The Office of Biostatistics Analytics and Informatics Staff

Enhancing the Statistical Review Process

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Disclaimer

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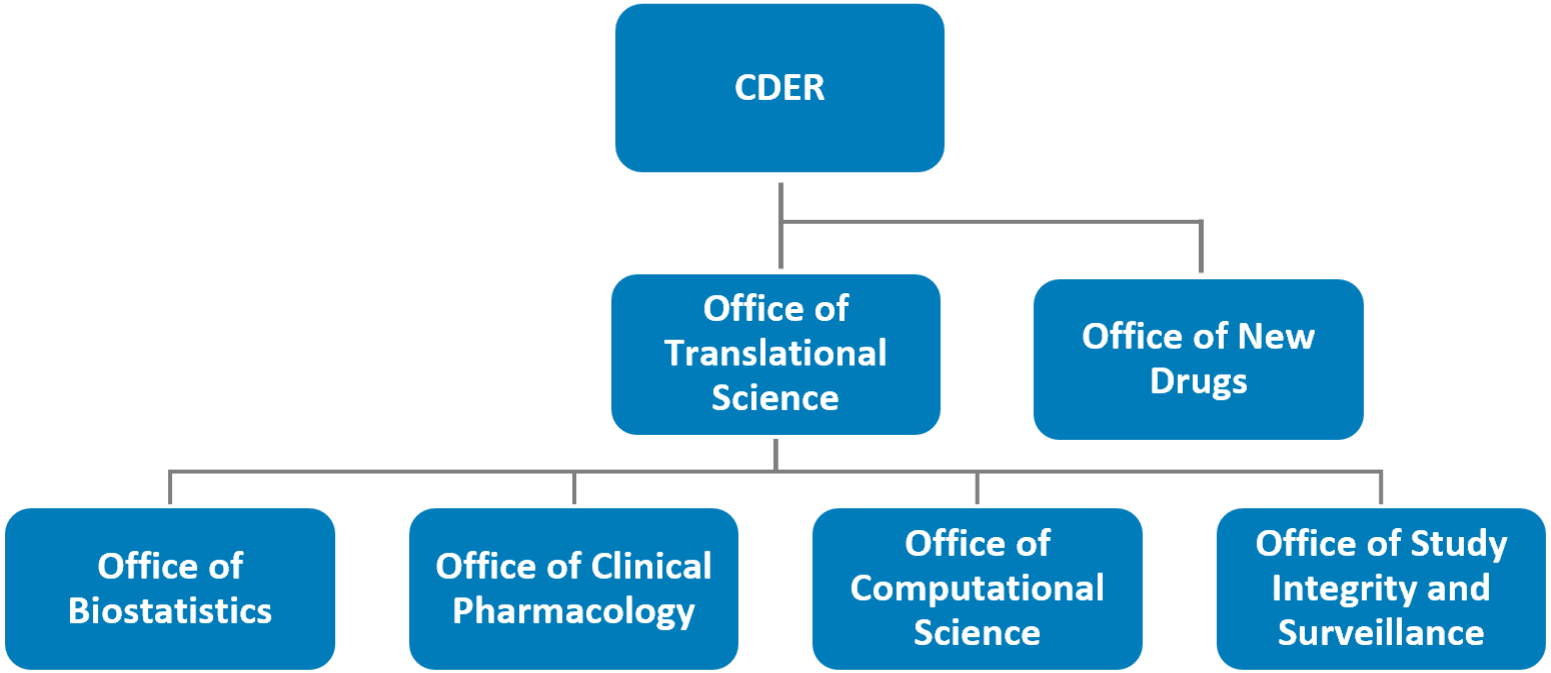
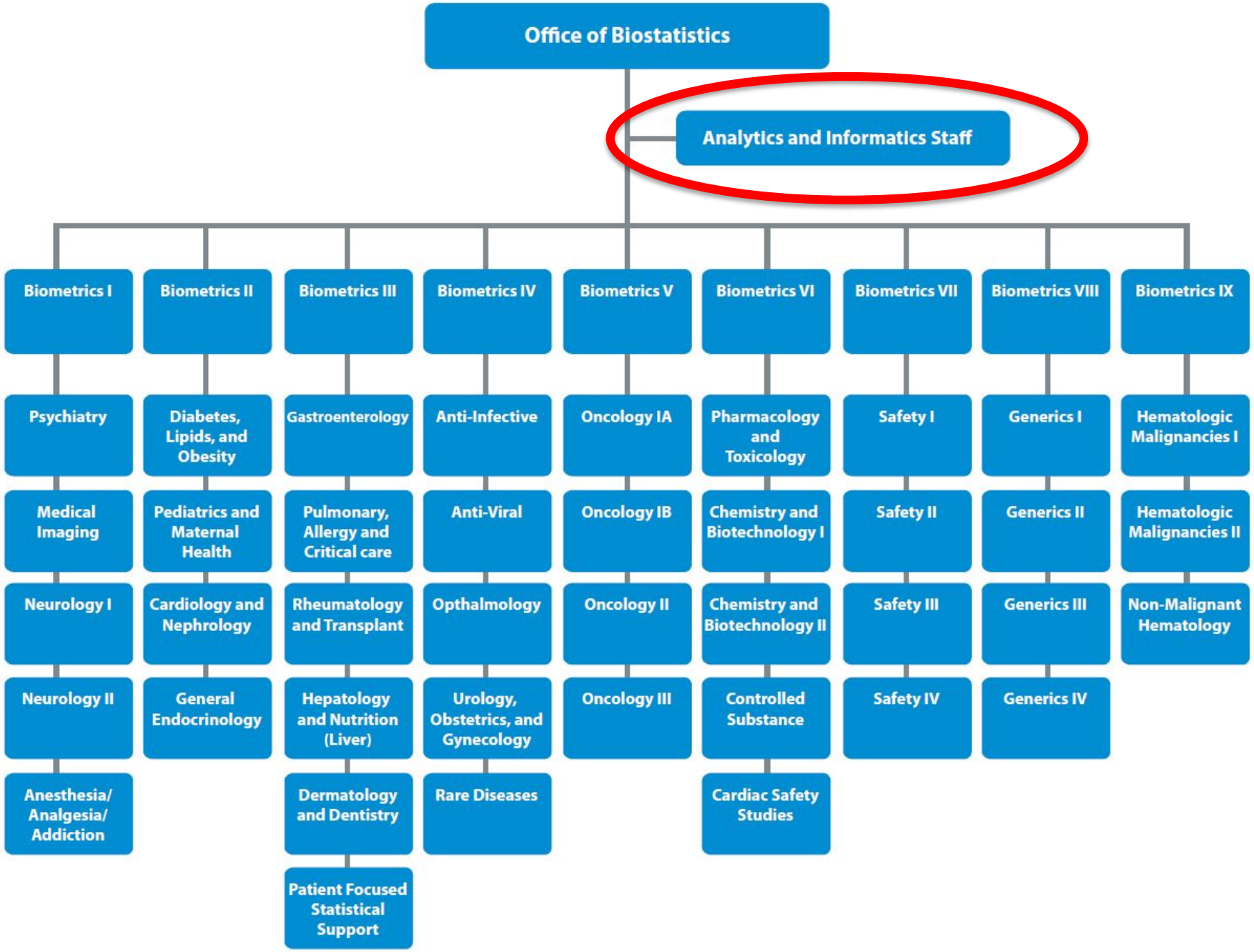
Outline

- Office of Biostatistics (OB) Overview
- Analytics Informatics Staff (AIS)
  - Initiatives and Projects
  - Enhancing the Statistical Review Process
    - Statistical Analyst Role
    - Programming Standardization Initiatives
    - Data Science and Data Tools
    - Scientific Computing

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

OB Analytics and Informatics Staff

- Works jointly with all 9 Divisions of Biometrics (DB)
- Provides leadership in the areas of:
  - Data Standards
  - Data Integrity and Data Quality
  - Data Science and Data Tools
  - Scientific Computing and Statistical Programming
  - Project Management
- Includes Statistical Analysts to enhance statistical IND/NDA/BLA review and special projects

Initiatives/Projects

- Analysis Data Standards (ADS) – PDUFA VI Goal
  - Enhance capacity to support ADS for product development and review
  - Repository of recent review experiences related to standardized datasets and programs
- Roles and responsibilities of Statistical Reviewer and Statistical Analyst
- Standardization and tools development
  - Standard tables and figures for efficacy analyses
  - Library of validated codes/scripts to support standard tables and figures
- Development of standard processes for:
  - Programming best practices
  - Program validation and documentation

Enhancing the Statistical Review Process

The Vision: Who's Doing What?

- Statistical Reviewers
  - Instrumental at planning stage (IND review)
  - NDA/BLA review is multi-faceted
- Statistical Analysts
  - New role to enhance NDA/BLA review

Statistical Analyst Role

- Assessing IND/NDA/BLA/ANDA review processes from a Statistical Reviewer's perspective
  - Pain Points for Statistical Reviewers
    - Checking for data integrity and quality
    - Statistical programming
    - Validating the sponsor's code
  - Analyses that can be standardized
    - Standard tables and figures for efficacy and safety analyses
    - Library of validated code/scripts to support standard tables and figures

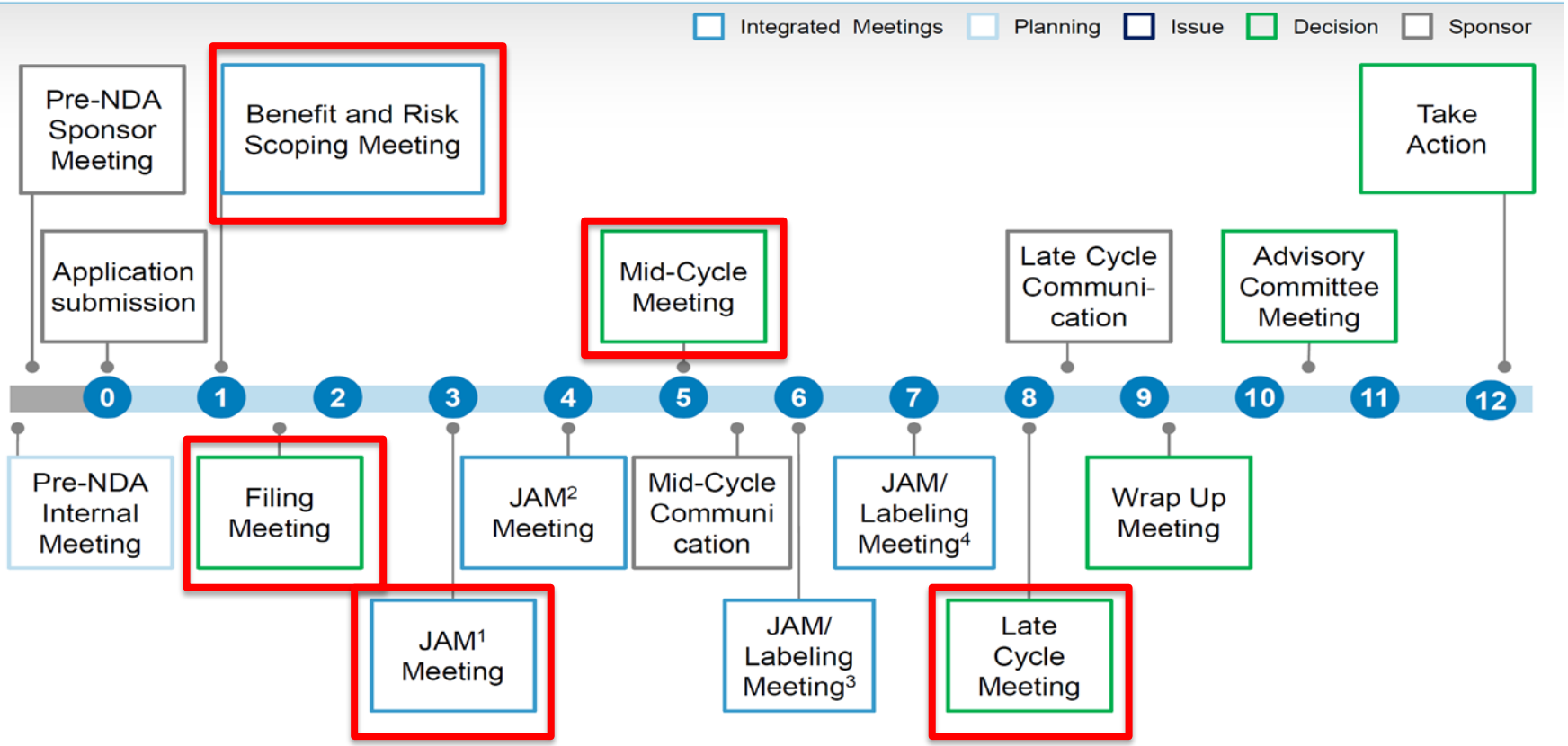
Statistical Analyst Role

- Participate in “Integrated Review Process”.
- Task Support:
  - Assist with IND/NDA/BLA/ANDA Reviews
  - Data Visualization
  - Coding Support/Validation
  - R Shiny App Development

Integrated Review Process

PRE-DECISIONAL – PROPRIETARY & CONFIDENTIAL

Meetings and milestones of the new integrated review process



1 Joint Assessment Meeting 2 Could be used for the Mid-cycle Safety Meeting 3 Could be used for labeling focused meetings

Benefit and Risk Scope Meeting

Objectives

- Establish review team
- Determine review planning and timeline, assess data sufficiency, integrity, and quality
- Characterize preliminary safety profile

To-Do-List for Analyst

- Go through the submission package: study protocol, statistical analysis plan, clinical study report, proposed product label, analysis data reviewer's guide, and define.xml file.
- Check the data quality and integrity

Filing Meeting

Objectives

- Determine fileability and review classification (standard or priority)
- Complete site selection determination (clinical sites for inspection)

To-Do-List for Analyst

- Assist statistical reviewers to complete the “Statistical Review and Evaluation” form
- Continue to assess the data quality and complete basic tables in the form

Joint Assessment Meeting (JAM)

Objectives

- Assess review issues
- Supporting key facts, analyses, principle relating to the review issue assessment
- When review issue assessments are completed, the team may propose possible conclusions and recommendations at the JAM, including labeling options, to prompt discussion with division and office leadership
- Discussion of regulatory impacts considering how the issue is likely to impact the overall benefit-risk balance for the drug and if there are additional analyses that could help better assess the impact on benefit or risk
- Identify labeling items for review team discussion

To-Do-List for Analyst

- Data quality/integrity
- Study site selection for inspection
- Issues with study design, such as screen failure patterns
- Missing data patterns
- Safety issues-check major AE, i.e., death
- Baseline characteristics and demographic tables
- Verify sponsor's results for primary and key secondary endpoints
- Alternative efficacy analyses as discussed with statistical reviewer
- Subgroup analyses—race, sex, age, regions

Mid-Cycle Meeting & Communication

Objectives

- Finalize conclusion and rationale for all identified review issues
- Work toward resolving review issues, including labeling and post-approval planning
- Major labeling issues identified

To-Do-List for Analyst

- Additional analyses as requested by statistical reviewer and clinical review team
- Tables and/or graphs for the review template

Late-Cycle Meeting

Objectives

- Finalize labeling negotiations
- Finalize risk mitigation strategies
- Pharmacovigilance plan determination

To-Do-List for Analyst

- Finalize tables and/or graphs for the review template

Programming Standardization Initiatives

- Developed standard efficacy and safety tables and figures
- Developed file naming convention, file structure and permissions for repository of NDA/BLA review work products
- Developed SOP for program validation and documentation
- Developed programming best practices guideline document
- Developed SOP for simulation plan
- Library of validated code/scripts/RShiny apps

Programming Standardization Initiatives

- Standard Tables and Figures Work Group
  - Draft a manual to standardize commonly used tables and figures to be used in review-related documents.
  - Provide general recommendations on the constructs of tables and figures.
  - Once tables and figures are finalized, statistical analysis code will be developed, validated, and deployed to be used in the review related work.
- Tables and Figures (Efficacy and Safety)
  - Develop “core” tables and figures
  - Table aesthetics, formats, and structures (shells, etc.)
- Macros/Scripts
  - Create a repository of standardized and validated code
  - Scripts will be available for both SAS and R
  - R-Shiny

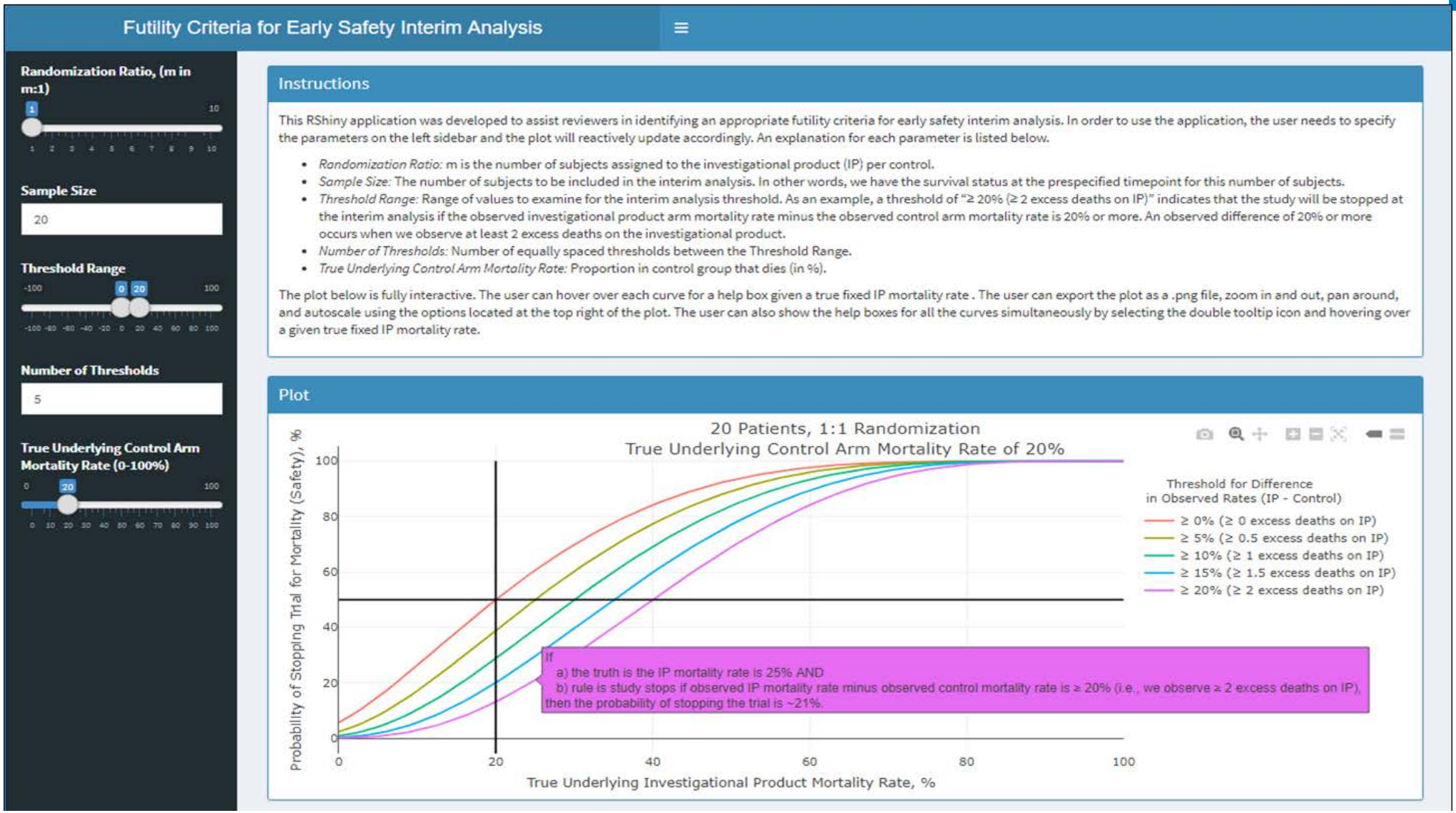
Data Science and Data Tools

- 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) and Office of Innovation in OIMT
- Help with data anomality, data visualization, data management and data preparation
  - Example: CluePoints CRADA
- Facilitate using simulations to evaluate Complex Innovative Designs, Adaptive Designs, and Bayesian analyses
- Develop tools/apps to assist with the COVID-19 application reviews
  - Example: Futility analyses for stopping trial

Futility Criteria for Early Safety Interim Analysis

- Hosted on Rstudio Connect by the Office of Computational Science (OCS).
- Describes stopping rules based on mortality rates and can be adapted to describe any binary endpoints.
- Used routinely in review of COVID-19 submissions to formulate recommendations to sponsors regarding safety and/or futility stopping criteria.

Futility Criteria for Early Safety Interim Analysis Demo



CluePoints CRADA

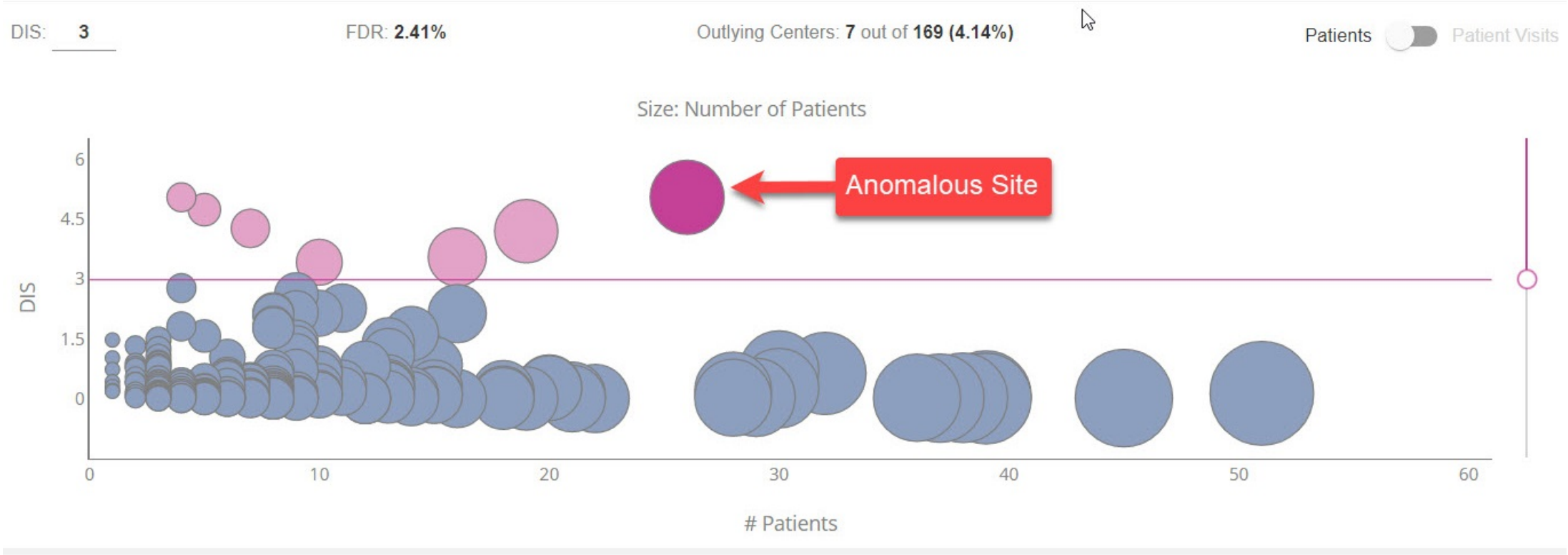
- Since 2016, OB has been working with CluePoints via a Cooperative Research and Development Agreement (CRADA) for site level data anomaly detection using subject level data.
- Goals:
  - Improve data quality and data integrity.
  - Assist site selection for inspection.
  - Assist reviewers by identifying potentially problematic sites for sensitivity analyses.

CluePoints CRADA

Statistical Monitoring Applied to Research Trials (SMART)

- Unsupervised Machine Learning.
- Applies battery of statistical tests (missing value, categorical, binary, means, standard deviations, date, outlier and propagated values) to SDTM domains.
- Compares subject/site level values for a variable to all sites in trial.
- Computes a p-value corresponding to the site and the test.

CluePoints CRADA Demo



Data Standards

- Mini training videos for ADaM and SDTM topics
- QRS and ADQRS data supplement reviews
- Statistical Review Info-Base (StatRIB) – repository of recent review experiences related to standardized datasets and programs to identify issues associated with regulatory submissions
- Natural Language Processing Pilot on Information Request from industry

Scientific Computing

- Software
  - SAS, SAS Studio, R, Rstudio
  - EAST, StatXAct, LogXact
  - nQuery, PASS, FACTS
  - MATLAB, Mathematica
  - LaTeX, MikTeX, WinEdt
  - Shiny apps (in progress)
- Hardware
  - Scientific Laptops (larger, more computing capability)
  - OB Shared Scientific Workstations (more RAM, more cores)
  - FDA High Performance Computing Environments: users need to go through approval process

Scientific Computing

- Programming Expertise:
  - Simulations
    - Help with simulations to verify operating characteristics for complex designs (Bayesian and Adaptive designs)
  - Data Visualization
    - Heat maps
    - Forest plots
    - Line plots

Analytics & Informatics Staff (AIS)

- Enhance statistical review process
- Provide expertise in the following areas:
  - Data Standards
  - Data Integrity and Data Quality
  - Data Science and Data Tools
  - Scientific Computing and Statistical Programming
  - Project Management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