysis Data Standards Public Workshop
June 12, 2019

Jessica Hu, PhD, CBER Division of Biostatistics
CBER’s Vision on ADS

Challenges
• Diversified products, e.g. vaccine, gene therapy, human tissues and cellular products, blood products, device products
• New products, e.g. CAR T-cell therapy
• Meta analyses with previous data, e.g. blood products
• Meta analyses with post-marketing data

Opportunities
• Guidance for new products, with consideration of new study design and new statistical methodologies
• Early stage intervention with the sponsor for new product development
• Collaboration with data scientist
• Implementation of ADS for other CBER database
Session V: Emerging Trends and Innovations for the Development and Use of Analysis Data Standards
Considerations regarding submission of Real World Data to FDA

David Martin, MD, MPH
Associate Director for Real World Evidence Analytics
FDA CDER Office of Medical Policy

Advancing the Development and Implementation of Analysis Data Standards: Key Challenges and Opportunities
June 12, 2019
Disclosure and Disclaimer

• The mention of commercial products, their sources, or their use in connection with material reported herein is not to be construed as either an actual or implied endorsement of such products by the Department of Health and Human Services

• David Martin received funding from the Patient Centered Outcomes Research Trust Fund to develop the FDA MyStudies Mobile App

• No conflicts of interest to disclose

• The views expressed are those of the author and should not be construed as FDA’s views or policies
Expectations in Law for Real-World Evidence: The 21st Century Cures Act

• FDA shall establish a program to evaluate the potential use of real world evidence (RWE) to support:
  o Approval of new indication for a drug approved under section 505(c)
  o Satisfy post-approval study requirements

• Program will be based on a framework that:
  o Categorizes sources of RWE and gaps in data collection activities
  o Identifies standards and methodologies for collection and analysis
  o Describes the priority areas, remaining challenges and potential pilot opportunities that the program will address

• Draft Guidance to be issued by 2021

• PDUFA commitments aligned with 21st Century Cures Act
Definitions

Real world evidence means data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than *traditional clinical trials*.

Real-World Data (RWD) are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.

Real-World Evidence (RWE) is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD.
Published in December 2018

Intended for drug and biological products

Outlines FDA’s plan to implement the RWE program

Multifaceted program
  – Internal process
  – Guidance development
  – Stakeholder engagement
  – Demonstration projects

Comment period closed April 16, 2019
Framework for Evaluating RWD/RWE for Use in Regulatory Decisions

Considerations

• Whether the RWD are fit for use

• Whether the trial or study design used to generate RWE can provide adequate scientific evidence to answer or help answer the regulatory question

• Whether the study conduct meets FDA regulatory requirements
RWD Fitness for Use

- Guidance on how to assess whether RWD from medical claims, EHRs and/or registries are fit for use to generate RWE in support of drug product effectiveness

- Explore the use of digital technology tools, electronic PROs, and wearables to potentially fill gaps

https://www.fda.gov/NewsEvents/Newsroom/FDAInBrief/ucm625228.htm
https://www.fda.gov/Drugs/ScienceResearch/ucm624785.htm
https://github.com/PopMedNet-Team/FDA-My-Studies-Mobile-Application-System
An aspirational view

Figure 4. Ontology-Based Mechanistic Classification of Disease.
Well-structured clinical data can be readily integrated with discovery research data by using ontologies, which make clinical and basic science observations “computable” in a way that reflects present knowledge and allows new inferences. Integrating the two streams of data enables a mechanistic classification of disease across many data types, making a more refined and dynamic classification of patients possible.¹

The current state

- Data in pathology, radiology and lab reports as well as clinical notes are often unstructured (80%)
  - Messaging standards enable transfer of machine interpretable structured data
  - But a substantial amount of data is merely machine organizable (e.g., clinic note text) or machine transportable (e.g., pathology, lab, or echo report scanned into the EHR)
- Structured data ≠ Standardized data
  - i.e., lab units and values
- Linkage may be necessary to capture care in multiple health systems
- Clinical outcome measures for drug approvals may not be used or consistently recorded in practice
  - Primary data collection may be needed
- Typing ≠ consistency/complete documentation
Machine transportable EHR data example

- EGFR testing status
- EGFR test result
- Specific mutation type (e.g., T790M)
- Date sample was collected
- Date sample was received in lab
- Date result was provided to physician
- Type of test (e.g., NGS)
- Type of sample (e.g., tissue)
- Sample collection site
Importance of Unstructured Data

Table 1. Comparison of cohorts generated using structured electronic health record data only versus structured electronic health record data supplemented with abstracted unstructured data.

<table>
<thead>
<tr>
<th>Goal</th>
<th>Structured data only</th>
<th>Structured and unstructured data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent LC patients</td>
<td>ICD-9 code of 162.x with at least two visits $\geq$2013 $\text{(n = 26,630)}$</td>
<td>ICD-9 code of 162.x with at least two visits $\geq$2013 $\text{(n = 26,630)}$</td>
</tr>
<tr>
<td>NSCLC patients</td>
<td>Patients without an administration for etoposide $\text{(n = 23,235)}$</td>
<td>Patients with confirmed NSCLC $\text{(n = 21,445)}$</td>
</tr>
<tr>
<td>Advanced NSCLC patients</td>
<td>Patients with a diagnosis for secondary metastases (ICD9 196.x–198.x) $\text{(n = 4382)}$</td>
<td>Patients with a confirmed diagnosis of advanced NSCLC $\text{(n = 10,826)}$</td>
</tr>
<tr>
<td>Patients with an advanced diagnosis date after 2013</td>
<td>Patients with a first diagnosis for secondary metastases $\geq$2013 $\text{(n = 3562)}$</td>
<td>Patients with a confirmed date of advanced diagnosis $\geq$2013 $\text{(n = 8324)}$</td>
</tr>
<tr>
<td>Squamous cell NSCLC patients</td>
<td>Unable to distinguish</td>
<td>Patients with a confirmed diagnosis of squamous cell carcinoma $\text{(n = 2092)}$</td>
</tr>
</tbody>
</table>

LC: Lung cancer; NSCLC: Non-small-cell lung cancer.

Opportunities and challenges in leveraging electronic health record data in oncology
Marc L Berger*, 1, Melissa D Curtis, Gregory Smith, James Harnett 1 & Amy P Abernethy

EHR Data Structure plus prospective outcome capture

mCODE™

Minimal Clinical Oncology Data Elements
Data standards to improve the quality and usability of EHR data

Collection of clinical trials data using the EHR

Courtesy of ASCO/MITRE
ICAREdata Outcome Questions

ICAREdata: Develop and validate mCODE-based outcome measures

Cancer disease status

Clinical Assessment
Based on the data available today (at the time of evaluation), categorize the patient’s disease extent.

ICAREdata Question Format

<table>
<thead>
<tr>
<th>Cancer disease status</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>primary tumor</td>
<td>&lt;lesion evaluated&gt;</td>
<td>&lt;status value&gt;</td>
</tr>
<tr>
<td>metastatic lesion</td>
<td>complete response</td>
<td>partial response</td>
</tr>
<tr>
<td></td>
<td>stable disease</td>
<td>progressive disease</td>
</tr>
<tr>
<td></td>
<td>not evaluated</td>
<td></td>
</tr>
<tr>
<td></td>
<td>imaging</td>
<td>pathology</td>
</tr>
<tr>
<td></td>
<td>symptoms</td>
<td>physical exam</td>
</tr>
<tr>
<td></td>
<td>markers</td>
<td></td>
</tr>
</tbody>
</table>

Sample Resulting Structured Phrase*
#Cancer disease status observed for #primary tumor was #progressive disease based on #imaging and #symptoms

* Blue font denotes controlled vocabularies

Treatment change

Clinical Assessment
Based on your evaluation today, are you making a change in treatment?

ICAREdata Question Format

<table>
<thead>
<tr>
<th>Treatment change...</th>
<th>&lt;treatment change?&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Yes - disease not responding</td>
<td></td>
</tr>
<tr>
<td>Yes - due to AE/toxicity</td>
<td></td>
</tr>
<tr>
<td>Yes - pre-planned therapy transition</td>
<td></td>
</tr>
<tr>
<td>Yes – patient request</td>
<td></td>
</tr>
<tr>
<td>Yes - due to other</td>
<td></td>
</tr>
</tbody>
</table>

Sample Resulting Structured Phrase*
#Treatment change #yes-disease not responding

* Blue font denotes controlled vocabularies
Patient-Generated Health Data (Digital Health Tools)

Patient as the data originator
- e.g., questionnaires, cognitive tests, coordination tests, episodic accelerometer based tests (six minute walk)

Biosensor as the data originator
- e.g., activity trackers, glucose sensors, wireless heart rate monitors
RWD Fitness for Use

- Guidance on how to assess whether RWD from medical claims, EHRs and/or registries are fit for use to generate RWE in support of drug product effectiveness

- Explore the use of digital technology tools, electronic PROs, and wearables to potentially fill gaps

https://www.fda.gov/NewsEvents/Newsroom/FDAInBrief/ucm625228.htm
https://www.fda.gov/Drugs/ScienceResearch/ucm624785.htm
https://github.com/PopMedNet-Team/FDA-My-Studies-Mobile-Application-System
Potential for Study Designs Using RWD to Support Effectiveness

Observational studies

• Transparency about study design and analysis before execution is critical for ensuring confidence in the result.

• Detailed reporting and access to analytic code and data enable unambiguous understanding of all aspects of study implementation because clinical constructs are converted to operational definitions and finally into analytic software code.

• Guidance about observational study designs using RWD, including whether and how these studies might provide RWE to support product effectiveness in regulatory decision making.
Identifying Documents Using RWD and RWE

- Published May 2019
- Comment period closes July 8, 2019

- Identify RWE being used as part of a regulatory submission in cover letter or table
- Provide information on the use of RWE in a simple, uniform format
- Internal tracking only

Purpose(s) of Using RWE as Part of the Submission (Select all that apply)
- Provide evidence in support of efficacy or safety for a new product approval
- Support labeling changes for an approved drug
  - Add or modify an indication
  - Change in dose, dose regimen, or route of administration
  - Use in a new population
  - Add comparative effectiveness information
  - Add safety information
  - Other labeling change. Specify:
- Use as part of a postmarketing requirement to support a regulatory decision

Study Design(s) Using RWE (Select all that apply)
- Randomized clinical trial
- Single arm trial
- Observational study
- Other study design. Specify:

RWD Source(s) Used to Generate RWE (Select all that apply)
- Data derived from electronic health records
- Medical claims and/or billing data
- Product and/or disease registry data
- Other data source that can inform health status. Specify:

LINK to Guidance: https://www.fda.gov/media/124795/download
Data Standards in the drug lifecycle

Data Standards and Implementation

- Identify and assess data standards and implementation strategies required to use RWD/ RWE
- Identify gaps between RWD/ RWE data standards and existing systems
- Collaborate with Stakeholders to adopt or develop standards and implementations strategies
Closing Remarks
Post Workshop

- https://healthpolicy.duke.edu/events/advancing-development-and-implementation-analysis-data-standards-key-challenges-and
- Meeting materials available
- Archived video footage will be available
Acknowledgements

• ADS Public Workshop Planning Group
  — FDA
    Matilde Kam, Laura Lee Johnson, Eileen Navarro Almaro, Vaishali Popat, Scott Proestel, Jessica Hu, Brenda Baldwin, Nhi Beasley, Scott Gordon, Jeffrey Florian, Helena Sviglin, Boris Brodsky, Ashley Caraway, Mary Jo Salerno
  — Duke Margolis Center for Health Policy
    Gregory Daniel, Morgan Romine, Adam Aten, Kerra Mercon
  — Critical Path Institute
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Thank you!
Adjournment