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for Health Policy

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

Matilde Kam, PhD
Associate Director for Analytics and Informatics
Office of Biostatistics, CDER

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

Regulatory Framework: Study Data Standards

FDASIA Act
authorizes electronic submissions

7/2012

"FDASIA Umbrella" Implementation Guidance

12/2014

eCTD Guidance
requires e-submission to be in eCTD format

5/2015

2012 | 2014 | 2016

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

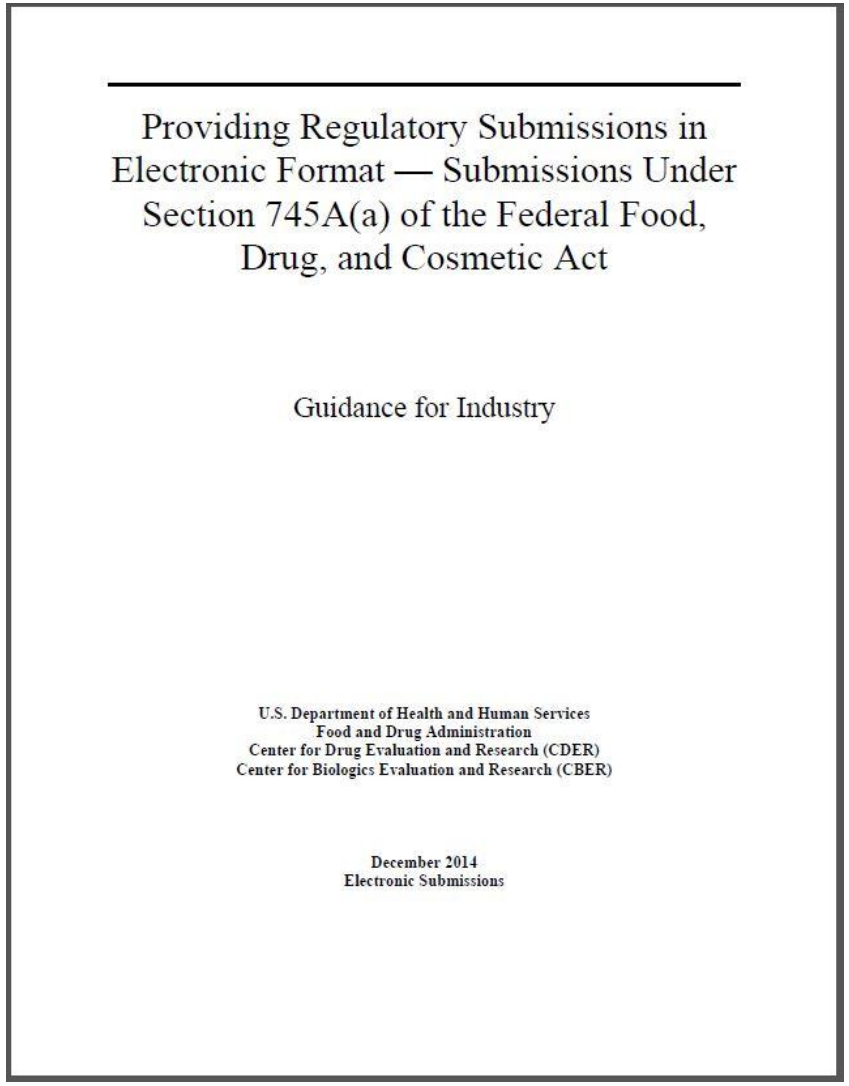
12/2014

eCTD Guidance Revision 6

1/2019

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

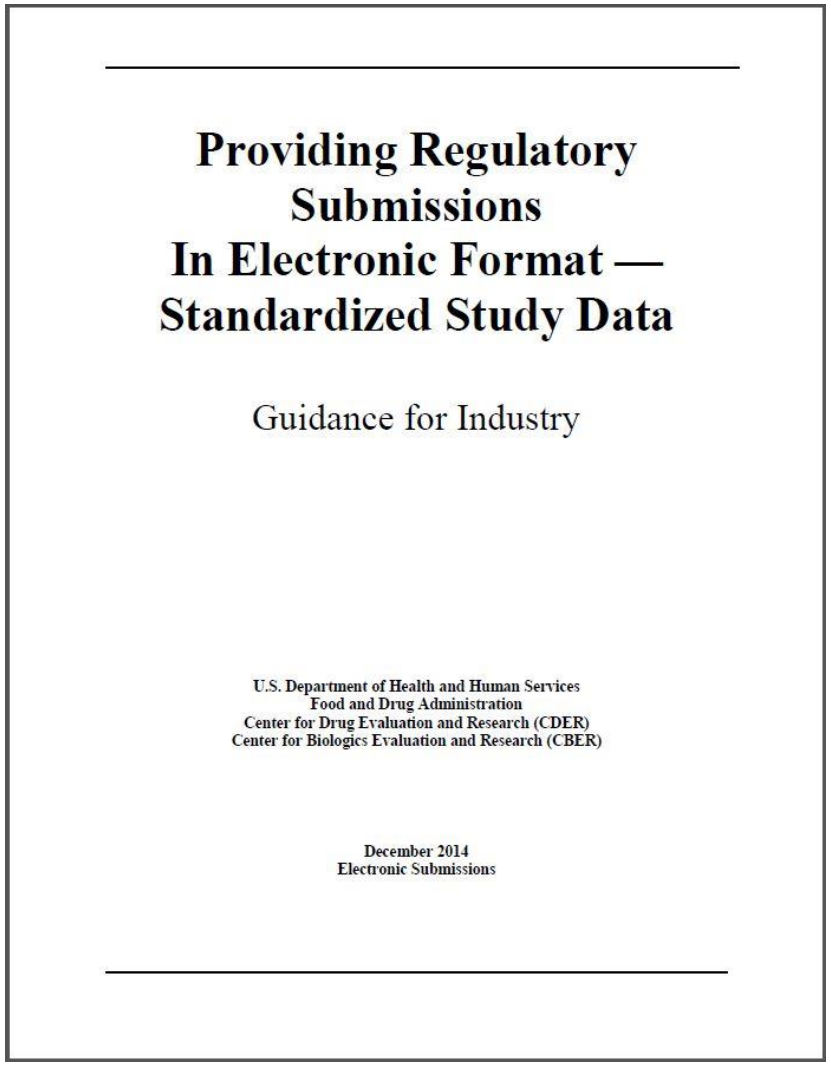
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

December 2014
Electronic Submissions

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

For details, see: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/providing-regulatory-submissions-electronic-format-submissions-under-section-745aa-federal-food-drug

Standardized Study Data Guidance



Providing Regulatory Submissions In Electronic Format — Standardized Study Data

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

NDAs, BLAs, ANDAs

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

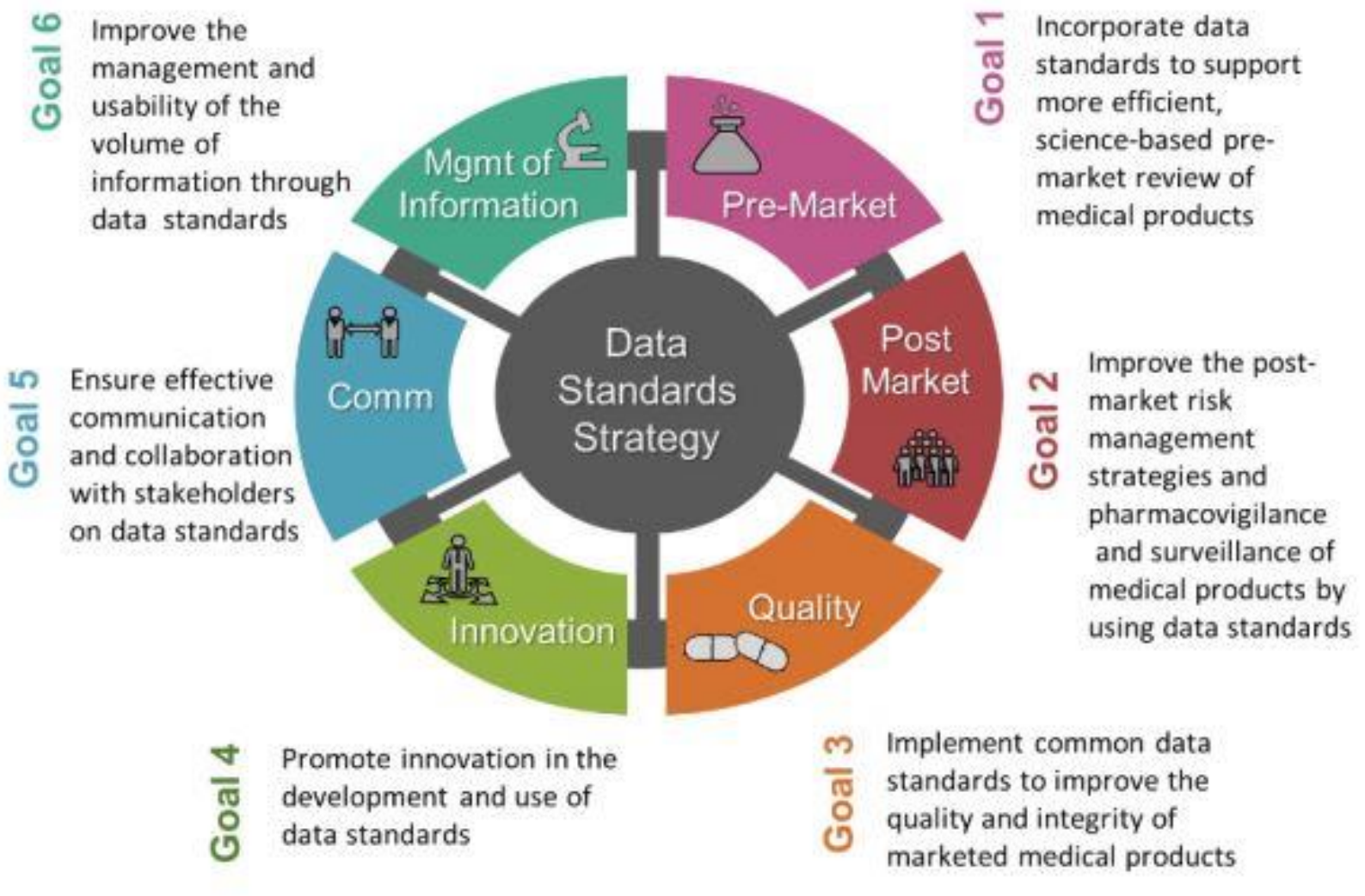
Commercial INDs

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

strategies and pharmacovigilance and surveillance of medical products by using data standards

FDA Data Standards Strategic Goals

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

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

Goal 5 Ensure effective communication and collaboration with stakeholders on data standards

Goal 3 strategies and pharmacovigilance and surveillance of medical products by using data standards

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

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

FDA Data Standards Strategic Goals

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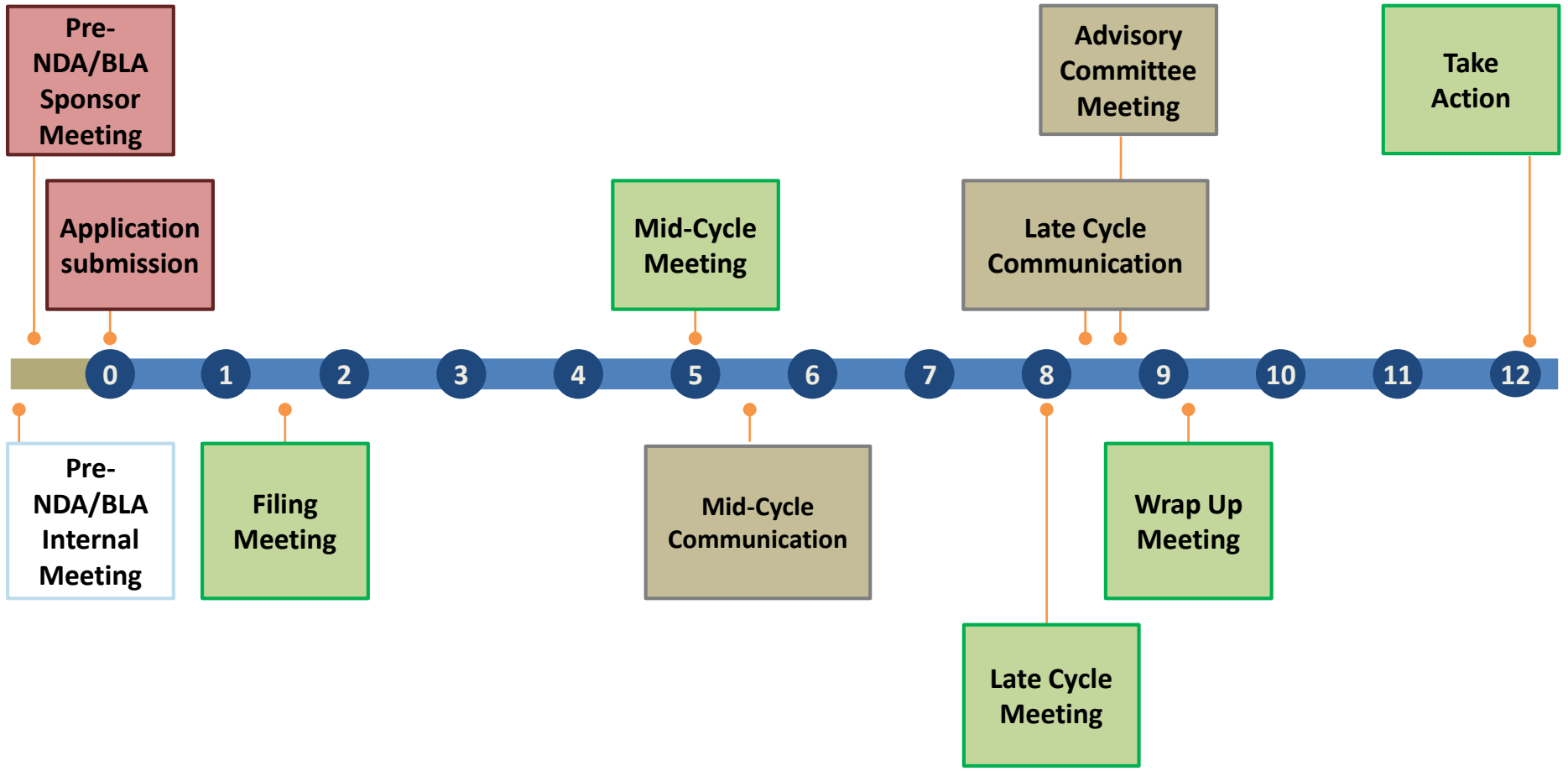
Goal 4 Promote innovation in the development and use of data standards

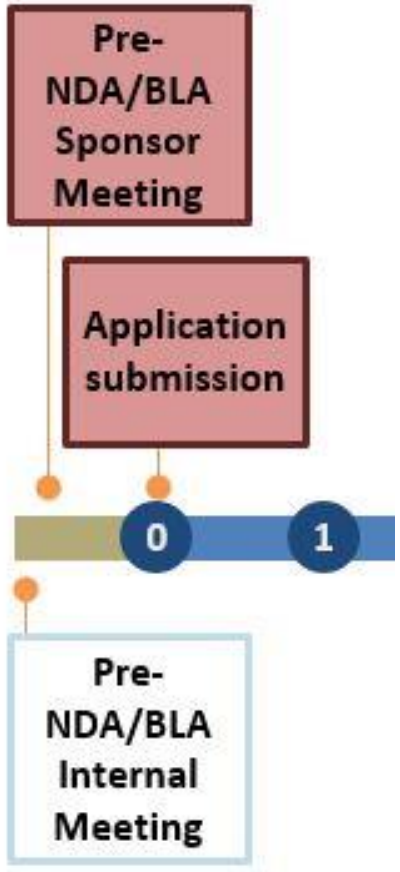
Implement common data standards to improve the quality and integrity of marketed medical products

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

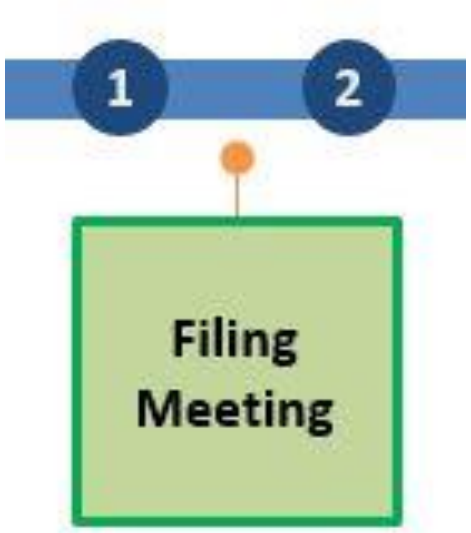
Planning Initiated by Sponsor

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?

Issue identification/Decision

For details, see https://www.fda.gov/media/109758/download

NDA/BLA Submission Review

Legacy Data

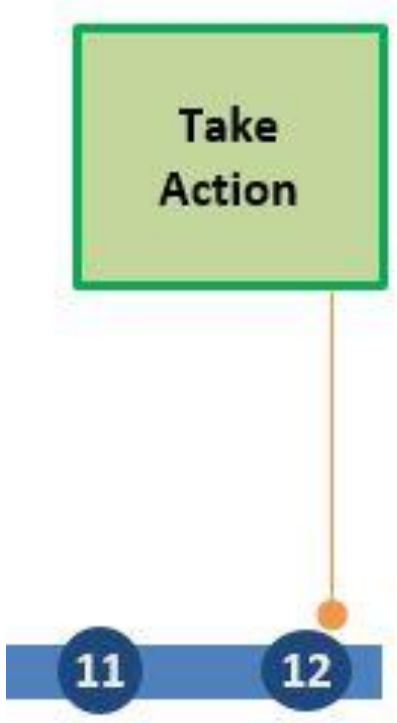
Standardized Study Data

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

Issue identification/Decision

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: cder-edata@fda.hhs.gov

CBER: cber.cdisc@fda.hhs.gov

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

U.S. FOOD & DRUG ADMINISTRATION

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

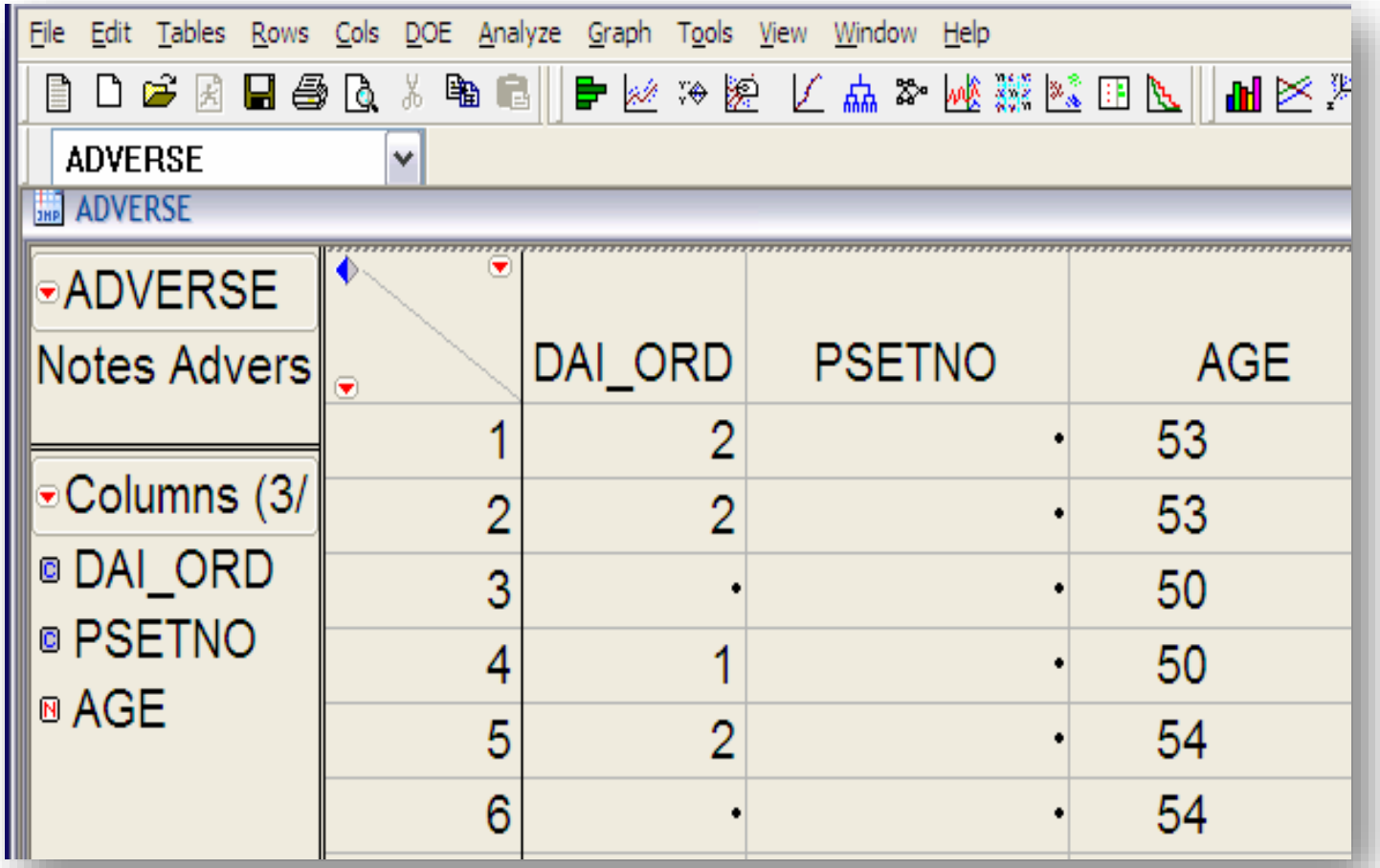
- Most are physicians
- Responsible for reviewing all clinical data
- Examine all submission types – preINDs, INDs, NDAs, meeting requests, safety reports, etc.

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)

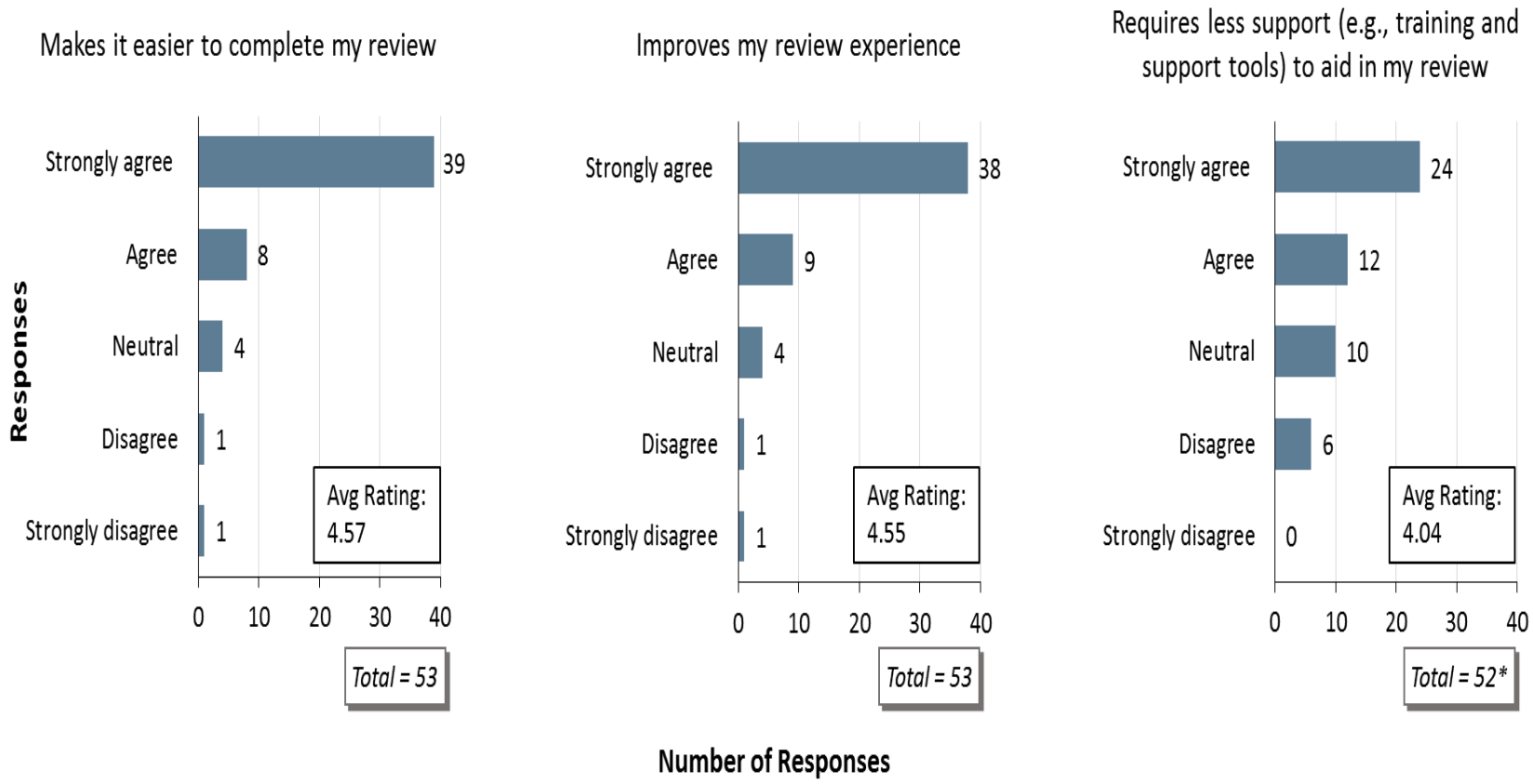
- Look for answers to review questions or issues that arise
- Confirm analyses or conduct them differently
- Look for outlier sites to advise inspectors for site selection

Data Without Standards
Obscure Datasets



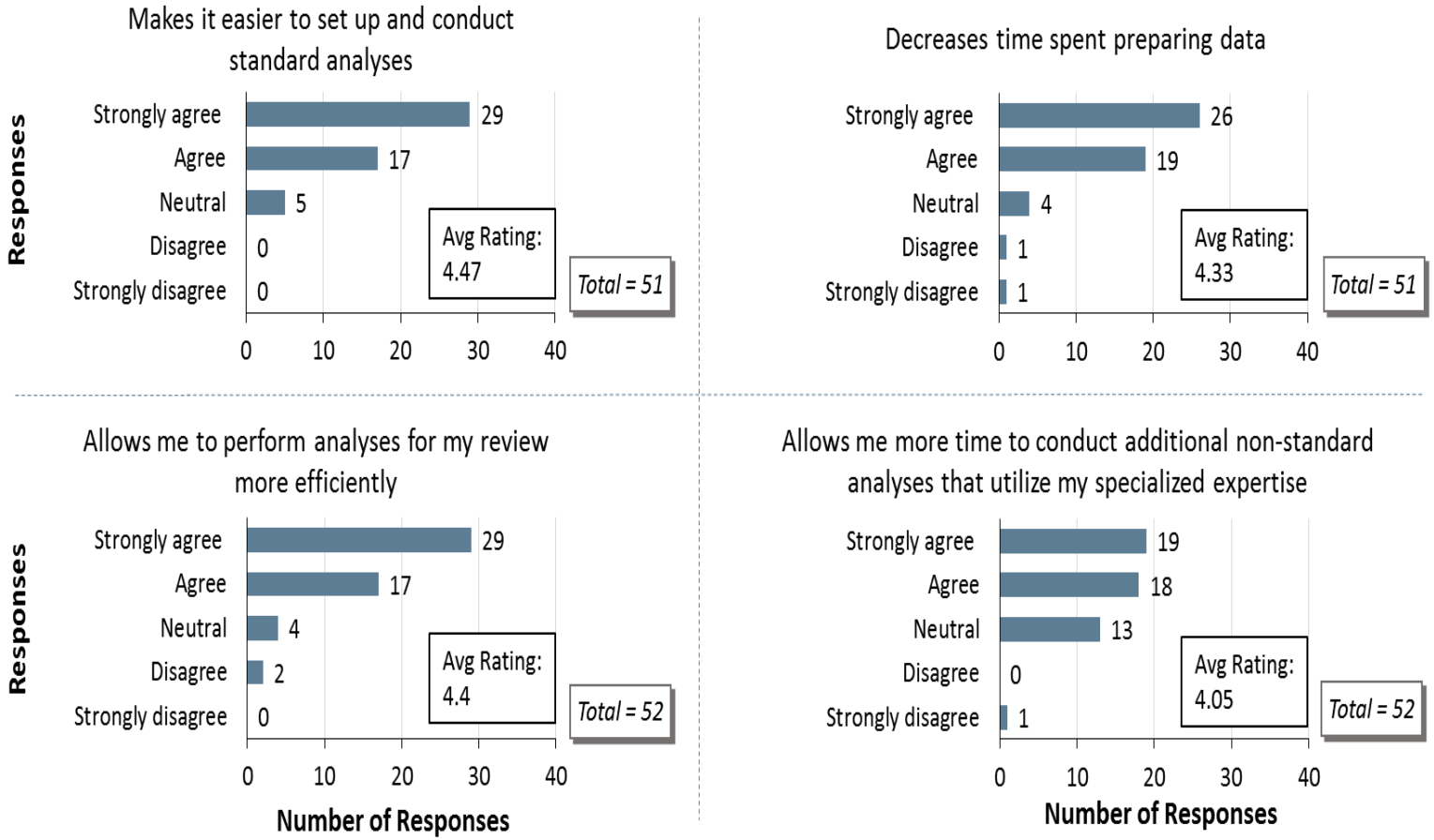
	DAI_ORD	PSETNO	AGE
1	2	.	53
2	2	.	53
3	.	.	50
4	1	.	50
5	2	.	54
6	.	.	54

Impact of Standardized Data on Overall Review



*Note: *1 respondent answered N/A. 27 primary reviewers did not answer theses questions; Average rating obtained from assigning values of 1-5 for strongly disagree to strongly agree responses*
Source: PDUFA Electronic Review Assessment Survey

Impact of Standardized Data on Review Time and Analyses



*Note: *27 primary reviewers did not answer the question, 1-2 reviewers responded N/A to each response; Average rating obtained from assigning values of 1-5 for strongly disagree to strongly agree responses*
Source: PDUFA Electronic Review Assessment Survey

Variability in the 'Standard' Datasets

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

ADAE.xpt from >4000 clinical trials CDISC IG: AEREL= Causality Char, * Perm, AE.AEREL

0	1	2	3	4	5
6	A reasonable possibility	After admin relationship to IMP is not suspected	ALMOST CERTAIN RELATED	ALMOST CERTAINLY	ALMOST CERTAINLY RELATED
Alternate Etiology	ALTERNATE ETIOLOGY	ASSOCIATED TO STUDY DRUG	B	BD	before trt
CANNOT BE CLASSIFIED	CD	Certain	CERTAIN	CERTAIN/VERY LIKELY	CONCOMITANT THERAPY
CONDITIONAL / UNCLASSIFIED	CONTRAST MEDIA	D	DAASNO REASONABLE POSSIBILITY	DAASREASONABLE POSSIBILITY	DEFINED
definite	Definite	DEFINITE	DEFINITE RELATED	definite relation	Definite relation
DEFINITE RELATION	DEFINITE/CERTAIN	Definitely	DEFINITELY	Definitely not	DEFINITELY NOT
DEFINITELY NOT CAUSED	DEFINITELY NOT RALATED	Definitely not related	Definitely Not Related	DEFINITELY NOT RELATED	DEFINITELY RELAT…..

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

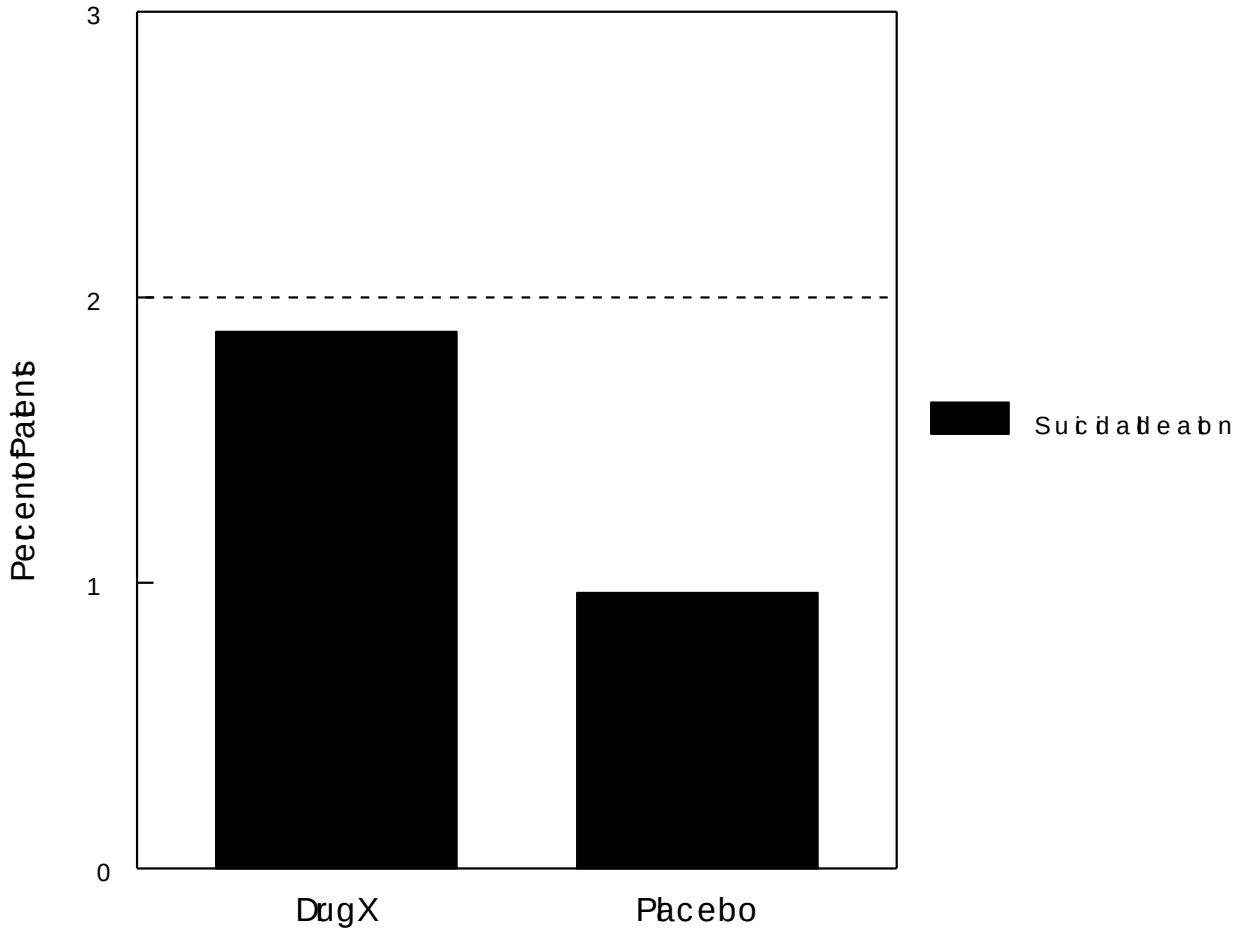
In their analyses of adverse events, Applicants code/translate verbatim terms to some 23,000 standard MedDRA Preferred Terms.

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

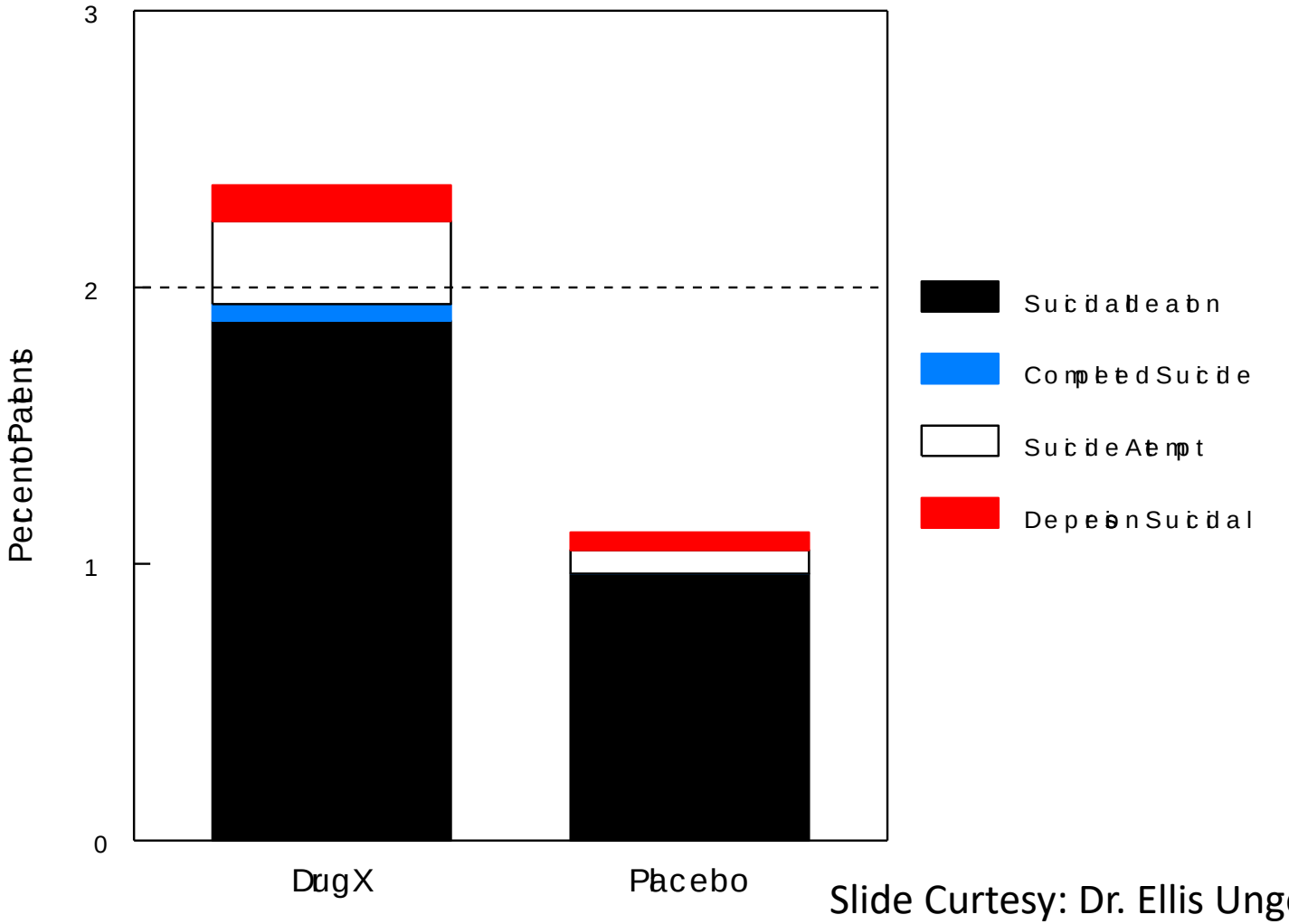
Generate an adverse event table with a 2% cut-off, "Suicidal Ideation" doesn't make the cut:



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):



Slide Curtesy: Dr. Ellis Unger

Goal and Methods

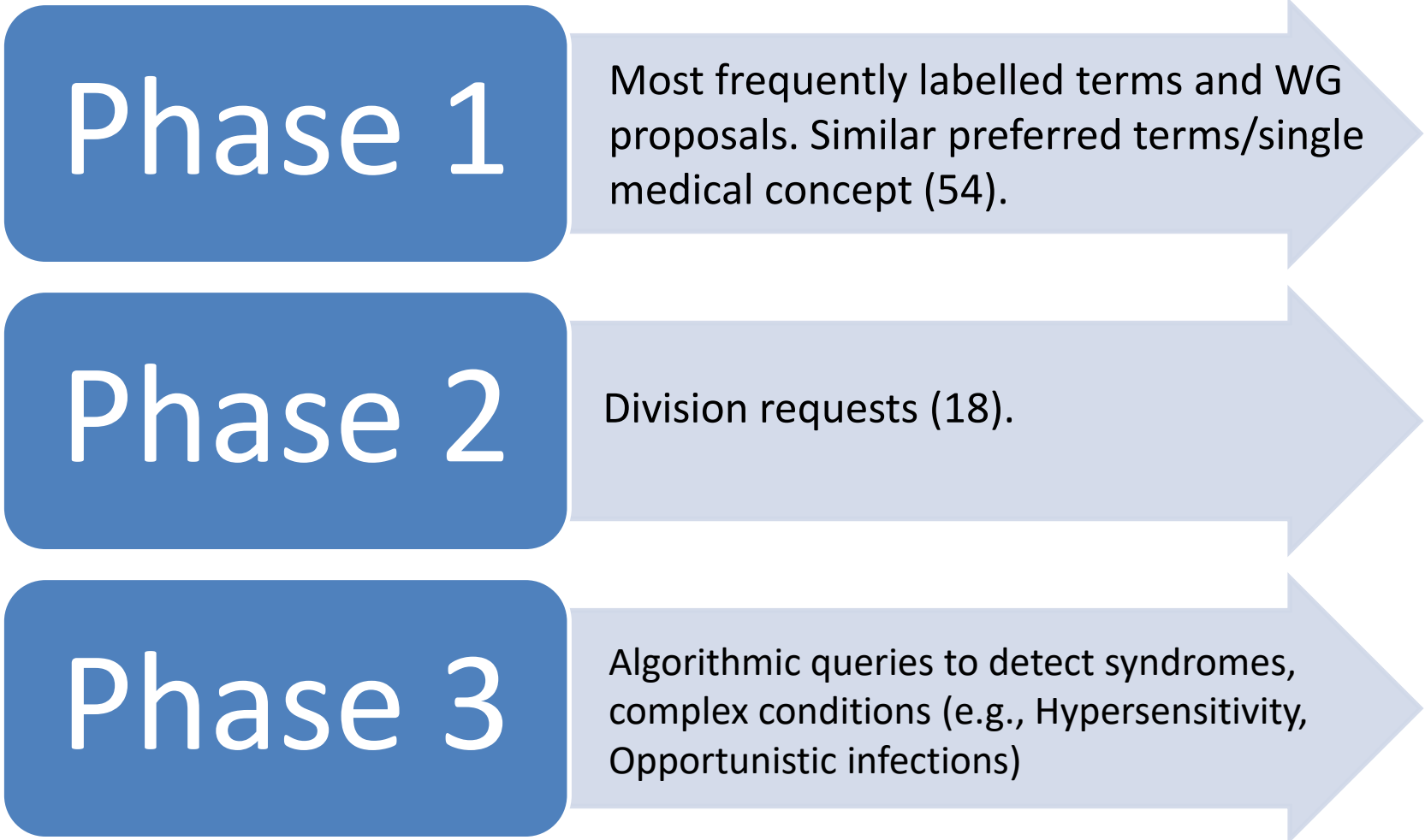
Goal:

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).

Spectrum of FDA Queries



Standard Tables and Figures for Premarket Safety Review

Standardized data makes uniform strategy for data presentation possible. These tables/figures

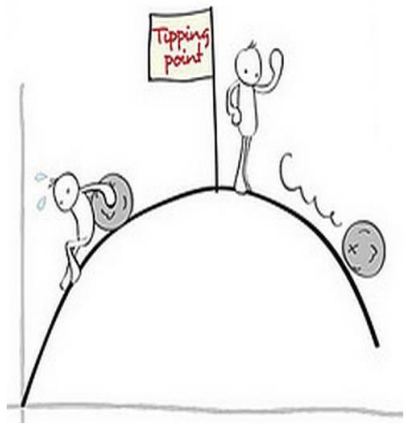
- Reflect formatting standards used in major medical journals
- Instructions are provided with each table/figure
- Modifiable as appropriate

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:
  http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm
- Electronic Submissions Gateway:
  http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm
- Electronic Submissions Presentations:
  http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm229642.htm
- Questions about submitting electronically to CDER: ESUB@fda.hhs.gov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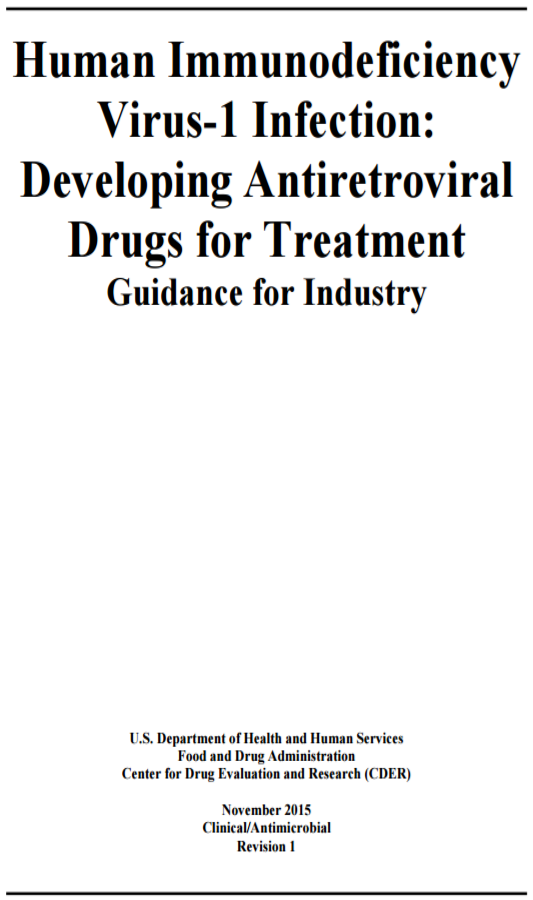
HIV Data Specifications

- 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.



Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment

Guidance for Industry

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

November 2015
Clinical/Antimicrobial
Revision 1

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

- This can be a resource intensive process
- Aligned safety (AE, LB and DM domains) related dataset specifications to current CDISC foundational standards
- Realized that there are no standards that were related to HIV specific safety and efficacy analyses
- Collaboration with External stakeholders is crucial
- 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

Opportunities

- Harmonizing FDA, CDISC Guidance Documentation and Pinnacle 21 Checks (e.g., one source of truth)
- Opportunity to version and publish Technical Conformance Guide with advance notice
- Potential expansion of the ability to apply Real Time Oncology Review (RTOR) to other divisions
- Continuing to conduct targeted workshops to explore industry lessons-learned

Challenges / Questions

- Naming Conventions for Reviewers Guides vary by Agency
- Derived variables in SDTM
- SUPPQUAL
- Optimal representation of Controlled Terminology (CT)
- Sponsor burden to maintain and update multiple sources of guidance
  - SDTM 3.1.3 > 3.2 > 3.3; Quarterly CDISC NCI CT release
  - Ongoing studies

Improving the Traceability of Data

Opportunities

- Consolidate the SDTM and ADaM Define.xml and Reviewers Guides
- Industry support to improve traceability
  - Understanding FDA reviewers challenges
  - Documentation (e.g., Define.xml, Data Reviewers Guides)
- Explicit guidance of split SDTM domains based on category vs. aggregate domains

Challenges / Questions

- Continue to reduce the need for listings
  - Listings can be made available upon request
  - Clarify role of listings, if any, in traceability
- Sponsor traceability starts at data collection
- FDA position on the use of CDASH standards
  - CDASH awareness is currently limited to safety
  - Impact of release frequency of TAUGs

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

HIV Datasets Tec Spec

Challenges and Opportunities

12 June, 2019

Ralph A. DeMasi
Head of Statistics
ViiV Healthcare

The person depicted in this photo is a model, for illustrative purposes only.

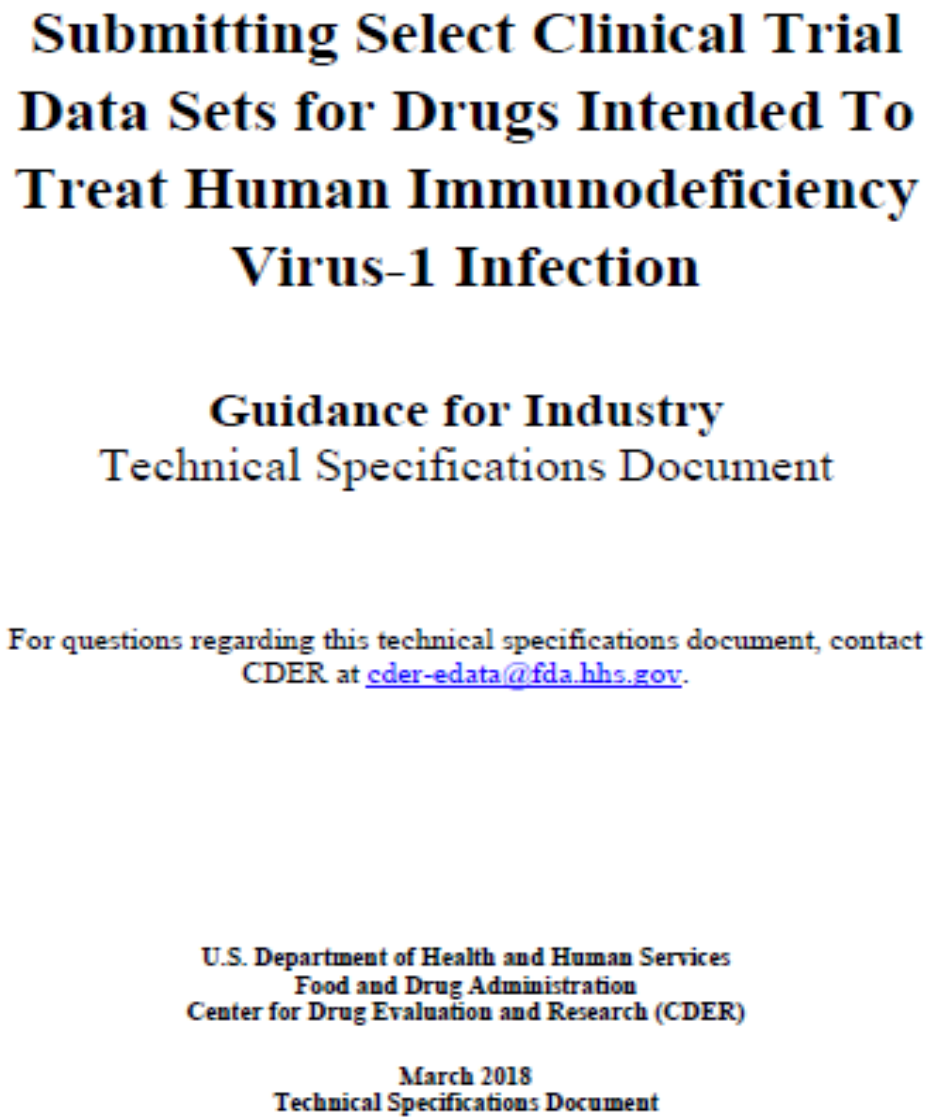
Outline

- 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

HIV Datasets Technical Specifications Guidance (2018)



Submitting Select Clinical Trial Data Sets for Drugs Intended To Treat Human Immunodeficiency Virus-1 Infection

Guidance for Industry
Technical Specifications Document

For questions regarding this technical specifications document, contact CDER at cder-edata@fda.hhs.gov.

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

March 2018
Technical Specifications Document

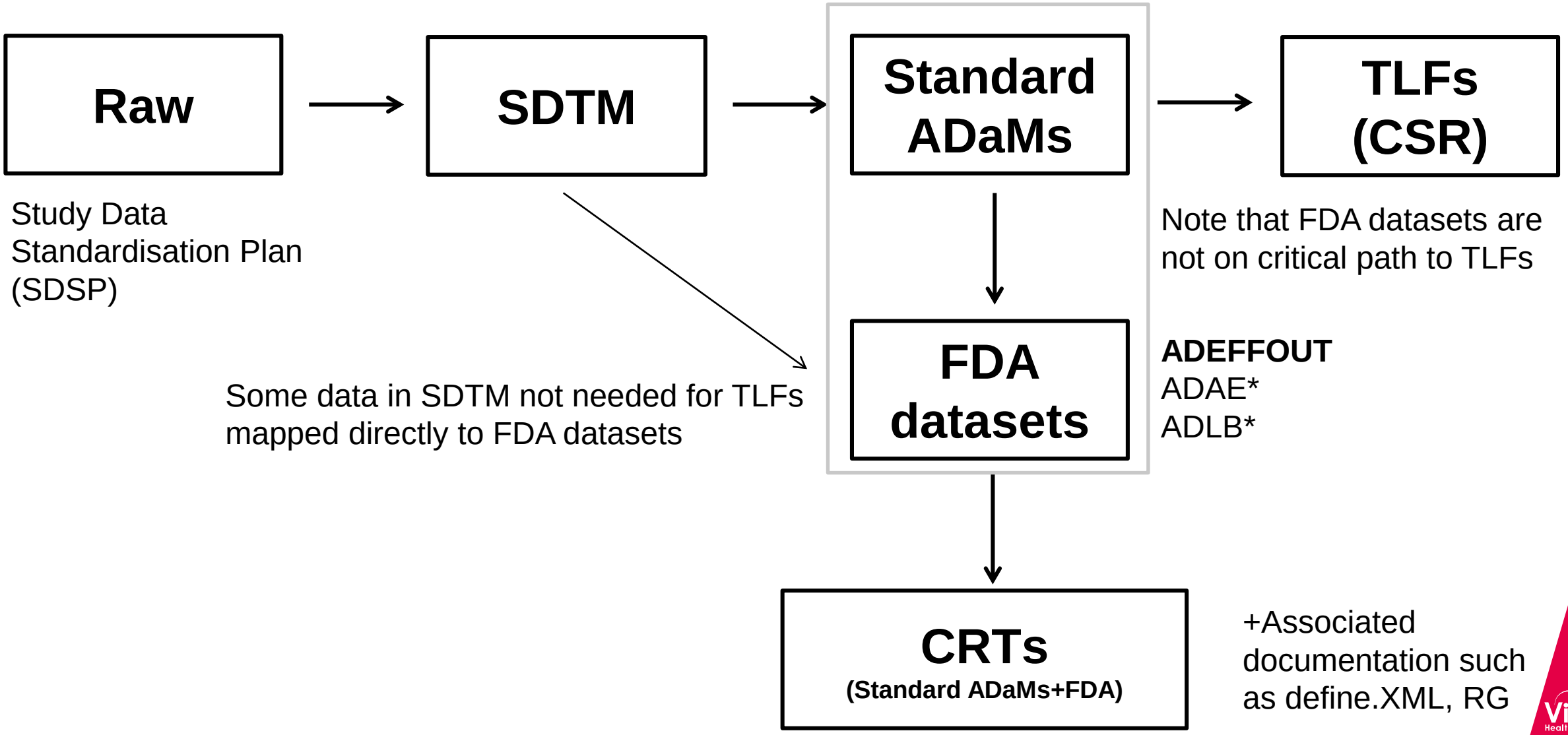
- **Recently issued HIV guidance (Mar 2018)**
- **Builds upon prior guidance documents:**
  - HIV drug development
    - Original: Oct 2002
    - Updated: Nov 2015
    - Attachment: Feb 2016
  - Role of resistance testing (Oct 2007)
  - Virology study resistance data (Feb 2014)
- **Specs for content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

HIV Tec Specifications – Content and Structure

Dataset Name	Content (key variables)	Structure
ADEFFOUT	• Demographics • Baseline disease characteristics • Baseline resistance • Treatment & exposure • Primary efficacy parameter • 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



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

ViiV Experience with HIV Tec Specs (since 2012)

Generic Name(s)	Brand Name	Indication(s)	NDA Filing Year	Tec Spec Used?
Dolutegravir	Tivacay	ARV-Naïve, TEP	2012	Precursor
Dolutegravir/ Lamvidudine/ Abacavir FDC	Triumeq	ARV-Naïve, TEP	2013	Precursor
Dolutegravir/ Rilpivirine FDC	Juluca	Suppressed Switch	2017	Precursor/ Draft
Dolutegravir/ Lamivudine FDC	Dovato	ARV-Naïve	2018	Precursor/ Draft
Cabotegravir/ Rilpivirine LA	TBD	Suppressed Switch	2019	Tec Spec
Fostemsavir	TBD	Highly Trt Exp’d	2019	Tec Spec

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

Data Standards in Research

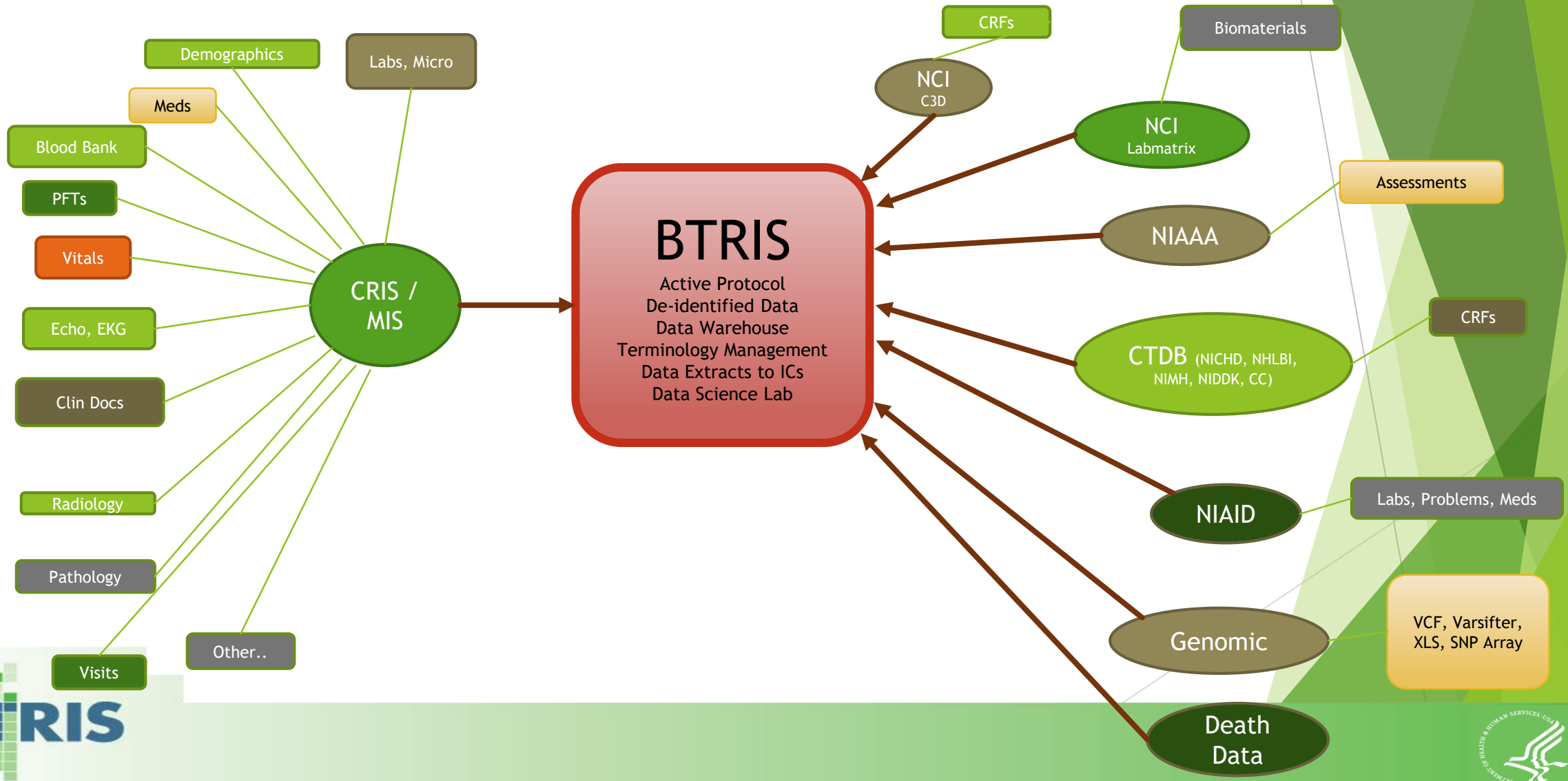
Jose Galvez, MD

12 June 2019

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

BTRIS Data


Demographics
Labs, Micro
Meds
Blood Bank
PFTs
Vitals
Echo, EKG
Clin Docs
Radiology
Pathology
Visits
Other..
CRIS / MIS
BTRIS
Active Protocol
De-identified Data
Data Warehouse
Terminology Management
Data Extracts to ICs
Data Science Lab
CRFs
NCI C3D
Biomaterials
NCI Labmatrix
Assessments
NIAAA
CRFs
CTDB (NICHD, NHLBI, NIMH, NIDDK, CC)
NIAID
Labs, Problems, Meds
Genomic
VCF, Varsifter, XLS, SNP Array
Death Data

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

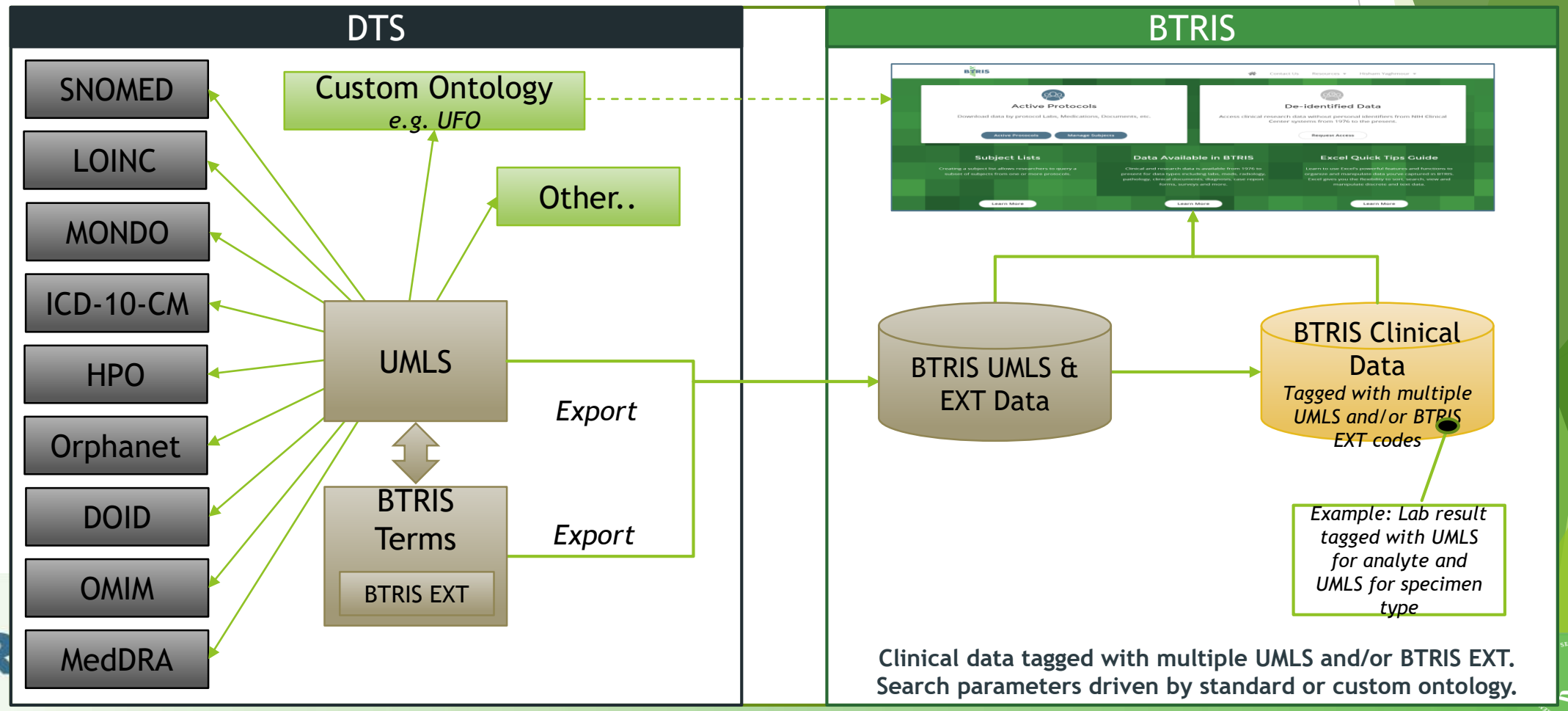
Use of Standards

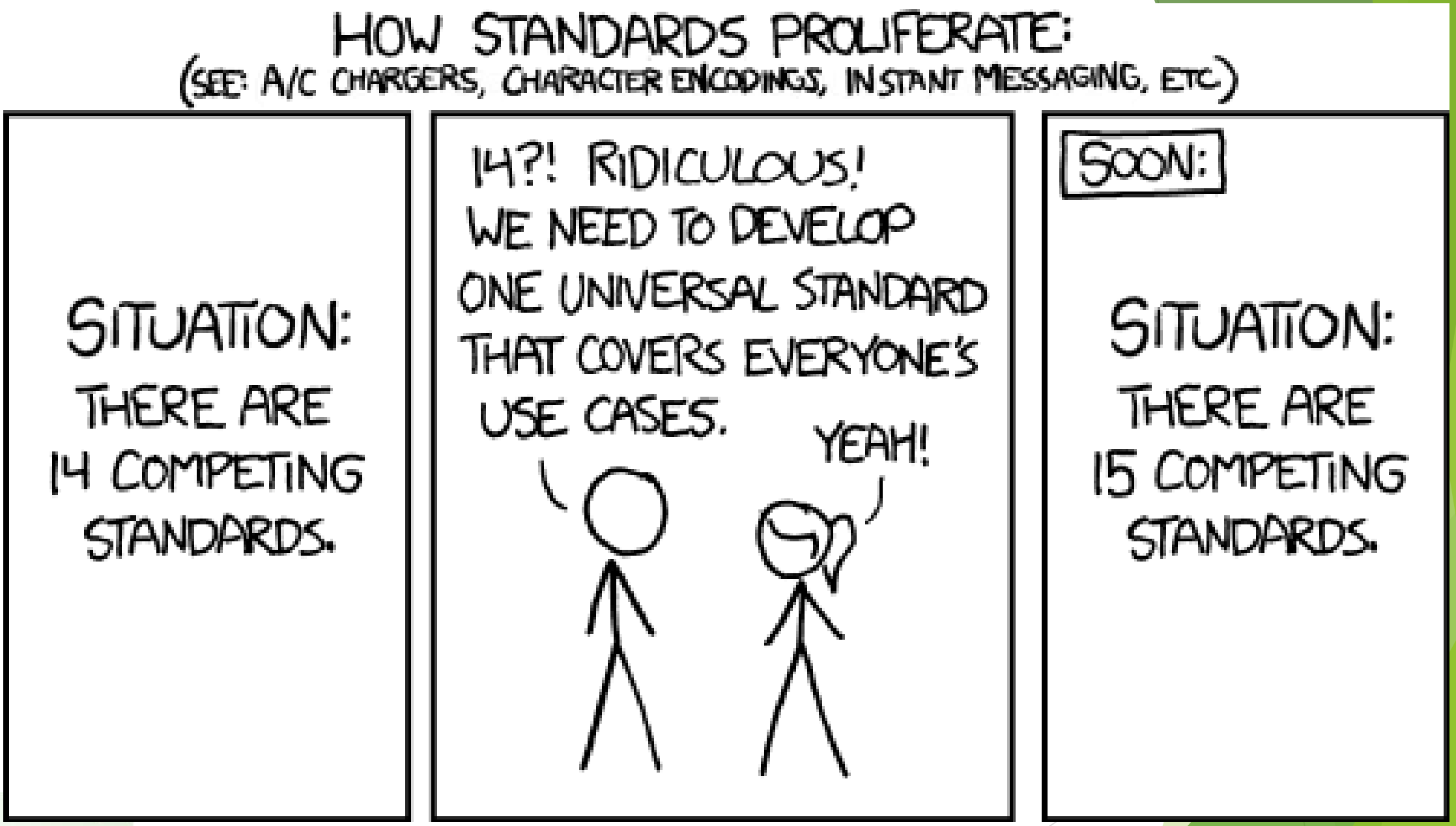
- Leverage healthcare industry standards to
  - Improve ability for researchers to find data using clinically meaningful terms and hierarchies
  - Improve interoperability
  - Improve machine readability, including use of NLP to standard terms from documents
- Rely on Standard Development Organizations (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

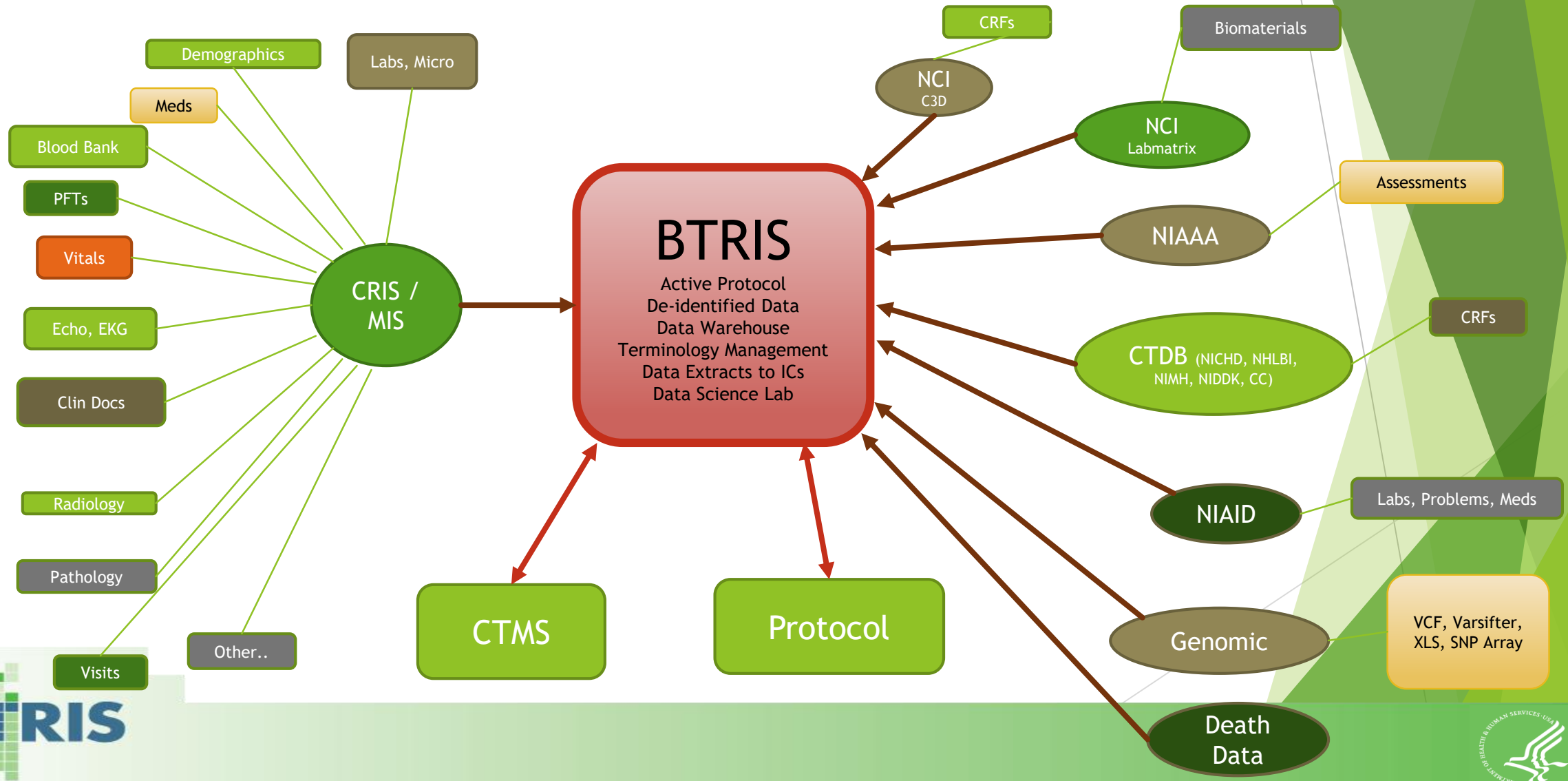
Standards – UMLS backed





https://imgs.xkcd.com/comics/standards.png

BTRIS Data – What's Missing?



What's Missing?
Protocols Information

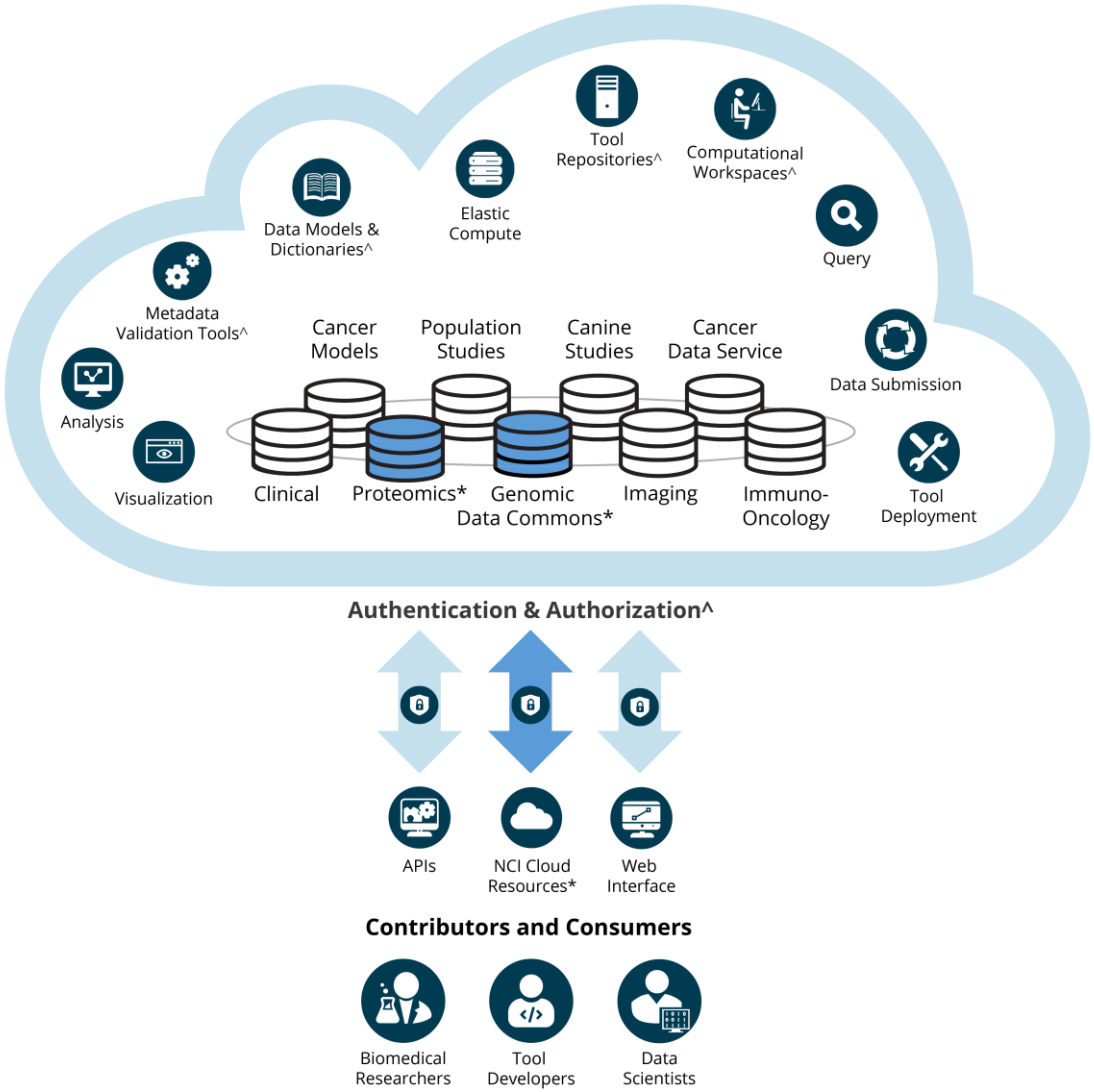
- Still written as a manuscript
  - Data elements are not defined in the protocol
  - Schedule of events are not defined in a machine readable format
  - Expected adverse events nor defined in a standard manner

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

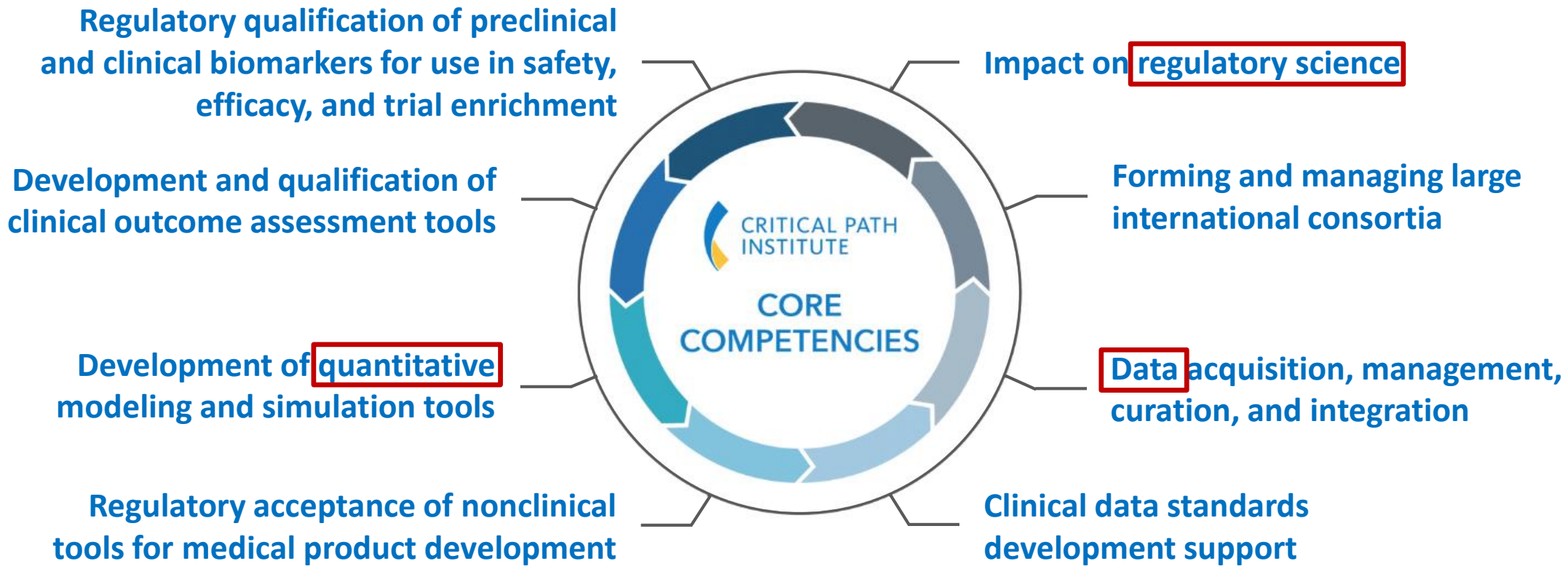
Jackson Burton, PhD

Associate Program Director, Quantitative Medicine

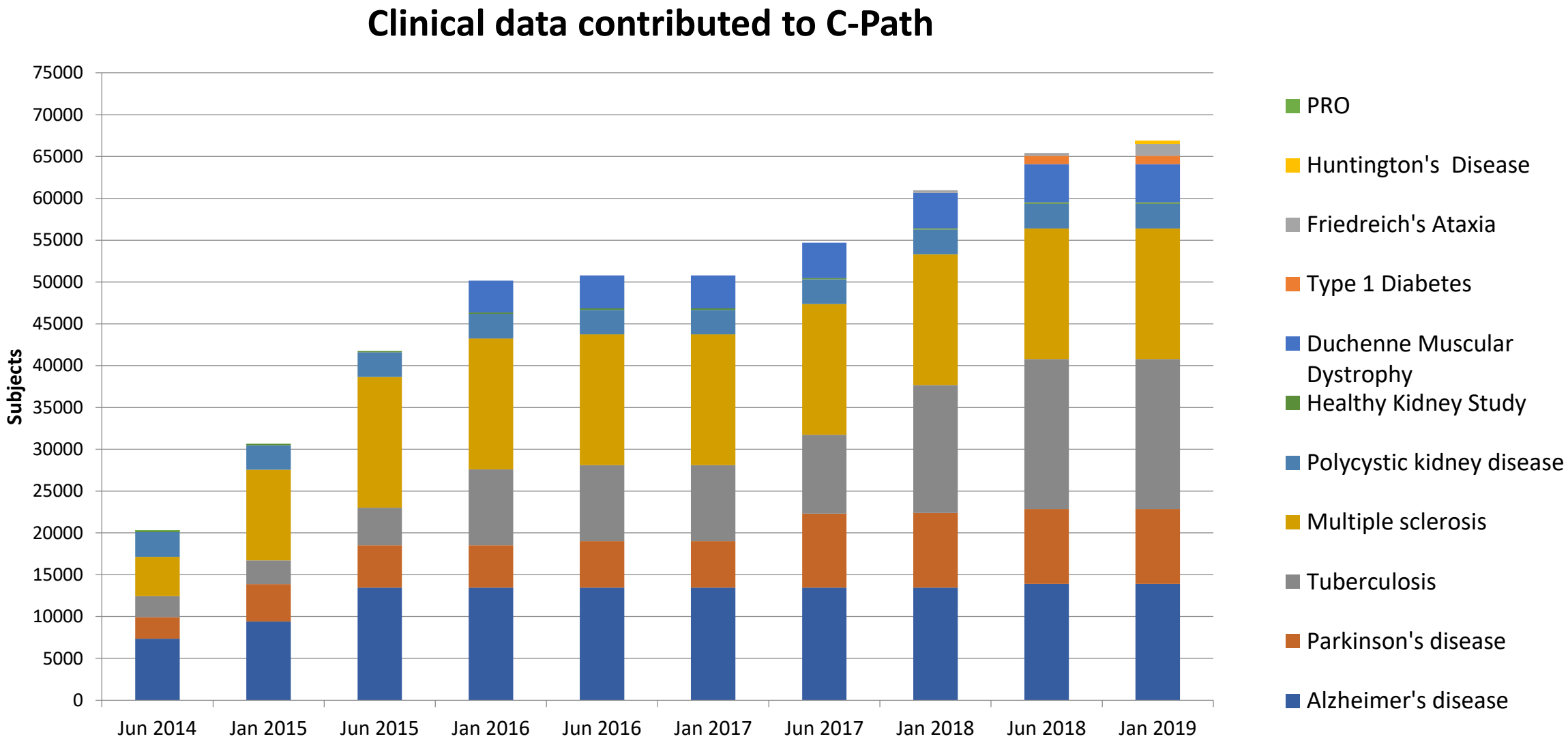
CRITICAL PATH INSTITUTE

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**



What: Data Acquisition and Management

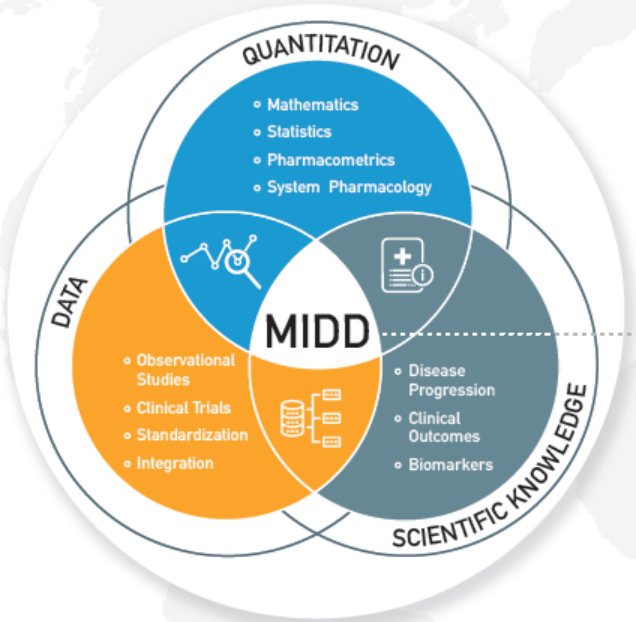


How: Quantitative Medicine

CRITICAL PATH INSTITUTE

C-PATH'S QUANTITATIVE MEDICINE PROGRAM

Creating solutions for bottlenecks in drug development through Model-Informed Drug Development (MIDD)



CPAD — ALZHEIMER DISEASE

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

CPP — 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)

HD-RSC — HUNTINGTON DISEASE

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

D-RSC — DUCHENNE MUSCULAR DYSTROPHY

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

T1D — TYPE 1 DIABETES

Clinical trial simulation tool to predict T1D diagnosis informed by Islet level autoantibody dynamics (in progress)

TTC — TRANSPLANT THERAPEUTICS

Clinical trial simulation tool to predict kidney graft failure (initiating)

CPTR — 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

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PD Clinical Trials

STUDY NAME	CONTRIBUTOR	# OF SUBJECTS	REFERENCE
START UP	Roche	201 untreated PD	Annals of Neurol 1993, 33: 350-356
SP513: Ropinirole	UCB	561 early stage PD	Mov Dis 2007; 22(16):2398-404
SP512: Rotigotine	UCB	273 early stage PD	J Park Dis 2016, 6(2): 401-11.
SURE PD PhII (Inosine)	Michael J Fox Fdn/ MGH / M. Schwarzschild/ Indiana Univ	75	JAMA Neurol. 2014 71(2):141-50.
CONFIDENT-PD	Michael J Fox Fdn/Junaxo	425	NCT01060878 (CT.gov)
PRECEPT	Teva	806 early PD	Neurol 20:82: 1791-7; 2014
ADAGIO	Teva	1,176 early PD	Lancet Neurol 2011; 10: 415–23
DATATOP	NINDS	800 early PD	Neurol 1990; 40: 1529-34
FS-1	Univ Rochester/NINDS	200 early PD	Clin Neuropharmacol. 2008 31(3):141-50
FS-TOO	Univ Rochester/NINDS	213 early PD	JAMA Neurol. 2014 71(6): 710–716.
ELLDOPA	Univ Rochester/NINDS	361 early PD	N Engl J Med 2004; 351:2498-508.

PD Observational Cohorts

STUDY NAME	CONTRIBUTOR	# OF SUBJECTS	REFERENCE
Parkinson Progression Marker Initiative (PPMI) Biomarker Study	Michael J. Fox Foundation	423 newly diagnosed PD, 196 controls, 64 SWEDD, 65 prodromal, 1,223 genetic registry participants	Prog Neurobio. 95: 629-35, 2011
CamPaIGN	University of Cambridge, UK	142 (diagnosed between 2000-2002)	JNNP 84: 1258-1264; 2013
ICICLE	Newcastle University , UK	160	Neurology 2014 82: 308-18
Tracking Parkinson's/PRoBaND study	University of Glasgow, UK	3,000 (2,000 patients within 3 years of diagnosis; 240 young onset and 760 relatives)	J Park Dis 2015 5: 947-59
OPDC Discovery cohort	University of Oxford, UK	1,630 (1,086 PD patients within 3 years of diagnosis; 111 first degree PD relative; 133 PSG-confirmed RBD; 300 control)	J Park Dis 2015 5: 269-79

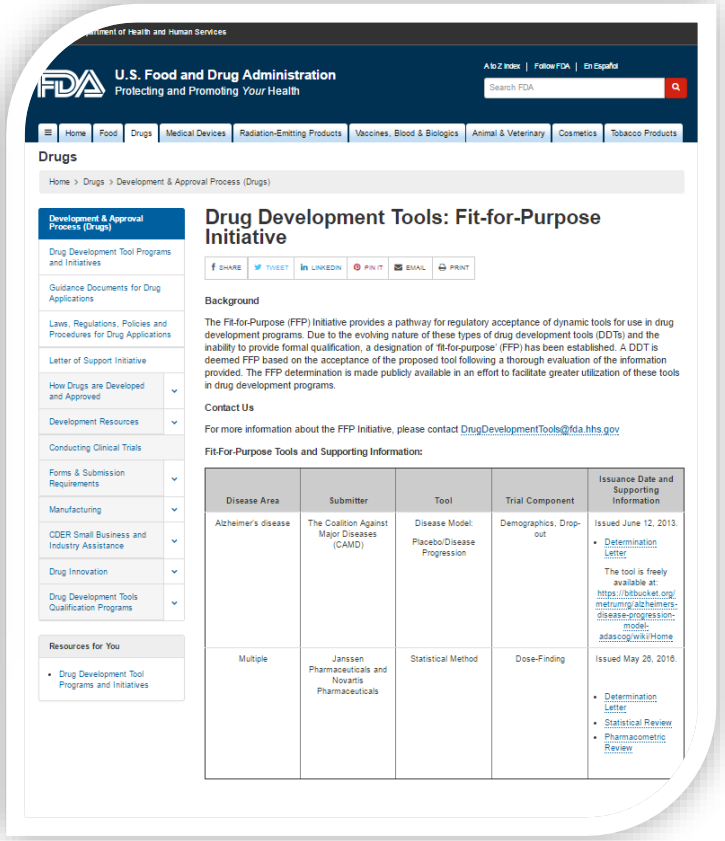
- 16 studies from industry and academics
- > 8,100 patients, 41K observations
- CDISC standard terminology for PD and SDTM were adopted early on to ensure interoperability of future acquired datasets

Stephenson D, Hu MT, Romero K, Breen K, Burn D, Ben-Shlomo Y, et al. Precompetitive Data Sharing as a Catalyst to Address Unmet Needs in Parkinson's Disease. J Park Dis. 2015;5(3):581–94.

FDA Review Pathways for Drug Development Tools

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

FDA: Qualification Program



http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm505485.htm

FDA: Fit-for-purpose Initiative

- 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

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)

STUDYID	USUBJID	AGE	SEX	FOLLOW_UP_TIME_IN_DAYS	MDS_UPDRS	END_POINT	S_UPDRS_III_TOTAL
PD-1000	PD-1000/03000	69	1	1	4	MDS_UPDRS_III_TOTAL	4
PD-1000	PD-1000/03000	69	1	1	0	MDS_UPDRS_II_TOTAL	1
PD-1000	PD-1000/03000	69	1	365	1	MDS_UPDRS_III_TOTAL	4
PD-1000	PD-1000/03000	69	1	365	0	MDS_UPDRS_II_TOTAL	2
PD-1000	PD-1000/03000	69	1	731	4	MDS_UPDRS_III_TOTAL	19
PD-1000	PD-1000/03000	69	1	731	0	MDS_UPDRS_II_TOTAL	
PD-1000	PD-1000/03000	69	1	1096	2	MDS_UPDRS_III_TOTAL	
PD-1000	PD-1000/03000	69	1	1096	0	MDS_UPDRS_II_TOTAL	
PD-1000	PD-1000/03000	69	1	1461	19	MDS_UPDRS_III_TOTAL	
PD-1000	PD-1000/03000	69	1	1461	0	MDS_UPDRS_II_TOTAL	

  - One r
  - Struc n parameter estimation in Rstan
  - Multiple records per time point

Neither are officially ADaM (although similar to ADaM BDS) but both are fully 'analysis ready' → No further transformations needed before NONMEM analysis input into analysis software.

- Structure dependent on the analysis: Best structure for use of

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

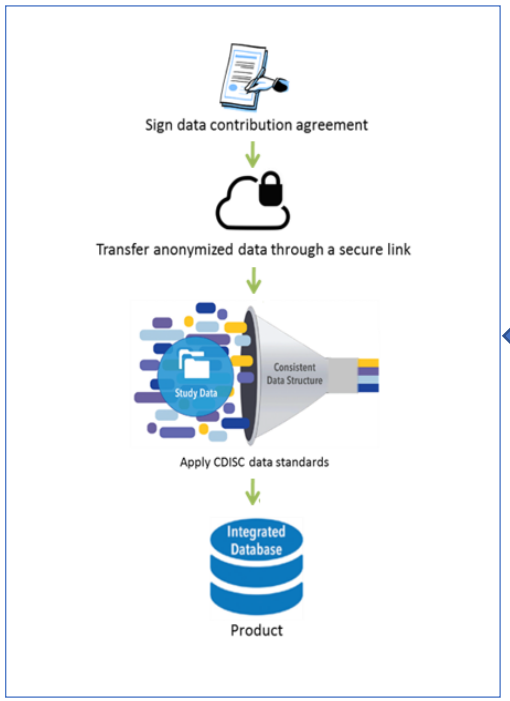
Thank you!

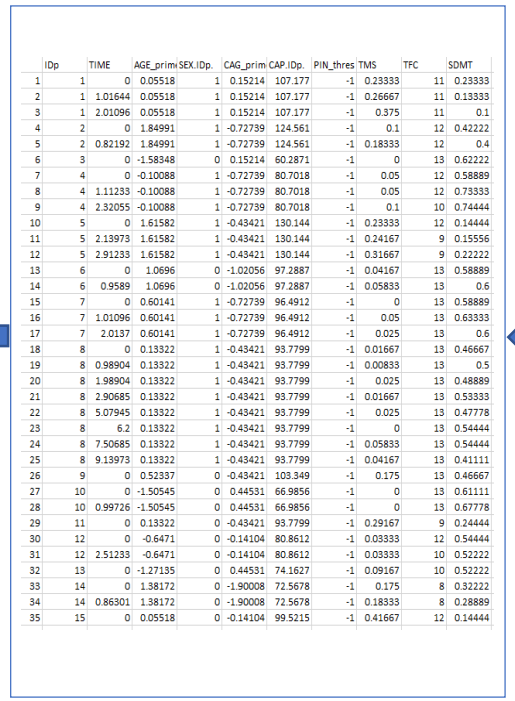
CRITICAL PATH INSTITUTE

collaborate · innovate · accelerate

Backup slides

Developing a Clinical Trial Simulator: Data as a Foundation





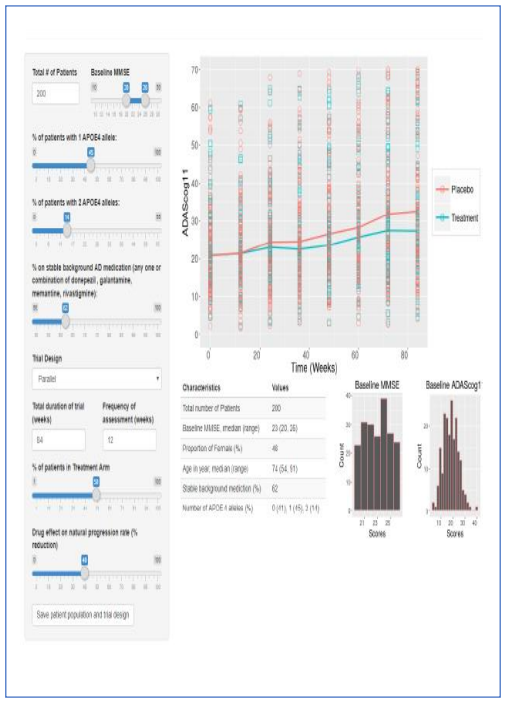
	IDp	TIME	AGE_prim	SEX.IDp.	CAG_prim	CAP.IDp.	PIN_thres	TMS	TFC	SDMT
1	1	0	0.05518	1	0.15214	107.177	-1	0.23333	11	0.23333
2	1	1.01644	0.05518	1	0.15214	107.177	-1	0.26667	11	0.13333
3	1	2.01096	0.05518	1	0.15214	107.177	-1	0.375	11	0.1
4	2	0	1.84991	1	-0.72739	124.561	-1	0.1	12	0.42222
5	2	0.82192	1.84991	1	-0.72739	124.561	-1	0.18333	12	0.4
6	3	0	-1.58348	0	0.15214	60.2871	-1	0	13	0.62222
7	4	0	-0.10088	1	-0.72739	80.7018	-1	0.05	12	0.58889
8	4	1.11233	-0.10088	1	-0.72739	80.7018	-1	0.05	12	0.73333
9	4	2.32055	-0.10088	1	-0.72739	80.7018	-1	0.1	10	0.74444
10	5	0	1.61582	1	-0.43421	130.144	-1	0.23333	12	0.14444
11	5	2.13973	1.61582	1	-0.43421	130.144	-1	0.24167	9	0.15556
12	5	2.91233	1.61582	1	-0.43421	130.144	-1	0.31667	9	0.22222
13	6	0	1.0696	0	-1.02056	97.2887	-1	0.04167	13	0.58889
14	6	0.9589	1.0696	0	-1.02056	97.2887	-1	0.05833	13	0.6
15	7	0	0.60141	1	-0.72739	96.4912	-1	0	13	0.58889
16	7	1.01096	0.60141	1	-0.72739	96.4912	-1	0.05	13	0.63333
17	7	2.0137	0.60141	1	-0.72739	96.4912	-1	0.025	13	0.6
18	8	0	0.13322	1	-0.43421	93.7799	-1	0.01667	13	0.46667
19	8	0.98904	0.13322	1	-0.43421	93.7799	-1	0.00833	13	0.5
20	8	1.98904	0.13322	1	-0.43421	93.7799	-1	0.025	13	0.48889
21	8	2.90685	0.13322	1	-0.43421	93.7799	-1	0.01667	13	0.53333
22	8	5.07945	0.13322	1	-0.43421	93.7799	-1	0.025	13	0.47778
23	8	6.2	0.13322	1	-0.43421	93.7799	-1	0	13	0.54444
24	8	7.50685	0.13322	1	-0.43421	93.7799	-1	0.05833	13	0.54444
25	8	9.13973	0.13322	1	-0.43421	93.7799	-1	0.04167	13	0.41111
26	9	0	0.52337	0	-0.43421	103.349	-1	0.175	13	0.46667
27	10	0	-1.50545	0	0.44531	66.9856	-1	0	13	0.61111
28	10	0.99726	-1.50545	0	0.44531	66.9856	-1	0	13	0.67778
29	11	0	0.13322	0	-0.43421	93.7799	-1	0.29167	9	0.24444
30	12	0	-0.6471	0	-0.14104	80.8612	-1	0.03333	12	0.54444
31	12	2.51233	-0.6471	0	-0.14104	80.8612	-1	0.03333	10	0.52222
32	13	0	-1.27135	0	0.44531	74.1627	-1	0.09167	10	0.52222
33	14	0	1.38172	0	-1.90008	72.5678	-1	0.175	8	0.32222
34	14	0.86301	1.38172	0	-1.90008	72.5678	-1	0.18333	8	0.28889
35	15	0	0.05518	0	-0.14104	99.5215	-1	0.41667	12	0.14444

$$\mu_{TMS,ij}(t_{ij}) = \left(f_{\boldsymbol{bl}}(X) + a_{bl} + \alpha_{bl,i}\right) + \left(f_{\boldsymbol{r}}(X) + a_r + \alpha_{r,i}\right)t_{ij} + \varepsilon_{TMS\_ij}$$

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

$$Y^* = \boldsymbol{X}\beta + \boldsymbol{Z}a + \epsilon$$

$$Y_{TFC} = \begin{cases} 6, Y^* \leq \tau_1 \\ 7, \tau_1 < Y^* \leq \tau_2 \\ \vdots \\ 12, \tau_7 < Y^* \leq \tau_8 \\ 13, \tau_8 \leq Y^* \end{cases}$$



Execution

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


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Session IV: Key Opportunities to Improve the Implementation of Analysis Data Standards

U.S. FOOD & DRUG ADMINISTRATION

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


FDA
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ADMINISTRATION

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

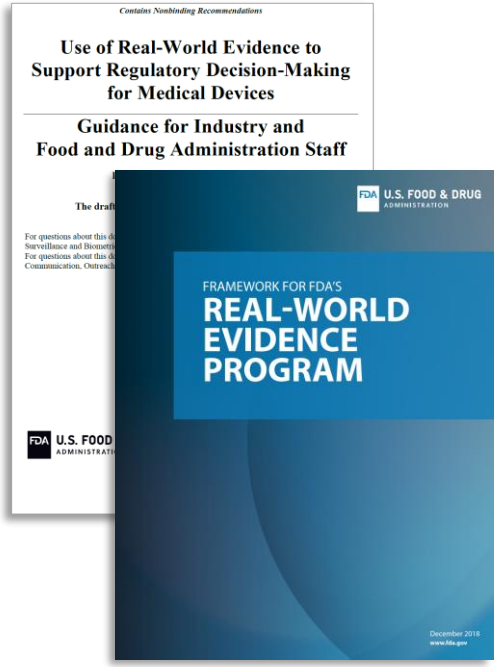
- The mention of commercial products, their sources, or their use in connection with material reported herein is not to be construed as either an actual or implied endorsement of such products by the Department of Health and Human Services
- David Martin received funding from the Patient Centered Outcomes 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:**
  - **Approval of new indication for a drug approved under section 505(c)**
  - **Satisfy post-approval study requirements**
- **Program will be based on a framework that:**
  - **Categorizes sources of RWE and gaps in data collection activities**
  - **Identifies standards and methodologies for collection and analysis**
  - **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**

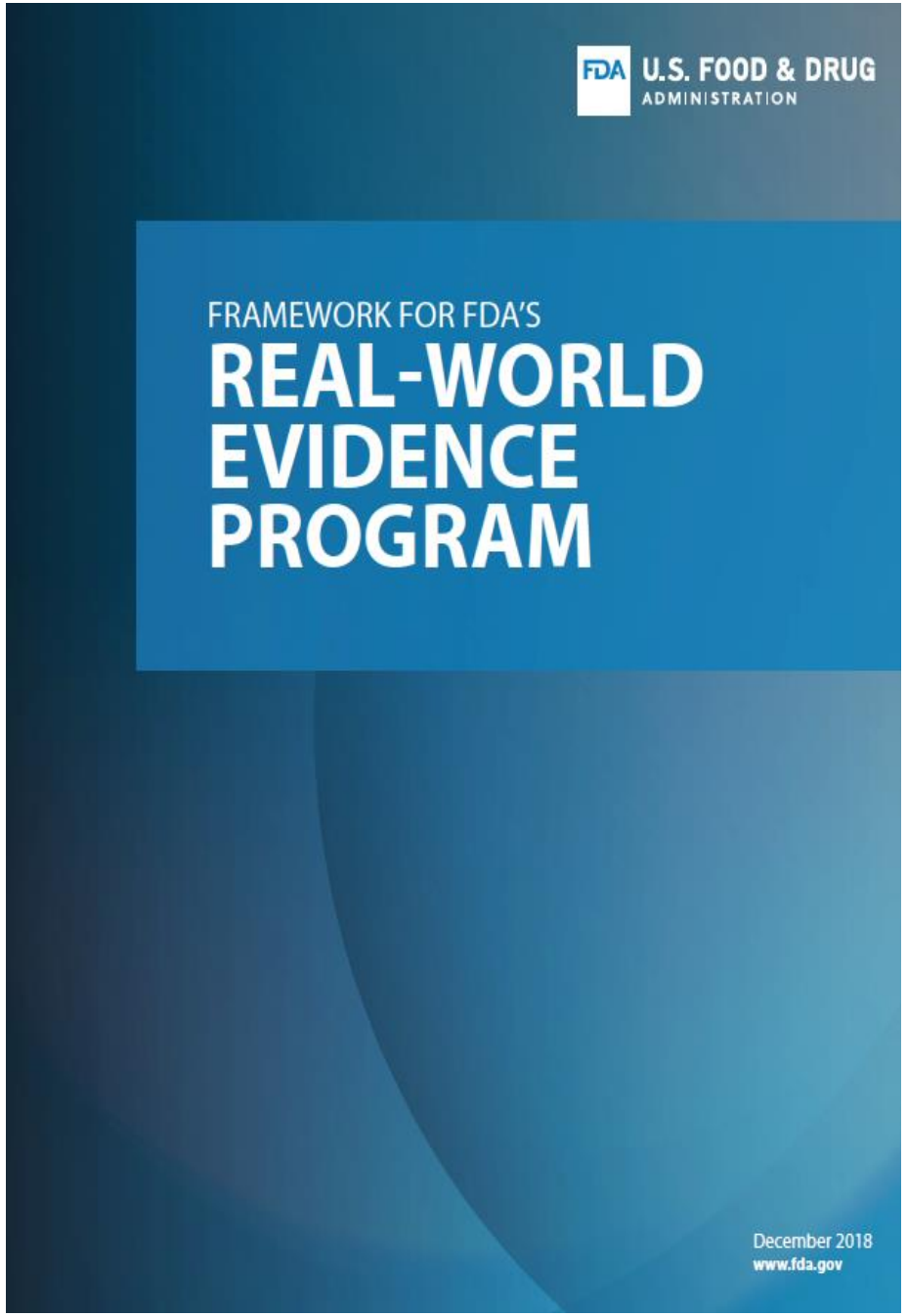
Definitions

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.

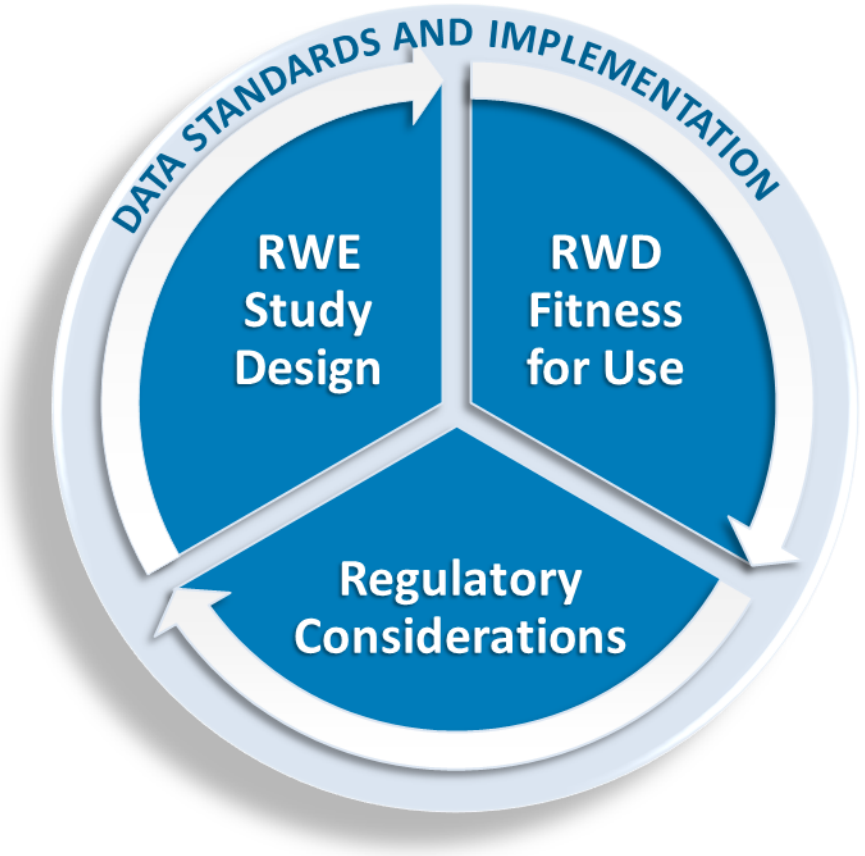
Real-World Evidence (RWE) is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD.



- 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

https://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RealWorldEvidence/UCM627769.pdf

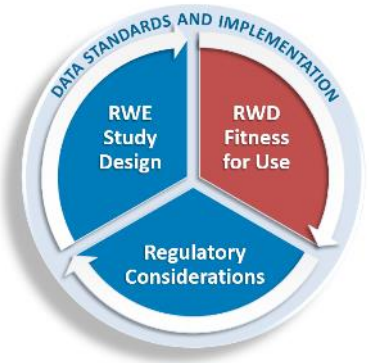
Framework for Evaluating RWD/RWE for Use in Regulatory Decisions



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**

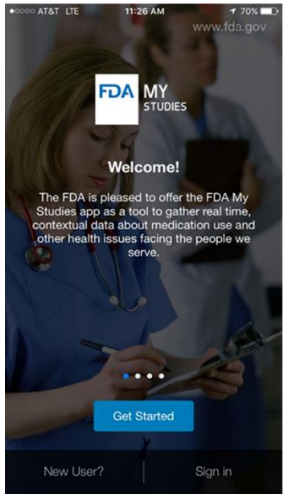
RWD Fitness for Use

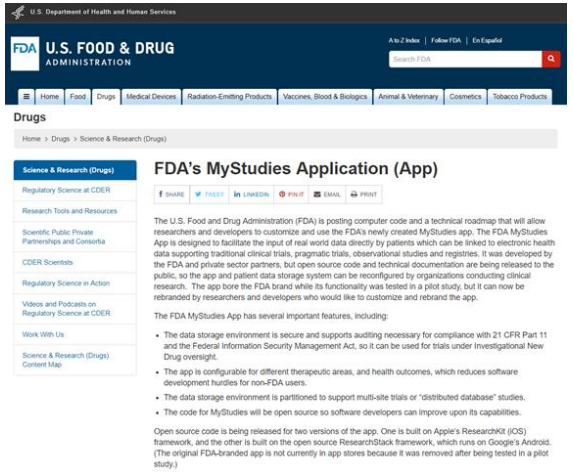


PROGRAM ITEMS:

- 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

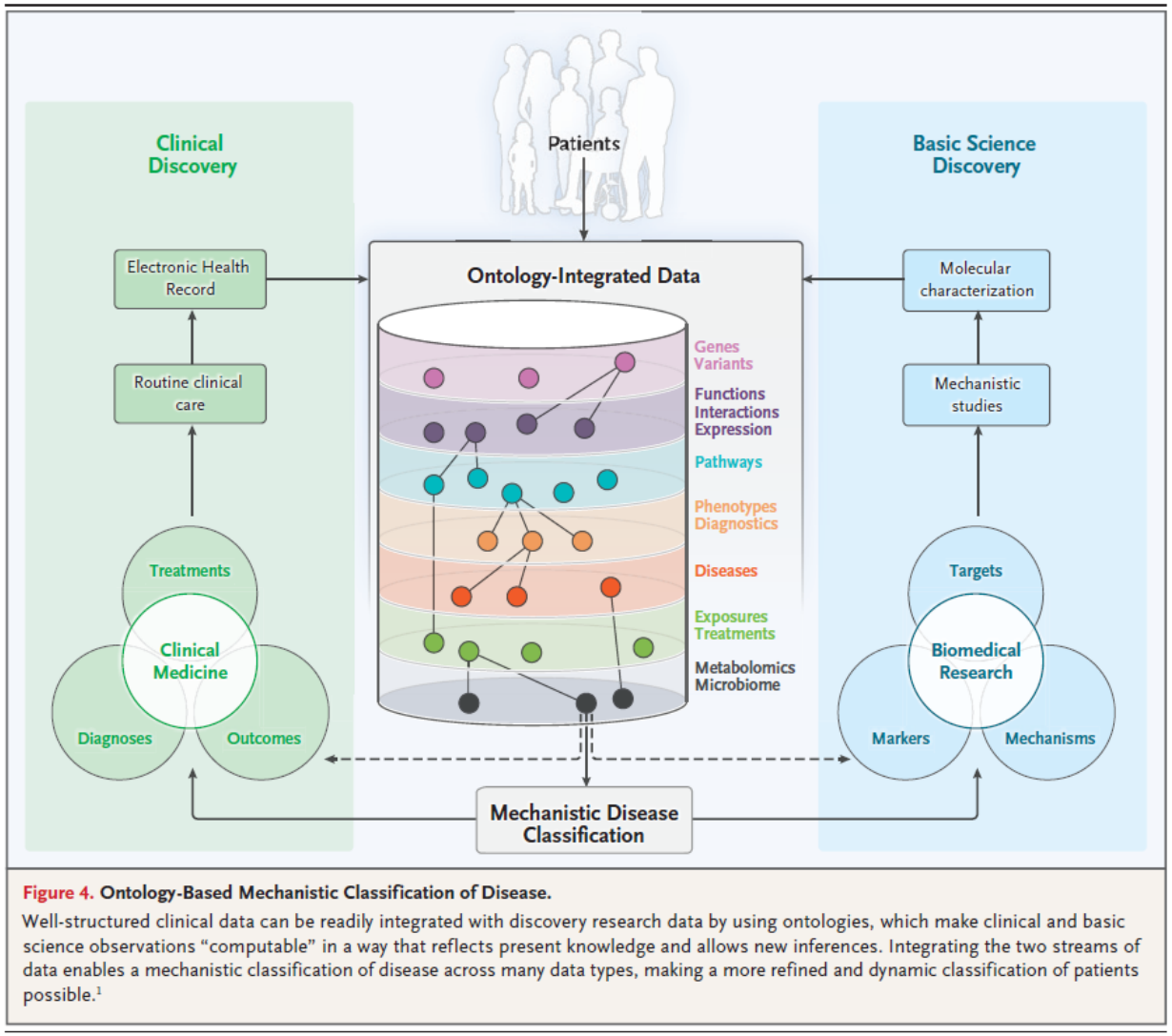


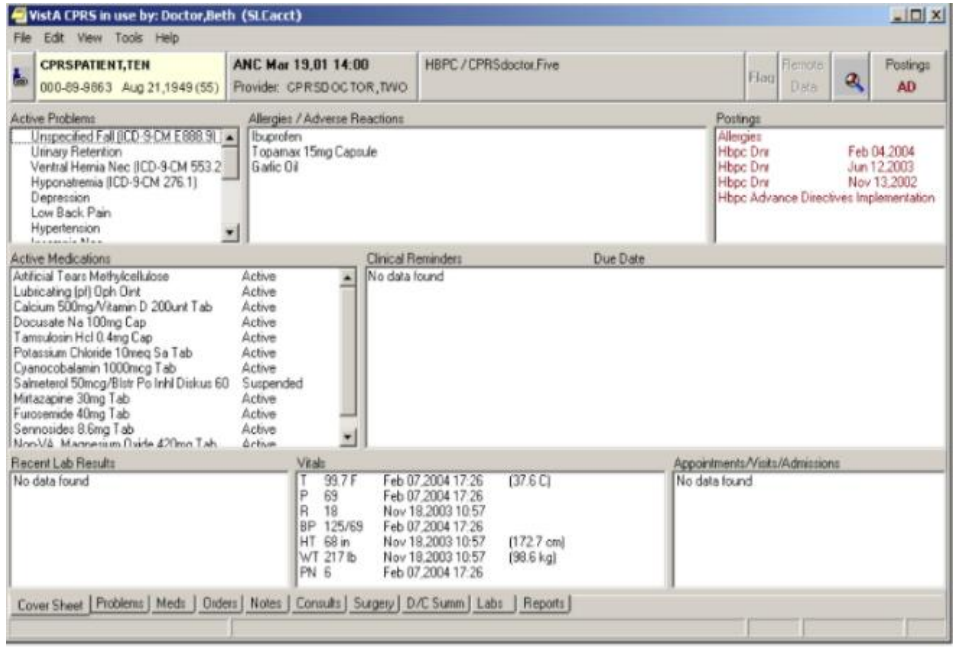
Figure 4. Ontology-Based Mechanistic Classification of Disease.

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]

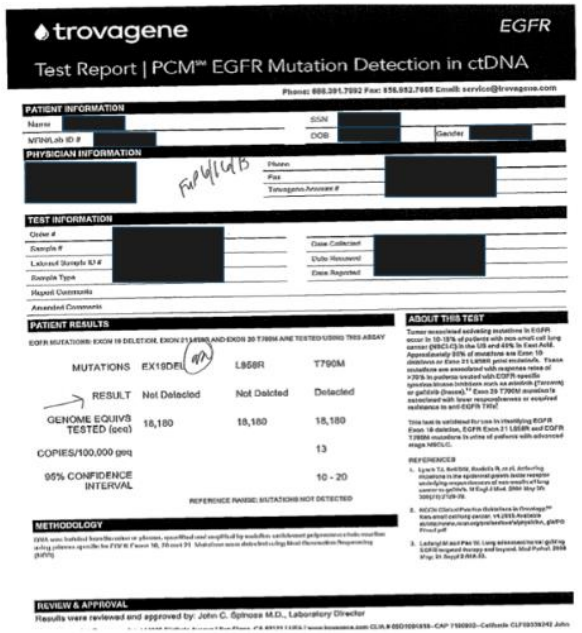
1. National Research Council, Committee on a Framework for Developing a New Taxonomy of Disease. Toward precision medicine: building a knowledge network for biomedical research and a new taxonomy of disease. Washington, DC: National Academies Press, 2011.

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


trovagene

EGFR

Test Report | PCM℠ EGFR Mutation Detection in ctDNA

PATIENT INFORMATION

PHYSICIAN INFORMATION

TEST INFORMATION

PATIENT RESULTS

MUTATIONS	EX19DEL	L858R	T790M
RESULT	Not Detected	Not Detected	Detected
GENOME EQUIVS TESTED (geq)	18,180	18,180	18,180
COPIES/100,000 (geq)			13
95% CONFIDENCE INTERVAL			10 - 20

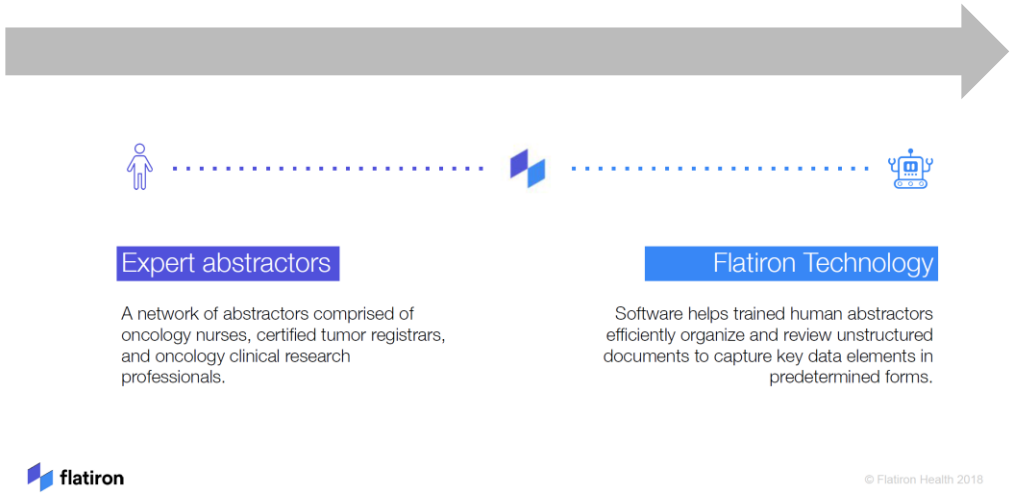
REFERENCE RANGE: MUTATIONS NOT DETECTED

ABOUT THIS TEST

METHODOLOGY

REVIEW & APPROVAL

Results were reviewed and approved by: John C. Spinosa M.D., Laboratory Director



- 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.

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

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 Harnett1 & Amy P Abernethy

Future Oncol. (2016) 12(10):1262–74

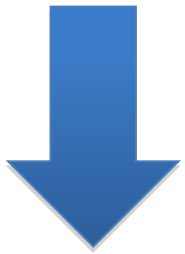
Future ONCOLOGY

EHR Data Structure plus prospective outcome capture

mCODE™

Minimal Clinical Oncology Data Elements

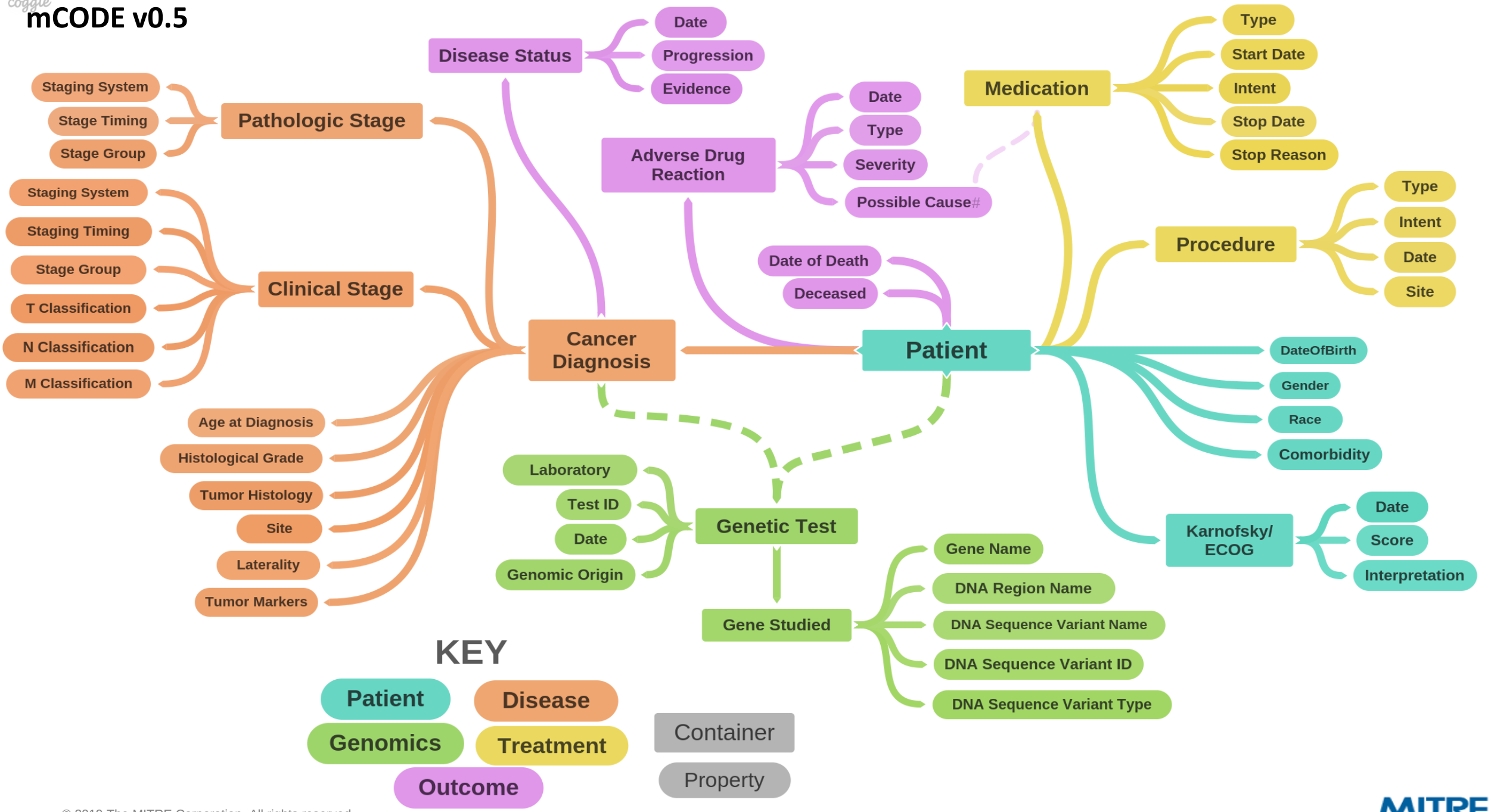
Data standards to improve the quality and usability of EHR data



Collection of clinical trials data using the EHR

Courtesy of ASCO/MITRE

mCODE v0.5



ICAREdata Outcome Questions

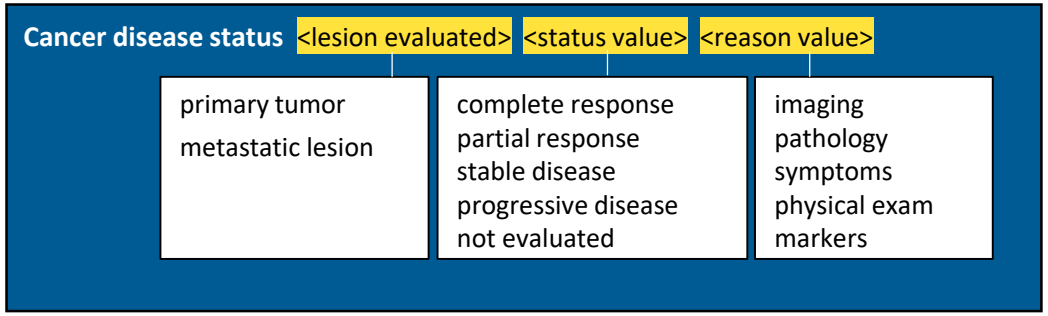
ICAREdata: Develop and validate mCODE-based outcome measures

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



Sample Resulting Structured Phrase*

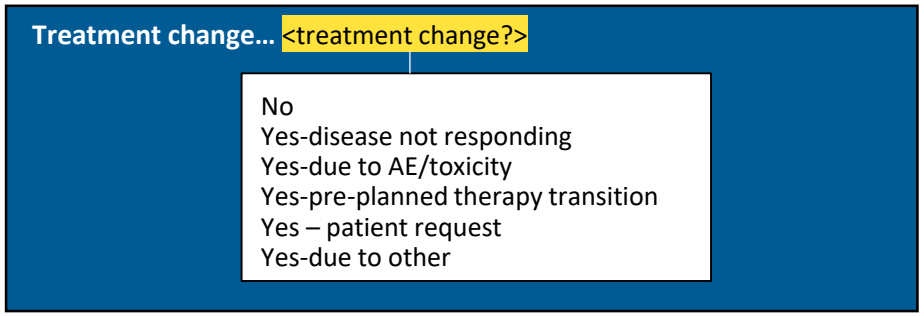
#Cancer disease status observed for #primary tumor was #progressive disease based on #imaging and #symptoms

Treatment change

Clinical Assessment

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

ICAREdata Question Format



Sample Resulting Structured Phrase*

#Treatment change #yes-disease not responding

* Blue font denotes controlled vocabularies

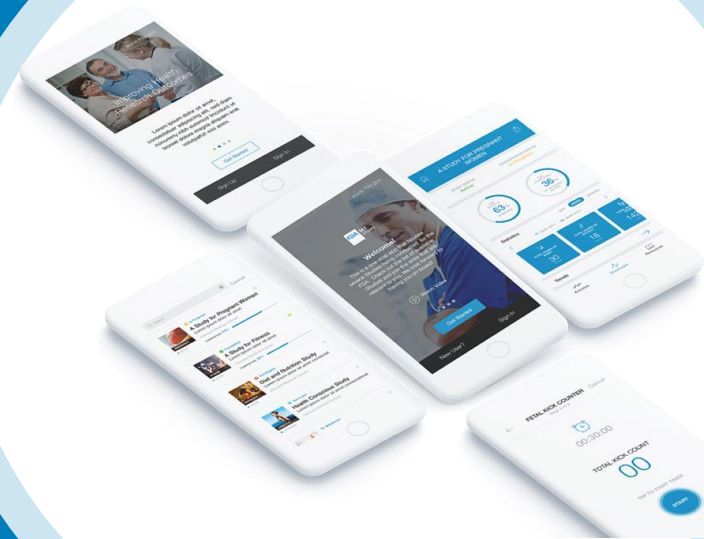
Patient-Generated Health Data (Digital Health Tools)

Biosensor as the data originator

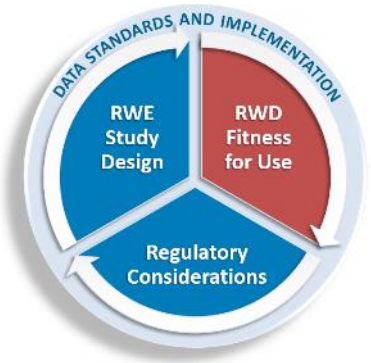
e.g., activity trackers, glucose sensors, wireless heart rate monitors

Patient as the data originator

e.g., questionnaires, cognitive tests, coordination tests, episodic accelerometer based tests (six minute walk)



RWD Fitness for Use



PROGRAM ITEMS:

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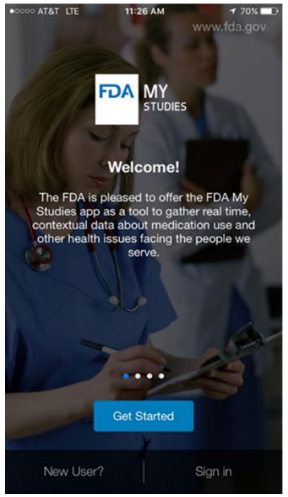

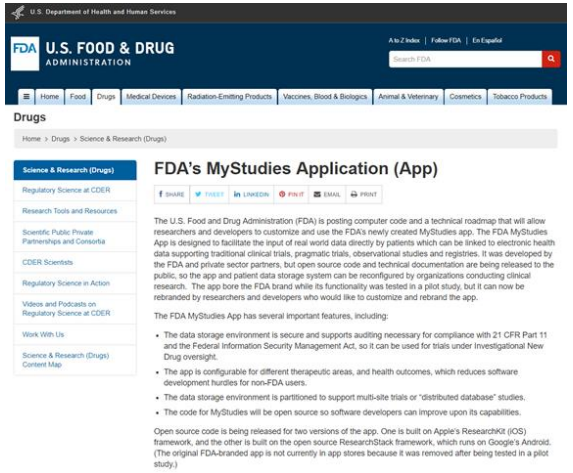

https://www.fda.gov/NewsEvents/Newsroom/FDAInBrief/ucm625228.htm
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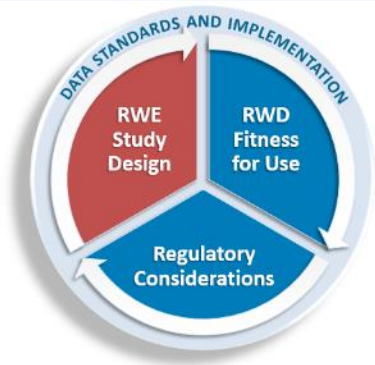
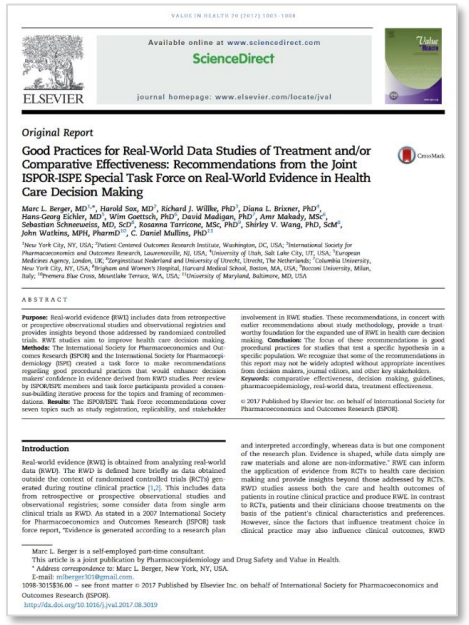
https://github.com/PopMedNet-Team/FDA-My-Studies-Mobile-Application-System



Potential for Study Designs Using RWD to Support Effectiveness



Available online at www.sciencedirect.com
ScienceDirect
journal homepage: www.elsevier.com/locate/jval

Original Report

Good Practices for Real-World Data Studies of Treatment and/or Comparative Effectiveness: Recommendations from the Joint ISPOR-ISPE Special Task Force on Real-World Evidence in Health Care Decision Making

Marc L. Berger, MD[1,*], Harold Sox, MD[2], Richard J. Willke, PhD[3], Diana L. Brixner, PhD[4], Hans-Georg Eichler, MD[5], Wim Goettsch, PhD[6], David Madigan, PhD[7], Amr Makady, MSc[6], Sebastian Schneeweiss, MD, ScD[8], Rosanna Tarricone, MSc, PhD[9], Shirley V. Wang, PhD, ScM[8], John Watkins, MPH, PharmD[10], C. Daniel Mullins, PhD[11]

ABSTRACT

Purpose: Real-world evidence (RWE) includes data from retrospective or prospective observational studies and observational registries and provides insights beyond those addressed by randomized controlled trials. RWE studies aim to improve health care decision making. **Methods:** The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the International Society for Pharmacoepidemiology (ISPE) created a task force to make recommendations regarding good procedural practices that would enhance decision makers' confidence in evidence derived from RWD studies. Peer review by ISPOR/ISPE members and task force participants provided a consensus-building iterative process for the topics and framing of recommendations. **Results:** The ISPOR/ISPE Task Force recommendations cover seven topics such as study registration, replicability, and stakeholder involvement in RWE studies. These recommendations, in concert with earlier recommendations about study methodology, provide a trustworthy foundation for the expanded use of RWE in health care decision making. **Conclusion:** The focus of these recommendations is good procedural practices for studies that test a specific hypothesis in a specific population. We recognize that some of the recommendations in this report may not be widely adopted without appropriate incentives from decision makers, journal editors, and other key stakeholders.

Keywords: comparative effectiveness, decision making, guidelines, pharmacoepidemiology, real-world data, treatment effectiveness.

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Introduction

Real-world evidence (RWE) is obtained from analyzing real-world data (RWD). The RWD is defined here briefly as data obtained outside the context of randomized controlled trials (RCTs) generated during routine clinical practice [1,2]. This includes data from retrospective or prospective observational studies and observational registries; some consider data from single arm clinical trials as RWD. As stated in a 2007 International Society for Pharmacoeconomics and Outcomes Research (ISPOR) task force report, "Evidence is generated according to a research plan and interpreted accordingly, whereas data is but one component of the research plan. Evidence is shaped, while data simply are raw materials and alone are non-informative." RWE can inform the application of evidence from RCTs to health care decision making and provide insights beyond those addressed by RCTs. RWD studies assess both the care and health outcomes of patients in routine clinical practice and produce RWE. In contrast to RCTs, patients and their clinicians choose treatments on the basis of the patient's clinical characteristics and preferences. However, since the factors that influence treatment choice in clinical practice may also influence clinical outcomes, RWD

Marc L. Berger is a self-employed part-time consultant.
This article is a joint publication by Pharmacoepidemiology and Drug Safety and Value in Health.
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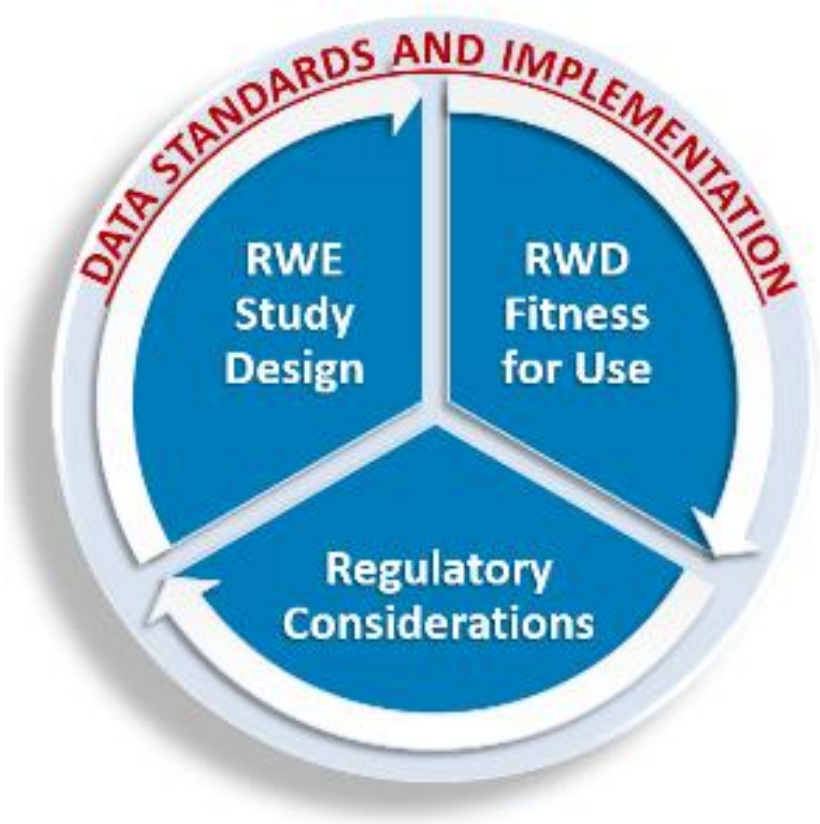
E-mail: mlberger301@gmail.com.

1098-3015$36.00 – see front matter © 2017 Published by Elsevier Inc. on behalf of International Society for Pharmacoeconomics and Outcomes Research (ISPOR).
http://dx.doi.org/10.1016/j.jval.2017.08.3019

PROGRAM ITEM:

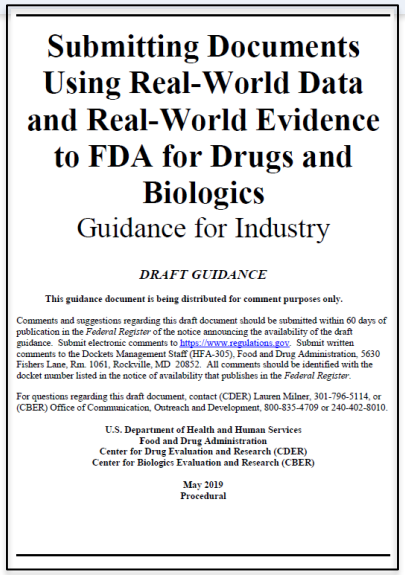
Observational studies

- 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 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



DATA STANDARDS AND IMPLEMENTATION

Identifying Documents Using RWD and RWE



Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drugs and Biologics

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Lauren Milner, 301-796-5114, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

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)

May 2019
Procedural

- 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

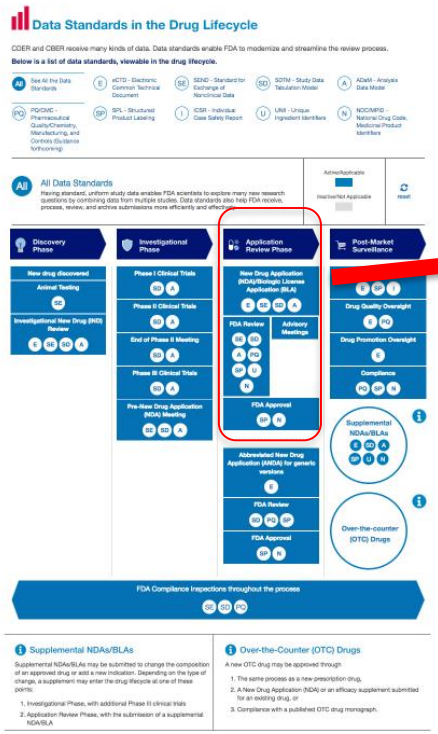
Purpose(s) of Using RWE as Part of the Submission (Select all that apply)
☐ Provide evidence in support of efficacy or safety for a new product approval
☐ Support labeling changes for an approved drug
☐ Add or modify an indication
☐ Change in dose, dose regimen, or route of administration
☐ Use in a 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:

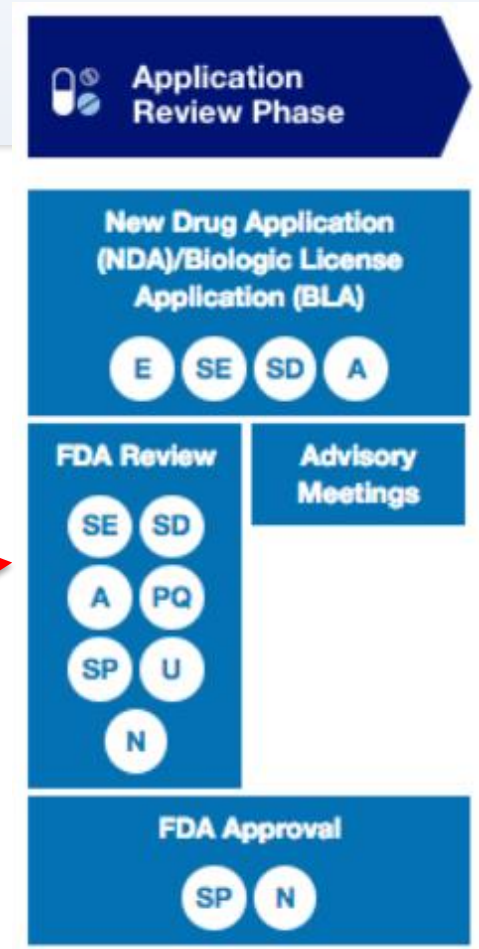
LINK to Guidance: https://www.fda.gov/media/124795/download

Data Standards in the drug lifecycle

Interactive "Data Standards in the Drug Lifecycle" Infographic

Click through this interactive infographic to get information about the data standards and their role in the drug lifecycle.





All — See All the Data Standards

E — eCTD - Electronic Common Technical Document

SE — SEND - Standard for Exchange of Nonclinical Data

SD — SDTM - Study Data Tabulation Model

A — ADaM - Analysis Data Model

PQ — PQ/CMC - Pharmaceutical Quality/Chemistry, Manufacturing, and Controls (Guidance forthcoming)

SP — SPL - Structured Product Labeling

I — ICSR - Individual Case Safety Report

U — UNII - Unique Ingredient Identifiers

N — NDC/MPID - National Drug Code, Medicinal Product Identifiers

https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/data-standards-drug-lifecycle

Data Standards and Implementation

Identify **gaps** between RWD/ RWE data standards and existing systems

Identify and assess data standards and implementation strategies **required** to use RWD/ RWE

Collaborate with Stakeholders to adopt or develop standards and implementations strategies

RWD Submission Standard

U.S. FOOD & DRUG ADMINISTRATION

CDERMedicalPolicy-RealWorldEvidence@fda.hhs.gov


FDA
U.S. FOOD & DRUG
ADMINISTRATION

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 Almario, 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

    Klaus Romero, Lynn Hudson, Enrique Aviles, Richard Liwski, Jackson Burton, Laura Butte

Thank you!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ADMINISTRATION

Adjournment