FDA’s Approach to R Shiny Standardized, Interactive Tools

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DISCLAIMER

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.
HIGHLIGHTS

We will focus on a (developing) model to illustrate how staff at the FDA:

1. Identify existing processes for streamlining
2. Develop standardized tools for higher efficiency and productivity
3. Communicate and share information with colleagues in different disciplines
FDA BACKGROUND
## FDA ACRONYMS

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Phrase</th>
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<tbody>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>CDER</td>
<td>Center for Drug Evaluation and Research</td>
</tr>
<tr>
<td>OB</td>
<td>Office of Biostatistics (CDER)</td>
</tr>
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<td>NDA</td>
<td>New Drug Application</td>
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<td>BLA</td>
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<td>NME</td>
<td>New Molecular Entity</td>
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<tr>
<td>CMC</td>
<td>Chemistry, Manufacturing, and Controls</td>
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1. IDENTIFY EXISTING PROCESSES FOR STREAMLINING
• Statistical review
• Medical review
• CMC review
• etc.
Statistical reviews can often share similar analyses and visualizations especially within the same therapeutic area.

Statistical reviewers are responsible for evaluating clinical study designs, statistical analyses, and other statistical practices in medical product reviews.

Statistical reviewers conduct their own data processing and analyses in software such as R and SAS.

Statistical reviewers have the flexibility to write their own code but outputs may lack visual consistency.

Great opportunity for some standardized tools to step in to streamline common, routine tasks.
FOUR SCENARIOS WHERE SHINY APPS ARE APPLICABLE

SCENARIO 1: Planning of a clinical study: multiple testing

SCENARIO 2: Evaluation of a clinical study: patient experience

SCENARIO 3: Evaluation of a clinical study: subgroup analysis

SCENARIO 4: Project management
Scenario 1
Planning of a clinical study: multiple testing

A statistical reviewer coauthored a paper on a novel multiple testing procedure.

Audience of the paper may better understand the procedure if they can test it out.

Other reviewers want to have this procedure as an option when faced with multiplicity issues.

The authors did not have any code for the procedure to accompany their paper.

We did not have an existing tool that can perform the methodology.

SOLUTION: MULTIPICLITY SHINY APP
Scenario 2
Evaluation of a clinical study: patient experience

A statistical reviewer produced several novel visualizations in her patient-reported outcomes (PRO) research.

She wanted these visualizations to be reproducible by her FDA and industry colleagues.

FDA reviewers are encountering the need to produce similar visualizations in reviews and research work.

These visualizations have many display options, which can equate to tedious coding.

We did not have an existing tool that can easily produce these PRO visualizations.

SOLUTION: PRO SHINY APP
Scenario 3
Evaluation of a clinical study: subgroup analysis

A statistical reviewer manually inputs SAS output results into R to generate a forest plot.

Manually entering results can be tedious and typos can occur.

Other FDA reviewers in his division can benefit from a streamlined tool.

These visualizations have many display options, which could equate to tedious coding.

We did not have an existing tool that can provide the needs of the reviewer.

SOLUTION: FOREST PLOTS SHINY APP
Scenario 4
Project management

Reviewers often have multiple concurrent projects that they are working on.

Different teams and divisions have their own method of keeping track of projects.

A neat output showing all concurrent projects and milestones is nice for weekly meetings and annual appraisals.

Supervisors would like to get a snapshot of their team's workload in order to properly assign work.

There are tools available but resources and time are limited at the agency.

SOLUTION:
PROJECT MILESTONES SHINY APP
2. DEVELOP STANDARDIZED TOOLS FOR HIGHER EFFICIENCY AND PRODUCTIVITY
WHY WE WENT WITH SHINY

- FDA *does not* favor one programming language over another
- Shiny is based on the open source software called R, which many statistical reviewers have been using in reviews and research work
- R is widely used in the statistics and data science community
  - R in Finance, R in Medicine, R in Pharma, etc.
- Shiny allows for flexible web application development
  - HTML, CSS, JavaScript
  - Integration of other languages, too
- Other alternatives include Python Dash, Tableau, and maybe SAS
1. A (TRADITIONAL) SHINY APP

- **REQUIRED**
  - ui.R
  - server.R
  - app.R

- **OPTIONAL**
  - HTML
  - CSS
  - JS
2. A SHINY DOCUMENT

Shiny app folder → Document.Rmd

REQUIRED
- Regular R code
- UI code
- Server code

OPTIONAL
- HTML
- CSS
- JS

Slide 19 of 36
This demonstrates how a standard R plot can be made interactive by wrapping it in the Shiny `renderPlot` function. The `selectInput` and `sliderInput` functions create the input widgets used to drive the plot.

```r
{r, echo=FALSE}

inputPanel(
  selectInput("n_breaks", label = "Number of bins:",
              choices = c(10, 20, 35, 50), selected = 20),
  sliderInput("bw_adjust", label = "Bandwidth adjustment:",
             min = 0.2, max = 2, value = 1, step = 0.2)
)

renderPlot(
  hist(faithful$eruptions, probability = TRUE, breaks = as.numeric(input$n_breaks),
       xlab = "Duration (minutes)", main = "Geyser eruption duration")
  dens <- density(faithful$eruptions, adjust = input$bw_adjust)
  lines(dens, col = "blue")
)
```
PRO SHINY APP SCREENSHOTS
1. What this app does

This app focuses on producing visualizations and summary tables to analyze patient-reported outcomes data as a web application, developed using the Shiny library in R. Users are required to upload their own datasets into the app and specify the data configurations. Example visualizations include the distribution of patients’ greatest deterioration or greatest improvement in patient-reported physical function from baseline, a line plot of PRO score over time by study arm with bootstrapped confidence intervals at each assessment time point. Users can download the visualizations produced by this app. In addition, users are encouraged to provide feedback on their experience and inputs on future developments after using the app.

2. Structure of app

Navigation of this app can be done through the tabs at the top panel:

1. **Overview**: Brief explanation of the app’s purpose, structure, and requirements.
2. **Data**: Users are required to upload their own dataset and make specifications on their data. They can proceed to the output of the uploaded dataset for verification of valid upload.
3. **Exploratory Analysis**: Display of sample sizes, missing data, a swimmer’s plot, and tables of improvement/deterioration.
4. **Score/Change (categorical)**: A variety of categorical trend graphs.
5. **Score/Change (numeric)**: A variety of numeric trend graphs, distributions, ECDF plots, etc.
6. **Feedback**: Likert scale items and a text field that help capture user experience and suggestions.

3. Data processing

The dataset must be either in XPT or CSV format. Each row should represent a record for each subject’s visit. At a minimum, the required variables for each row include:

- Unique subject ID
- Study arm
- Visit
- Baseline total score
- Total score (at that visit)
- Individual baseline item scores (optional)
- Individual post-baseline item scores (optional)

Documentation on an example of how to process raw datasets to create a suitable dataset for the app is available at the link below:

Data processing documentation hosted on CDERWiki

4. Reference

- Information on the formulas for the bootstrap calculations can be found in Chapter 5 of Davison and Hinkley’s Bootstrap Methods and their Application (1997).
- Information on the color palettes are available at this link:

Color palettes using the ‘wesanderson’ R package
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</table>

**Red:** These are the required variables.

**Green:** These are the individual item variables (optional).

**Blue:** Data collected on each subject at each visit; number of records may differ across subjects.
Please upload a processed data set to be used in the graph sections. Your processed data set should be in wide format where each row is a record collected on a patient at a study visit/time point. At a minimum, your data set should contain the following variables:

- Unique subject ID
- Study arm
- Study visit
- Baseline comprehensive score
- Post-baseline comprehensive score
- Baseline individual scores
- Post-baseline individual scores

In Step 5:
- Specify a seed of your choice or use the default for the purpose of bootstrapping in the graph sections
- Enter abbreviations for the study arms in the data set. They are limited to three characters.
- Specify if you would like grayscale or color graphs in several of the graph sections

In Step 6:
- Specify the baseline visit category
- Specify the order of visits in the data set. You have the option to specify the filler visits, which are visits to bridge the gap between the visits in the data set. Then you will again have to specify the order of visits with the filler visits that you have added.
- Specify any visits after the last treatment cycle (optional). The continuous trend graphs will show a break in the trend between visits during the treatment cycle and after the last treatment cycle. If your specified visits are not evenly spaced, there will further be a break in trend between these visits.
**Step 1: Dataset**

Upload dataset:
XPT

**Step 2: Study Info**

**Step 3: Demographics**

- Unique subject ID
- Study arm
- Visit
- 'Units' of visit variable
- Baseline score (comprehensive)

**Step 4: Score variables (numeric)**

- Post-baseline score (comprehensive)
- Baseline items
- Post-baseline items

**Step 5: Graph Settings**

- Set a random seed
  - 10993
- Response variable
- Graph colors
  - Grayscale
  - Color

**Step 6: Visit Order**

- Baseline visit
- Order of visits
- Any filler visits?
- Order of visit(s) after last treatment cycle (if any)
- Are these visit(s) spaced at the same set amount of time for each patient?
Sample Size Info
Please enter the (desired) sample size at each visit for each study arm. If you enter only one sample size value for each study arm, the graph will use that one sample size value across all visits (within each arm).

Sample sizes for Placebo:
500,400,400,300,250,250,200,200,200

Sample sizes for Treatment:
500,400,400,300,250,250,200,200,200

Outcome measure
Percent of missing

GENERATE GRAPH

DOWNLOAD GRAPH
Mean change in PF score from baseline, by study arm

With accelerated bias-corrected 95% bootstrap confidence intervals.
Where mean change in PF score from baseline to cycle m = mean(Cycle m PF score) - [Baseline PF score]

Improvement

Deterioration

Cycle

Study Arm
Placebo Treatment
Sample interpretation language:

Condition for using sample interpretation language:

Note:

Cautionary Note:

Example (tolerability data for an approved drug):
3. COMMUNICATE AND SHARE INFORMATION WITH COLLEAGUES IN DIFFERENT DISCIPLINES
SHARING SHINY APPS

**What to do**
- Deploy on a server
- Deploy with RStudio services

**What not to do**
- Share apps on a shared drive (interim solution)
- Send apps through emails

**WHY?**

**Advantages**
- Traffic tracking
- Easy access
- Version control (packrat)

**Disadvantages**
- More prone to errors
- Version issues
- Users can “mess up” your code
COMMUNICATION MEDIA

Reference: https://thebusinesscommunication.com/types-of-media-communication/
FDA’S VERBAL COMMUNICATION

**ORALLY**
- Shiny users group
- FDA town halls
- FDA internal conferences
- External conferences (such as FCSM)

**IN WRITING**
- Shiny wiki
- OB quarterly newsletters
- FDA daily announcements
- Code documentation
SHINY USERS GROUP

**Goal:** a cross-center initiative to promote and increase the development of standardized clinical review tools

- Initiated in May, 2017
- Includes Shiny developers at various levels and users including statistical and medical reviewers
- Each session involves topics such as app demos, Shiny challenges, deployment options, etc.
- Provides training such as from RStudio
SUMMARY

1. Identify existing processes for streamlining
   ▪ Four scenarios at the FDA where we developed a Shiny app to streamline each process

2. Develop standardized tools for higher efficiency and productivity
   ▪ Two methods to create a Shiny, interactive environment
     ▪ PRO Shiny app

3. Communicate and share information with colleagues in different disciplines
   ▪ Methods to deploy Shiny apps
   ▪ FDA’s communication approach
THANK YOU!

QUESTIONS?

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