BIOGRAPHIES

Rachel Dlugash

Rachel Dlugash is a Statistical Analyst at the FDA, in the Analytics and Informatics Staff Division of the Office of Biostatistics in CDER. She is involved in efforts to improve the implementation and use of data standards within the agency, as well as participating in outside agency collaborations. Prior to the FDA, she performed data analysis and data monitoring for academic clinical trials at Johns Hopkins. She has also worked with patients and collected clinical trial data at the University of Pennsylvania after starting her career at Octagon Research Solutions (now Accenture) where she prepared pharmaceutical clinical trial data to be SDTM compliant.

Stephen Wilson

Dr. Wilson has worked as a mathematical statistician at FDA for more than 32 years. He is currently a Senior Staff Fellow with the Office of Biostatistics at the Center for Drug Evaluation and Research. Steve received his doctorate in Biostatistics from the University of North Carolina, Chapel Hill, in 1984. His professional interests are centered on working collaboratively to continuously improve the science and practice of clinical trials and the regulatory review of drugs and biologics.

Building a Bigger Analytics Tent at CDER

Rachel Dlugash
Steve Wilson
Analytics and Informatics Staff (AIS)
Office of Biostatistics, OTS/CDER/FDA
Food and Drug Administration

Analytic Evolution: Exploring the Next Phase of Drug Development & Submission

PharmaSUG Single Day Event
Virtual Meeting
1:15 – 1:45 PM (EDT)
October 29, 2021

Disclaimer

The views and opinions presented here represent those of the speakers and should not be considered to represent advice or guidance on behalf of the U.S. Food and Drug Administration.

Acknowledgements

- Bryant Chen
- Matilde Kam
- Paul Schuette
- Liping Sun

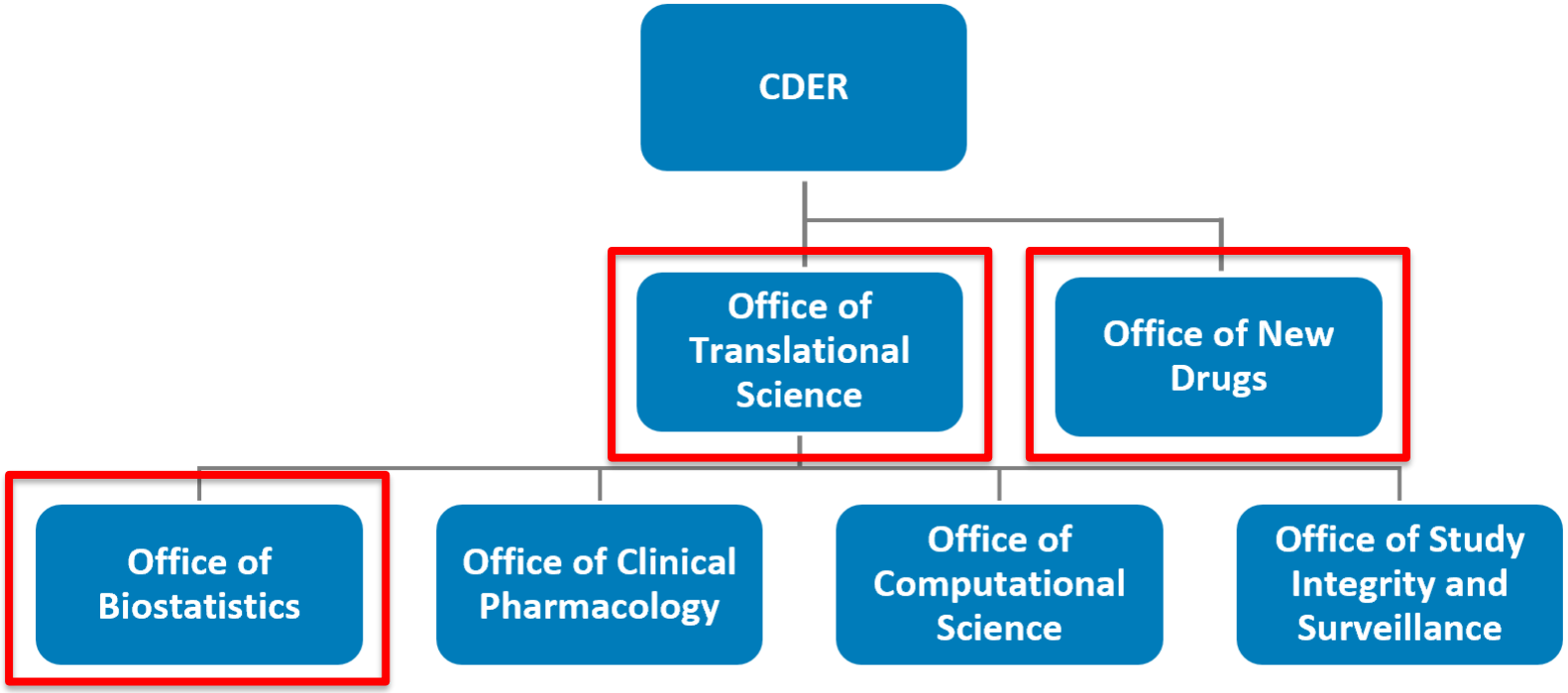
Abstract

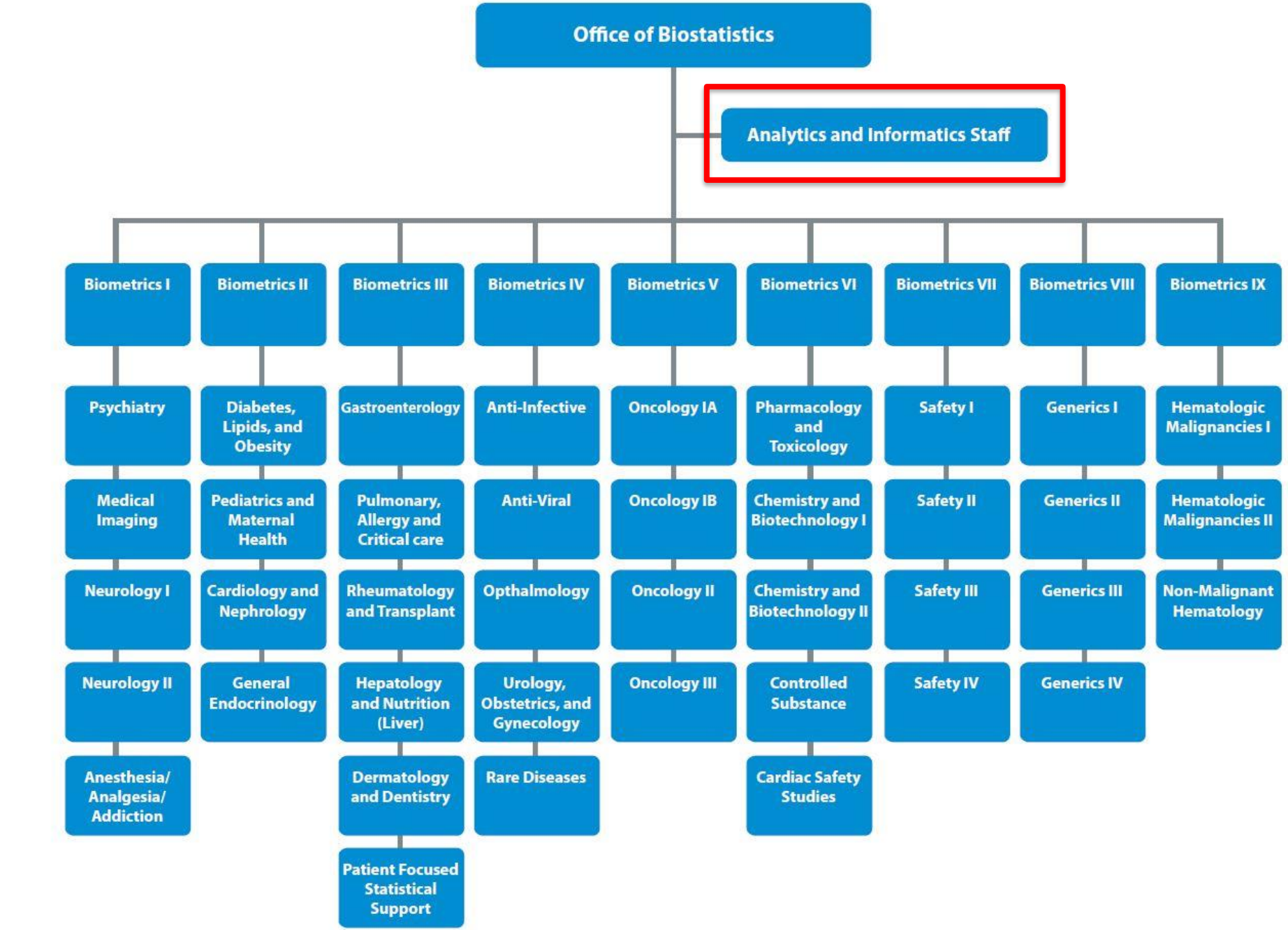
- The Analytics and Informatics Staff (AIS) works within the Office of Biostatistics at FDA's Center for Drug Evaluation and Research (CDER) to help push for improvements and efficiencies associated the regulation of drugs and biologics. The AIS, though relatively new to the Agency, is deeply involved in a number of important projects to promote operational efficiency, support standardization and enhance/expand regulatory review processes at CDER. These activities include the creation of an AIS CDISC Data Standards Study Group for OB, the close collaborative development of high-priority COA/QRS supplements for the Agency, a pilot project to assess natural language processing (NLP) for information base development and the promotion of open source tools. We view this session as an opportunity for all of us to learn about each other and continue to work together to improve.

Outline

- The Office of Biostatistics (OB) and the Analytics and Informatics Staff (AIS)
- A Job Description for the Analytics and Informatics Staff (AIS)
- A Sample of OB/AIS Initiatives and Activities

An Abbreviated CDER Organizational Chart




Office of Biostatistics
Analytics and Informatics Staff
Biometrics I
Biometrics II
Biometrics III
Biometrics IV
Biometrics V
Biometrics VI
Biometrics VII
Biometrics VIII
Biometrics IX
Psychiatry
Medical Imaging
Neurology I
Neurology II
Anesthesia/ Analgesia/ Addiction
Diabetes, Lipids, and Obesity
Pediatrics and Maternal Health
Cardiology and Nephrology
General Endocrinology
Gastroenterology
Pulmonary, Allergy and Critical care
Rheumatology and Transplant
Hepatology and Nutrition (Liver)
Dermatology and Dentistry
Patient Focused Statistical Support
Anti-Infective
Anti-Viral
Opthalmology
Urology, Obstetrics, and Gynecology
Rare Diseases
Oncology IA
Oncology IB
Oncology II
Oncology III
Pharmacology and Toxicology
Chemistry and Biotechnology I
Chemistry and Biotechnology II
Controlled Substance
Cardiac Safety Studies
Safety I
Safety II
Safety III
Safety IV
Generics I
Generics II
Generics III
Generics IV
Hematologic Malignancies I
Hematologic Malignancies II
Non-Malignant Hematology

A Job Description for the Analytics and Informatics Staff (AIS)

- Work jointly with all 9 Review Divisions of Biometrics (DBs) in OB
- Enhances/supports statistical IND/NDA/BLA review processes
- Provides leadership in the areas of:
  - Data Standards
  - Data Integrity and Data Quality
  - Data Science and Data Tools
  - Scientific Computing and Statistical Programming

A Sample of AIS Initiatives and Activities

- The AIS Data Standards Working Group (DSWG)
- The FDA/CDISC QRS Supplement Review Collaboration
- Data Science Tools Development
- Natural Language Processing (NLP)
- “R for Regulatory Submissions: Challenges and Approaches” … Paul Schuette

The AIS Data Standards Working Group (DSWG)

Support for Analysis Data Standards

PDUFA Reauthorization
Performance Goals
and Procedures
Fiscal Years
2018 through 2022

https://www.fda.gov/media/99140/download

5. Enhancing Capacity to Support Analysis Data Standards for Product Development and Review

To support the enhancement of analysis data standards for product development and review in the human drug review program, FDA will conduct the following activities during PDUFA VI:

a. FDA will develop the staff capacity to efficiently review and provide feedback to sponsors on the readiness of submitted analysis data sets and programs for statistical review. This staff will support pre- and post-submission discussion of standardized datasets and programs, and maintain the knowledge of and engage in collaborations about standards models used in the design, analysis and review of clinical and non-clinical studies. Examples of these standards models could include the Standard for Exchange of Nonclinical Data (SEND), Clinical Data Acquisition Standards Harmonization (CDASH), Study Data Tabulation Model (SDTM), and Analysis Data Model (ADaM).

b. In parallel, FDA will improve staff capacity to assist with FDA development and updating of therapeutic area user guides (TAUGs) to include the appropriate content for the analysis data standards used in submission and review.

c. By end of FY 2019, FDA will convene a public workshop to advance the development and application of analysis data standards.

d. FDA will collaborate with external stakeholders and participate in public workshops held by third parties such as standards development organizations, on development of data standards, processes, documentation and continuous improvement of clinical trials and regulatory science.

e. By end of FY 2020, FDA will develop or revise, as appropriate, relevant guidance, MAPPs, SOPPs and training associated with submission and utilization of standardized analysis datasets and programs used in review, and on the processes, procedures, and responsibilities related to the receipt, handling, and documentation of submitted analysis data and programs.

745A(a) of the FD&C Act & Binding Guidance – Requiring the Submission of Standardized Data

Section 745A(a) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), added by section 1136 of the Food and Drug Administration Safety and Innovation Act (FDASIA) (Public Law 112-144), requires that submissions under section 505(b), (i), or (j) of the FD&C Act2 and submissions under section 351(a) or (k) of the Public Health Service Act (PHS Act)3 be submitted in electronic format specified by the Food and Drug Administration (FDA or the Agency) …

- To comply with the GGP regulations and make sure that regulated entities and the public understand that guidance documents are nonbinding, FDA guidances ordinarily contain standard language explaining that guidances should be viewed only as recommendations unless specific regulatory or statutory requirements are cited.
- FDA is not including this standard language in this guidance because it is not an accurate description of the effects of this guidance.
- Insofar as this guidance specifies the format for electronic submissions, or provides for exemptions pursuant to section 745A(a) of the FD&C Act, it will have binding effect.

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

AIS CDISC Data Standards Working Group

The AIS CDISC Standards Working Group was established to:

- Develop experts in data standards within the Office of Biostatistics
- Identify and develop materials for data standards training and regulatory review case studies to provide resources for statistical reviewers and new statistical analysts
- Assess data standard issues/problems associated with IND/NDA/BLA reviews and develop/propose solutions to management

AIS CDISC Data Standards Working Group

The AIS CDISC Data Standards Working Group provides a forum for statistical analysts to learn about established data standards. Existing CDISC training materials are focused on using data standards to generate datasets, but there are unique challenges when using data standards in the context of reviewing data.

Referencing the SDTMIG, each member led discussions on a specific SDTM domain.

AE	EC	QS
CM	EX	RS
DM	FA	FT
DS	LB	SUPPQUAL
DV	MH	

AIS CDISC Data Standards Working Group

We have also studied and discussed available reference materials describing:

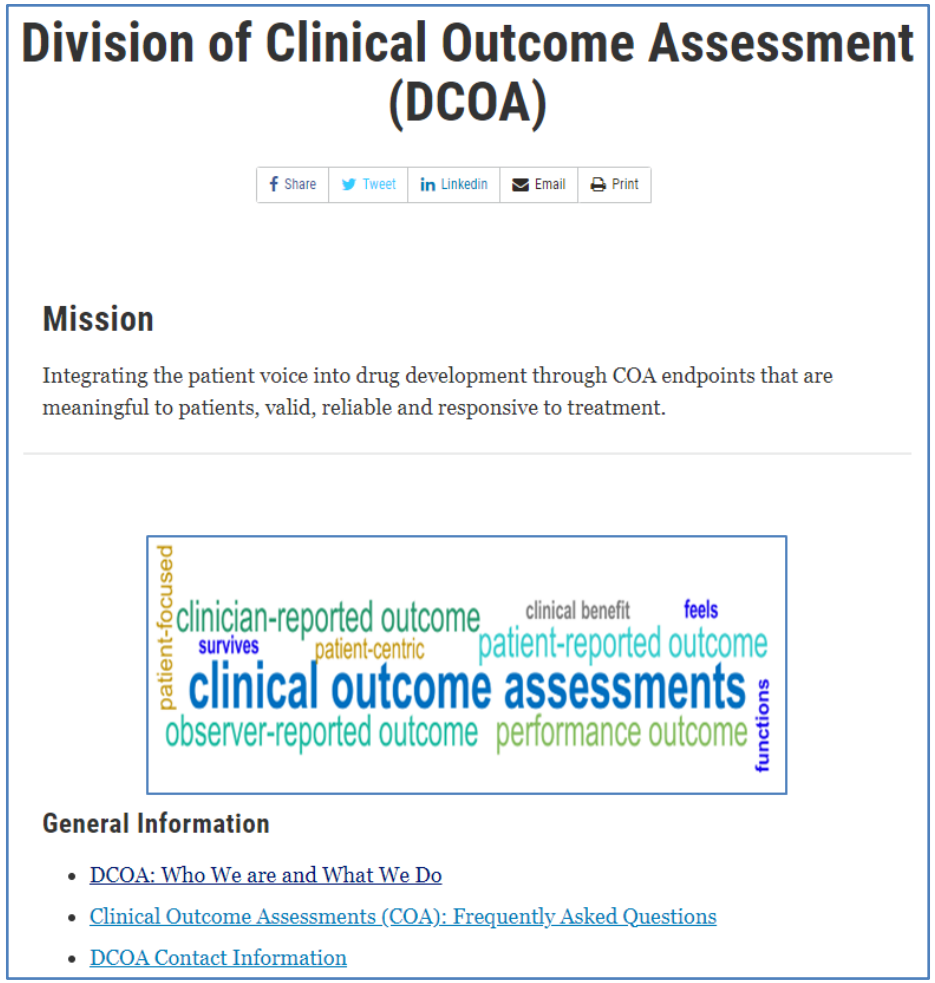
- ADaM IG
- Technical Conformance Guide
- CDISC Guidance for Studies Disrupted by COVID-19
- CDISC Therapeutic Area User Guide for COVID-19

Collaboration with CDISC

- CDISC ADaM Team
- CDISC ADQRS Sub-team
- FDA Clinical Outcomes Assessment (COA) Data Standards collaborating with the CDISC QRS Sub-team

The FDA/CDISC QRS Supplement Review Collaboration

COAs (Clinical Outcome Assessments) at CDER



Division of Clinical Outcome Assessment (DCOA)

Share Tweet Linkedin Email Print

Mission

Integrating the patient voice into drug development through COA endpoints that are meaningful to patients, valid, reliable and responsive to treatment.

General Information

- DCOA: Who We are and What We Do
- Clinical Outcome Assessments (COA): Frequently Asked Questions
- DCOA Contact Information

Mission

Integrating the patient voice into drug development through COA endpoints that are meaningful to patients, valid, reliable and responsive to treatment

https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/division-clinical-outcome-assessment-dcoa

FDA-CDISC QRS Supplement Sub-team Collaboration

After a relevant Questionnaires, Ratings, and Scales (QRS) instrument has been identified for supplement development and approved by the CDISC team leads, the volunteer QRS sub-team members draft the QRS supplement and annotate the instrument with SDTM variables (Controlled Terminology).

The goal of the CDISC QRS internal review is to affirm the following:

- Modeling is logically consistent both internally and with other CDISC standards
- Assumptions listed in the supplement are clear and align with CDISC standards
- Reference documents conform to CDISC quality standards

If the QRS draft supplement is on the FDA priority list (developed by the FDA COA Team), then the QRS instrument is submitted to the FDA as part of the CDISC internal review.

Establishing Priorities for the FDA Review of QRS Draft Supplements

- CDER Office of New Drugs is primarily responsible determining FDA QRS Supplement Priorities
  - New Drug Divisions (Reorganization from 19 to 27 Clinical Review Divisions)
  - https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/office-new-drugs
- FDA priorities incorporate thoughts and perspectives of FDA clinical reviewers and external stakeholders (patient groups, industry, NIH, Critical Path Institute, etc.), taking into account the information/evidence needed to develop new medical products.
- Assessment/scoping of FDA priorities is done on both a regular and as-needed basis.
- FDA only reviews QRS supplements that are described in our Priority List.

FDA QRS Draft Supplement Review Process – Initial Submission

- The CDISC QRS Subteam drafts a CDISC QRS Supplement document for a given instrument (i.e., the annotated CRF, controlled terminology and supplement document).
- The QRS Subteam submits a draft supplement review package, including an annotated CRF, a draft supplement and references in a request (or "Ask") for FDA review that is sent to the Office of Strategic Programs (OSP) in Center for Drug Evaluation and Research (CDER) using the e-mail address established for this work (COADataStandards@fda.hhs.gov)
- This draft review package is uploaded to the COA Data Standards SharePoint site and the OB QRS Review Team is notified.

FDA QRS Draft Supplement Review Process – FDA Review

- In the initial review of the QRS Draft Supplement Package, the OB QRS Review Team reviews the submitted documents, assesses completeness, and identifies any need for SME (Subject Matter Expert) input.
- If required, internal/external SMEs are identified/notified and requested to provide input regarding specific review questions/comments.
- Following a process in which the Review Team collects/flags, coalesces and reconciles comments and issues the final review document is submitted to the OSP for posting to the COA Data Standards SharePoint Site and transmittal to the CDISC QRS Subteam.
- In subsequent review cycles, the CDISC QRS Subteam includes an Excel spreadsheet describing Jira issues and responses to FDA questions/comments in the review package submitted to the Agency.

FDA QRS Draft Supplement Review Process – Finalizing

- The FDA review of QRS Draft Supplements is completed when the Review Team reports to CDISC that there are no additional comments.
- Published QRS Supplements that have gone through FDA review include the following comment in Section 1.1. Representations and Warranties, Limitations of Liability, and Disclaimers --

Although the United States Food and Drug Administration has provided input with regard to this supplement, this input does not constitute US FDA endorsement of any particular instrument.

QRS Supplements Recently Reviewed by FDA

QRS supplements that have been developed following this process in the last year are:

- Ten Meter Walk/Run
- Non-Small Cell Lung Cancer Symptom Assessment Questionnaire (NSCLC)
- Symptoms of Major Depressive Disorder Scale (SMDDS)
- Asthma Daytime Symptom Diary (ADSD)
- Asthma Nighttime Symptom Diary (ANSD)
- Brief Psychiatric Rating Scale 1988 Version (BPRS 1988 VERSION)
- Children's Depression Rating Scale, Revised (CDRS-R)
- Kurtzke Expanded Disability Status Scale (EDSS)
- Hamilton Depression Rating Scale 17-Item (HAMD 17)

Data Science Tools Development

- Help with data visualization, data management and data preparation
- Explore tools to facilitate & enable simulations to evaluate Complex Innovative Clinical Trial Designs (CID), adaptive designs, and Bayesian analyses
- Developed tools/apps to assist with the COVID-19 application reviews
  - Example: Futility analysis for stopping trial
- Pilot of a R shiny server to support R Shiny applications developed by OB and other OTS staff in collaboration with the Office of Computational Science (OCS)

NLP Pilot Review Issues/Experience -- Motivation

- Find and document data quality and data standards issues in NDA/BLA submissions/correspondence/reviews [e.g., data issues/problems that were the reasons for a Refuse-to-File (RTF), Complete Response (CR) or Information Requests (IRs)] and develop metrics for important data standards issues
- Utilize NLP packages within R and Python to build text classification models
- Create a predictive/diagnostic/measurement set of tools/processes for OB and a reference for data issues in submissions, correspondence and reports.
- Identify reasons for “review disruptions” in order to gain “actionable insights” that can be used to address these data review issues
- Potentially applicable to a wide variety of regulatory science and process issues and actions

R for Regulatory Submissions: Challenges and Approaches

Paul Schuette
Scientific Computing Coordinator
FDA/CDER/OTS/OB/IO/AIS
Paul.Schuette@fda.hhs.gov

[The ASA Biopharmaceutical Section Regulatory-Industry Statistics Workshop
September 24, 2021]

Statistical Software Clarifying Statement (1)

"FDA does not require use of any specific software for statistical analyses, and statistical software is not explicitly discussed in Title 21 of the Code of Federal Regulations [e.g., in 21CFR part 11]. However, the software package(s) used for statistical analyses should be fully documented in the submission, including version and build identification."

Schuette, 2021

Statistical Software Clarifying Statement (2)

"As noted in the FDA guidance, E9 Statistical Principles for Clinical Trials …`The computer software used for data management and statistical analysis should be reliable, and documentation of appropriate software testing procedures should be available.' Sponsors are encouraged to consult with FDA review teams and especially with FDA statisticians regarding the choice and suitability of statistical software packages at an early stage in the product development process."

https://www.fda.gov/files/about%20fda/published/Statistical-Software-Clarifying-Statement-PDF.pdf

Schuette, 2021

MSA Framework

TransCelerate's Modernization of Statistical Analytics (MSA) Framework

"A lack of evolution within the pharmaceutical industry's analytic capabilities has given rise to inefficiency and a failure to leverage modern technologies within the clinical development space. Moreover, the limited regulatory perspective on this matter has become a barrier in implementing and leveraging newer analytical software capabilities."

Schuette, 2021

MSA Framework continued

"This Framework is based upon a methodology that establishes the principles of accuracy, traceability, and reproducibility for a modern analytical software environment to demonstrate that results it generates is reliable."

https://www.transceleratebiopharmainc.com/wp-content/uploads/2021/04/MoA-Initiative_MSAFramework_April-2021.pdf

Schuette, 2021

Emerging Trends

Simulations

- Complex Innovative Clinical Trial Designs (CID) Pilot Program
- Bayesian Designs and Analyses

Specialized open-source products such as JAGS and Stan can be used in combination with R, Python.

Analytics & Informatics Staff (AIS)

- Works jointly with all 9 Review Divisions of Biometrics (DBs) in OB
- Enhances/supports statistical IND/NDA/BLA review processes
- Provides leadership in the areas of:
  - Data Standards
  - Data Integrity and Data Quality
  - Data Science and Data Tools
  - Scientific Computing and Statistical Programming


FDA
U.S. FOOD & DRUG
ADMINISTRATION