Conducting Statistical Reviews at CDER:
Present State and Hopes of a Collaborative Future State

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Disclaimer

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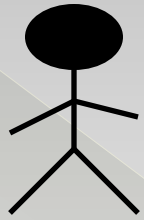
Outline

- Background on CDER Review Environment
- Today's CDER Statistical Reviewer
- The Future CDER Statistical Reviewer
- Concluding Remarks

Today's CDER Statistical Organization

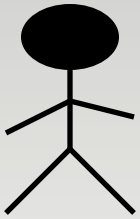
Office Level



OD: Bob O'Neill, PhD

DOD: Ed Nevius, PhD

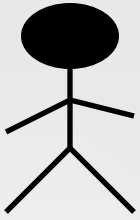
Division Level



Seven Divisions

- 1 Director (DD), 1 Deputy (DDD)

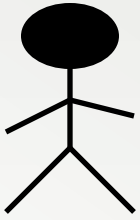
Team Level



Three to Four Teams per Division

- 1 Team Lead (TL) per Team

Reviewer Level



Four to Eight Reviewers per Team

~ 150 reviewers

Operational Aspects w/in CDER

- Reviewers work independently (for the most part) with coordination from Team Lead
- Typically a primary review (Reviewer), secondary review (TL), and occasionally tertiary (DD) on IND's and NDA's
- Statistical reviewers work closely with the medical divisions which are organized by therapeutic areas. Statistical Reviewer conclusions are based on statistical reasoning and medical division uses this to form a regulatory action.

Software Solutions

- Reviewers have access to a broad range of software packages to analyze data
  - Needs are often based on training
    - Medical: JMP, jReview, WebSDM, Excel, others
    - Statistics: SAS, R, S-Plus, East, Stata, others
- Review work is typically done on the standard issue personal laptops
  - More recently, have access to CDRH Sun Grid Engine & super computing environment for more intensive work
- Complex analyses are typically done by statistical reviewers
  - May be requested by medical officer

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Today's CDER Statistical Reviewer

- Data Manager
- Trial Specialist
- Researcher
- Critic
- Data Analyst
- Medical Writer

Today's CDER Statistical Workload

NDA Reviews

- Multiple NDA's
- Often times 3+

IND Reviews

- Multiple IND's
- Includes SPA's
- New methodology assessments

Research/Other

- Research Grants
- Internal Working Groups (Guidance)
- Collaborations

The NDA Review – Today's Practice

- Reliance on sponsors to provide electronic data sets
  - Ideally, moving towards CDISC standards; namely, ADaM data sets
  - Clear **Define** files enhance understanding of data structure
  - Communication with sponsor's at Pre-NDA meetings about data structures improves process
- Reviewer deconstructs analysis conclusions, conducts additional analysis, provide written documentation of the findings
  - Coding is done by the reviewer

NDA Review Clock

- Standard Review: 10 month clock
- Priority Review: 6 month clock
- Milestones within the standard review clock
  - *Day 0 – 45*: Identify sites for Division of Scientific Investigations
  - *Day 45*: Internal Filing Meeting
    - Determine if application is "fileable"
    - Request additional information from sponsor
  - *Day 74*: Division provides 74 Day Letter to Sponsor
  - *Month 5*: Mid-cycle review
    - Status of review to Division
    - Review issues that may affect regulatory decision should be identified
  - *Month 8*: Complete primary review
  - *Month 9*: Internal labeling discussions

NDA Review – Need for Improvement

Need for improvement within the current review environment

- *Little* to *no* information sharing (code or otherwise) among reviewers
- Lack of reviewer *analysis tools*
- Inefficient process – a lot of *repeated* work
- Potential for *transcription errors* when the reviewer serves as the interpreter between analysis software and written report
- Allows for less think time for complex issues arising in all areas (IND's, NDA's, research, etc.)

Example: Assess Change in SBP

- Background
  - Product is administered at baseline (three measurements) and if no response it is administered a second time at time tx.
  - Five studies included in ISS
- Study Report Contents of the ISS:
  - 40+ pages of *just* table listings!
  - Tabled output was difficult to assess temporal relationship.
  - No presentation comparing those with one or two administrations
- **Refined Question**: How does blood pressure (systolic) change across time and does the second administration alter it?

Example: Continued (1)

Options to address refined question

1. Reviewer must manipulate the data (even with SDTM this requires much data manipulation), explore the data, and then summarize the findings (e.g. graphic).
2. Ask the sponsor to run the analysis and report the findings.
3. Hybrid: ask for ADaM data set (defining desired structure and content) which can easily be assessed with analysis software.

But, these still don't completely aid the statistical reviewer…

Example: Continued (2)

Problems with the approaches

1. Reviewer manipulating the data and doing analysis
   - Resource intensive; no external validation of data manipulation; requires solid programming skill set
2. Ask the sponsor to run the analysis and report the findings.
   - Subject to sponsor's representation of the data results; no data set to confirm results; lack ability to present alternate presentations
3. Hybrid: ask for ADaM data set
   - Reduces resources; still requires programming skill set to present the data (what if complex analysis?)

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Future CDER Statistical Reviewer

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Trial Specialist

Researcher

Critic

Data Analyst

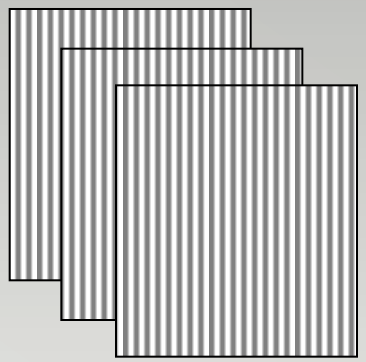
Medical Writer

Getting to the Future State…

Needs

1. Standard Data Sets – ADaM discussions *prior* to submission are important!
   - Study Data Specifications Guidance: http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM199599.pdf
2. Improved communication between reviewers (medical, statistical, others)
3. Access to analytical tools/solutions to perform critical analyses
4. Training

How The Future Might Look



Database

- SDTM
- ADaM

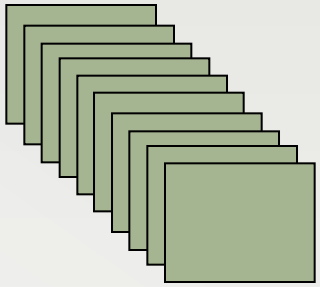
source

Analytical Engine(s)

Script/Code/Tools

- manipulate data
- run analyses
- generate tables
- generate graphics

export



Tables

Graphics

source

NDA Review

How The Industry Can Help

- First and foremost, move towards adopting and submitting data following CDISC data standards
  - Communicate with Divisions about data submission needs *prior to submission*
  - Discuss ADaM structure; provide description of structure *prior to submission*
  - Provide descriptive Define files in submission
- Consider moving towards a collaborative paradigm where code/tools are shared and discussed in a public environment
  - Benefit of not having to reinvent the wheel
  - Can adopt best practices of presenting data to FDA
  - Everyone (reviewers and industry) work from a common public set of tools and information

Collaborative Environment(s)

- Building on successful applications which rely on a community, goal is to have a community share materials
  - **Code Repository**
    - Analytical tools developed for custom purposes are shared in a public repository
    - Version control on tools; validation information provided; rating scale for tools; meta data specifications
    - Stay tuned!
  - **FDA/Industry/Academia Safety Graphics Working Group**
    - Developing a palette of graphical approaches for presenting safety data
    - Graphical approaches will be developed; will require help of statistical programming community to develop code for implementation
    - http://ctspedia.org – Graphics section will be live SOON!

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Concluding Remarks

- Despite working in non-optimal conditions, CDER statistical reviewers are able to get the job done
  - There is room for improvement
  - Efficiencies can be gained
  - Need for more "think time"
- Sponsor organizations can help/facilitate NDA/BLA review
  - Data following data standards helps a great deal
  - Moving towards a collaborative state will result in all parties using the same tool set; allows familiarity and improves reproducibility

Thank You!

Feel Free to Contact Me

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