U.S. FOOD & DRUG ADMINISTRATION

FDA's Approach to R Shiny Standardized, Interactive Tools

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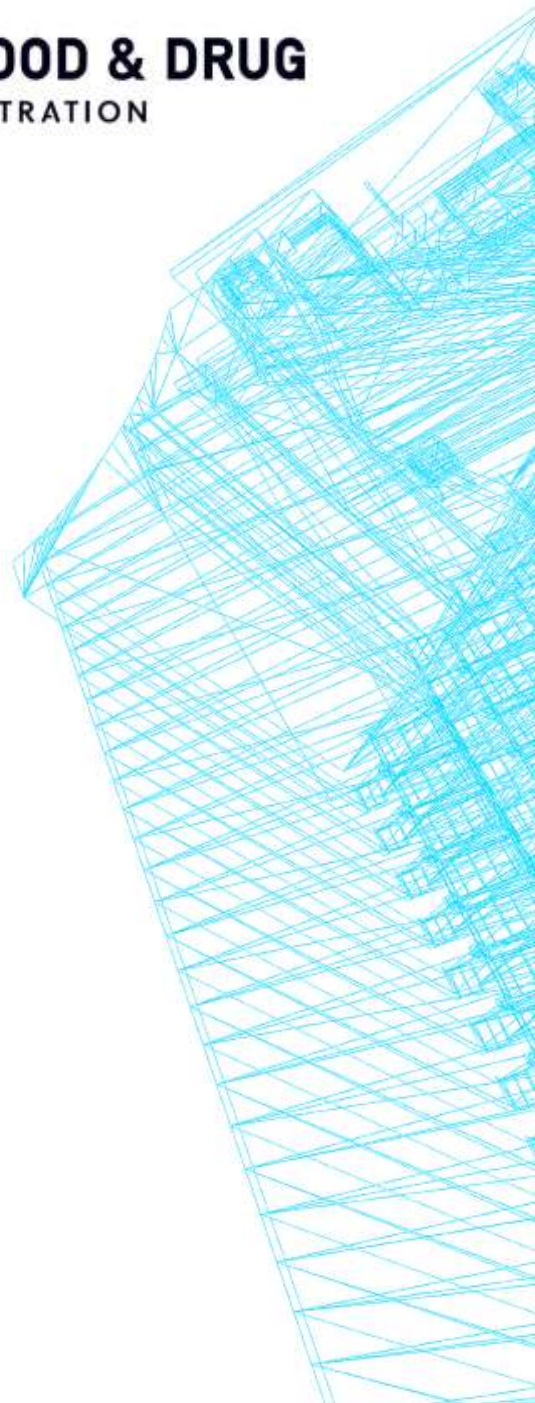

DISCLAIMER

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

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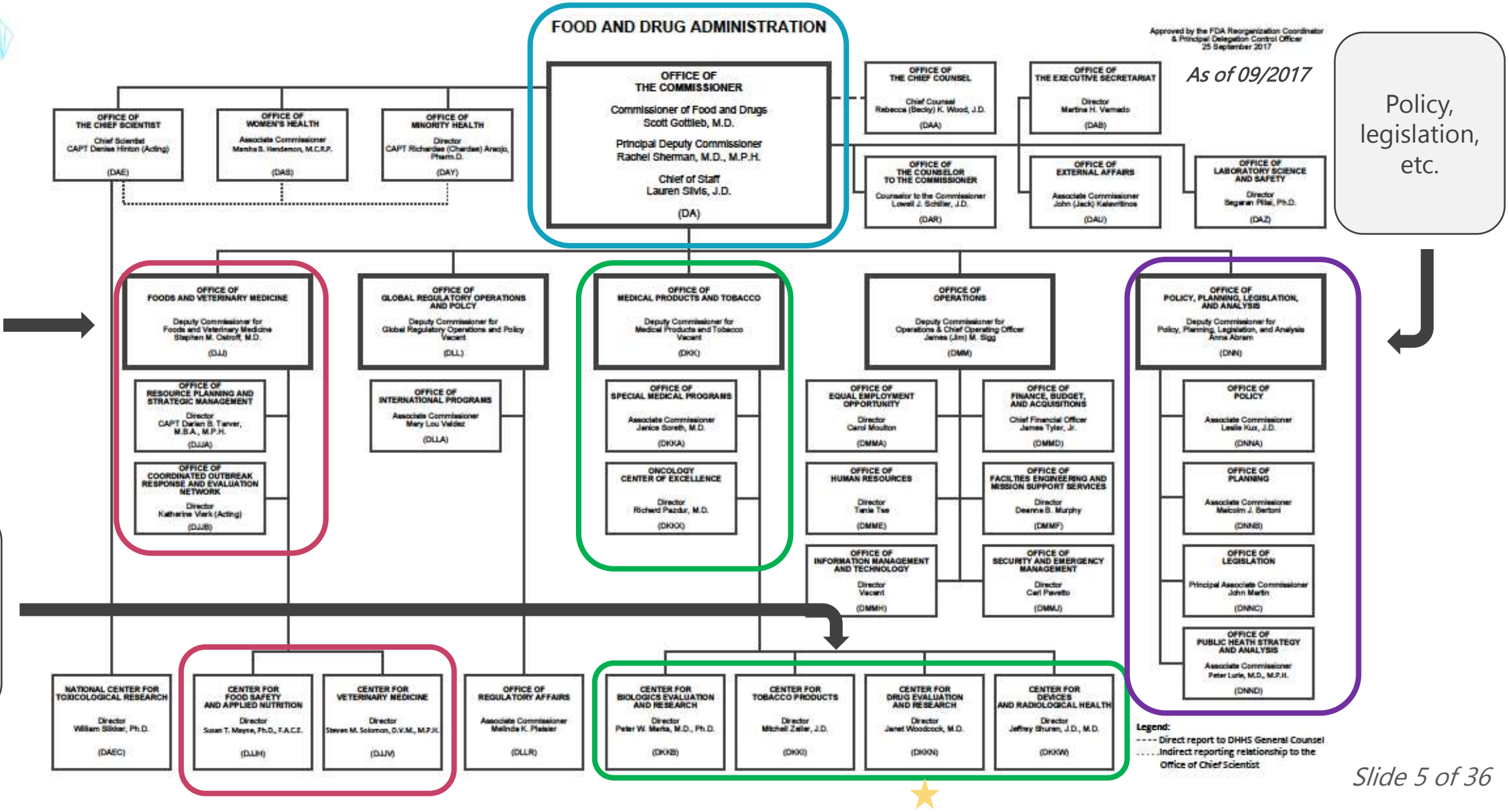
FDA BACKGROUND

FDA ORGANIZATION HIGHLIGHTS

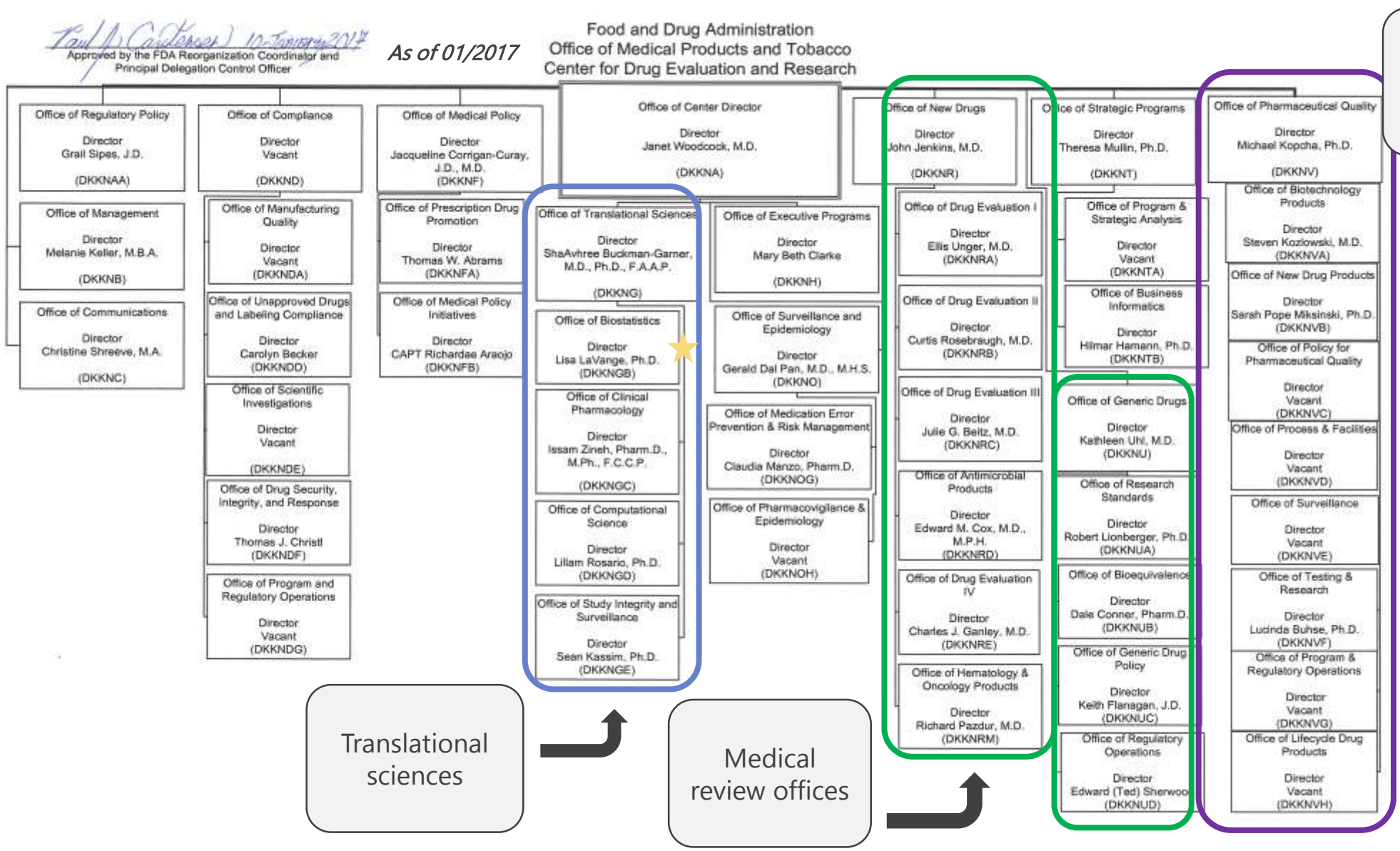


Food and animals

Different centers for medical products

Policy, legislation, etc.

CDER ORGANIZATION HIGHLIGHTS



FDA ACRONYMS

Acronym	Phrase
FDA	Food and Drug Administration
CDER	Center for Drug Evaluation and Research
OB	Office of Biostatistics (CDER)
NDA	New Drug Application
BLA	Biologic License Application
NME	New Molecular Entity
CMC	Chemistry, Manufacturing, and Controls

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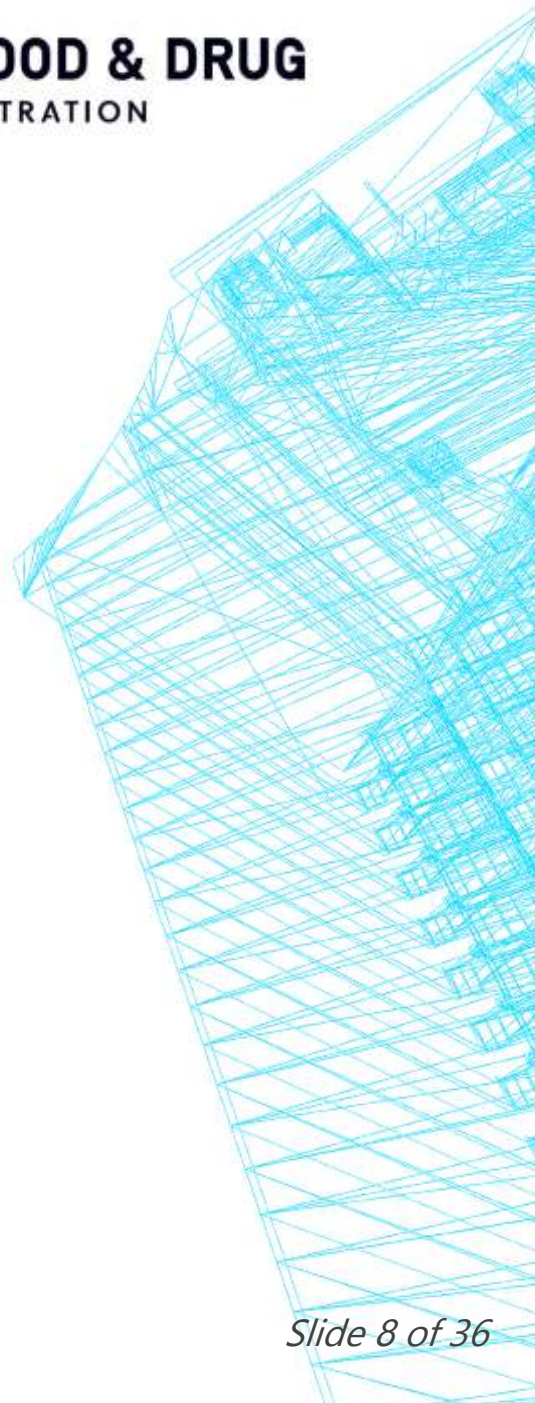
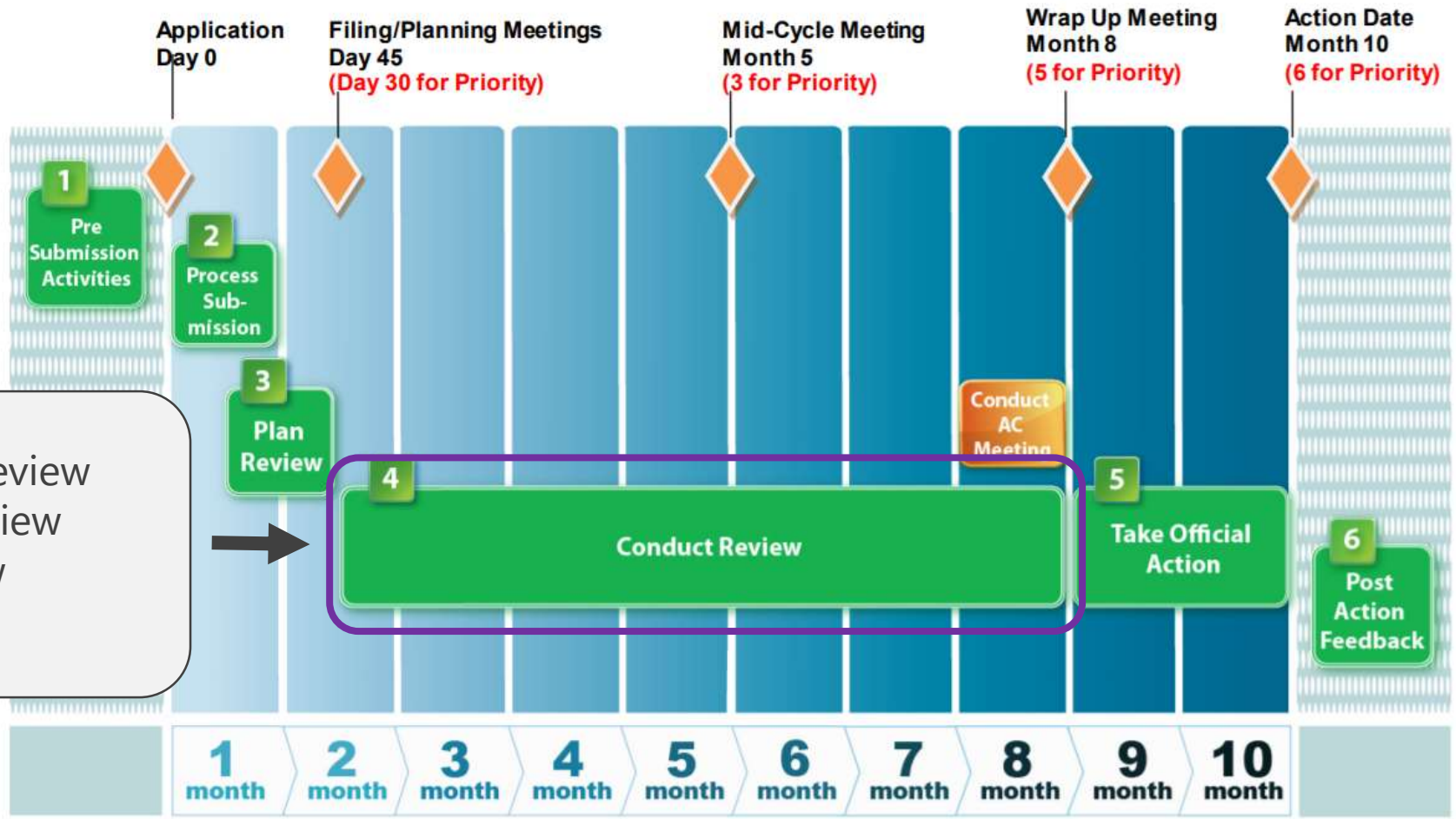
1. IDENTIFY EXISTING PROCESSES FOR STREAMLINING



Overview of the NDA/BLA Review Process and Major Steps for Completing the Review

Under PDUFA V



- Statistical review
- Medical review
- CMC review
- etc.

Note: The timeline for review of NMEs/BLAs under PDUFA V's "Program" Review extends the *Conduct Review* Phase by two months.

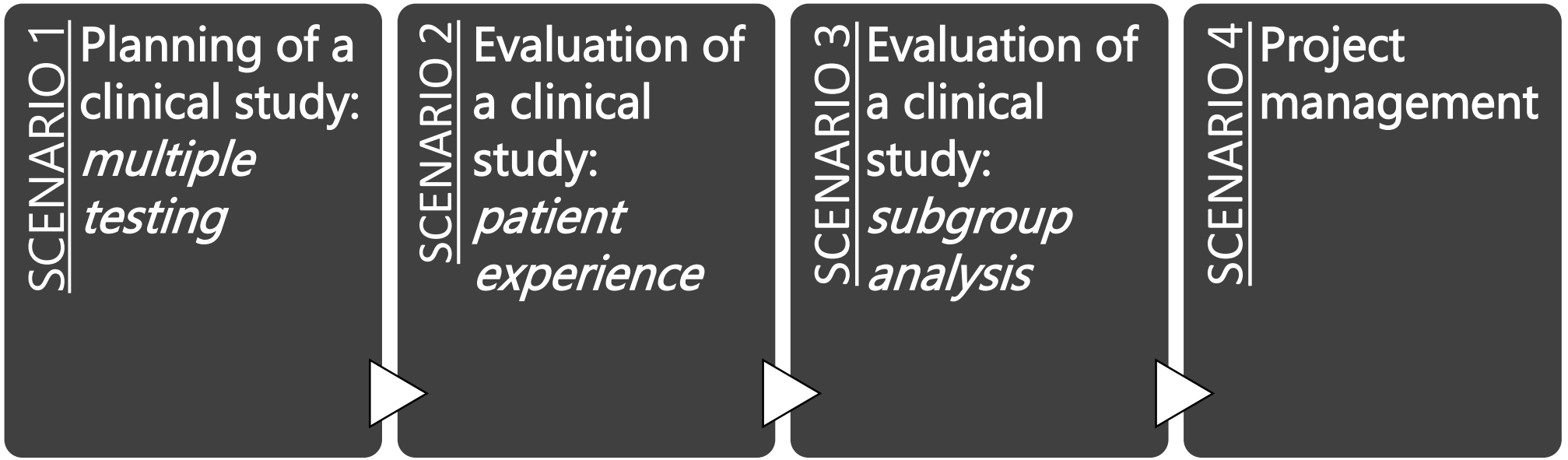
See Appendix A for a timeline diagram for PDUFA V.

Reference: CDER 21st Century Review Process Desk Reference Guide
https://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/UCM218757.pdf

STATISTICAL REVIEWS & REVIEWERS

- 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

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

SOLUTION: MULTIPLICITY SHINY APP

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.

Scenario 2

Evaluation of a clinical study: patient experience

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

SOLUTION: PRO SHINY APP

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.

Scenario 3

Evaluation of a clinical study: subgroup analysis

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

SOLUTION: FOREST PLOTS SHINY APP

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.

Scenario 4

Project management

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

SOLUTION: PROJECT MILESTONES SHINY APP

- **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.

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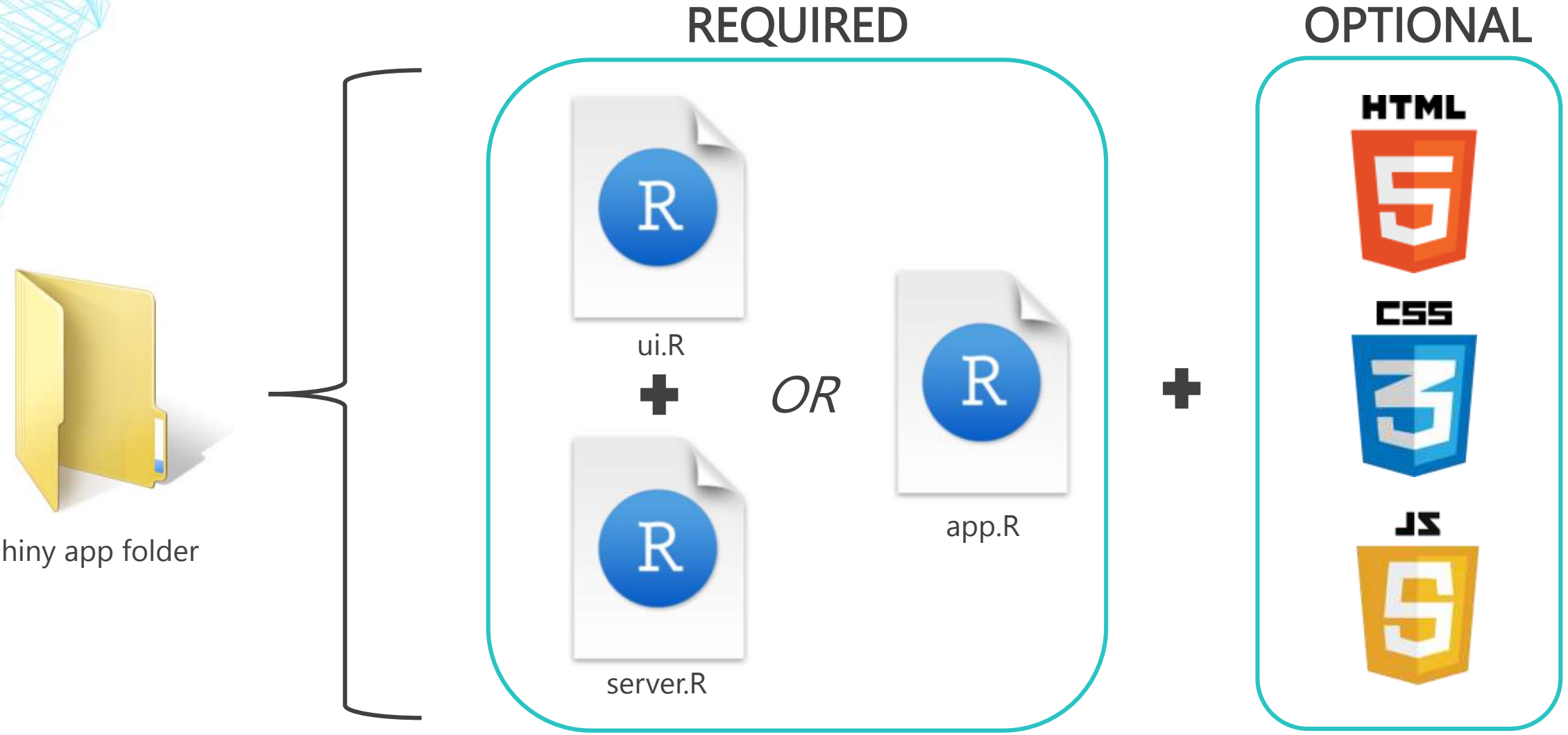
2. DEVELOP STANDARDIZED TOOLS FOR HIGHER EFFICIENCY AND PRODUCTIVITY

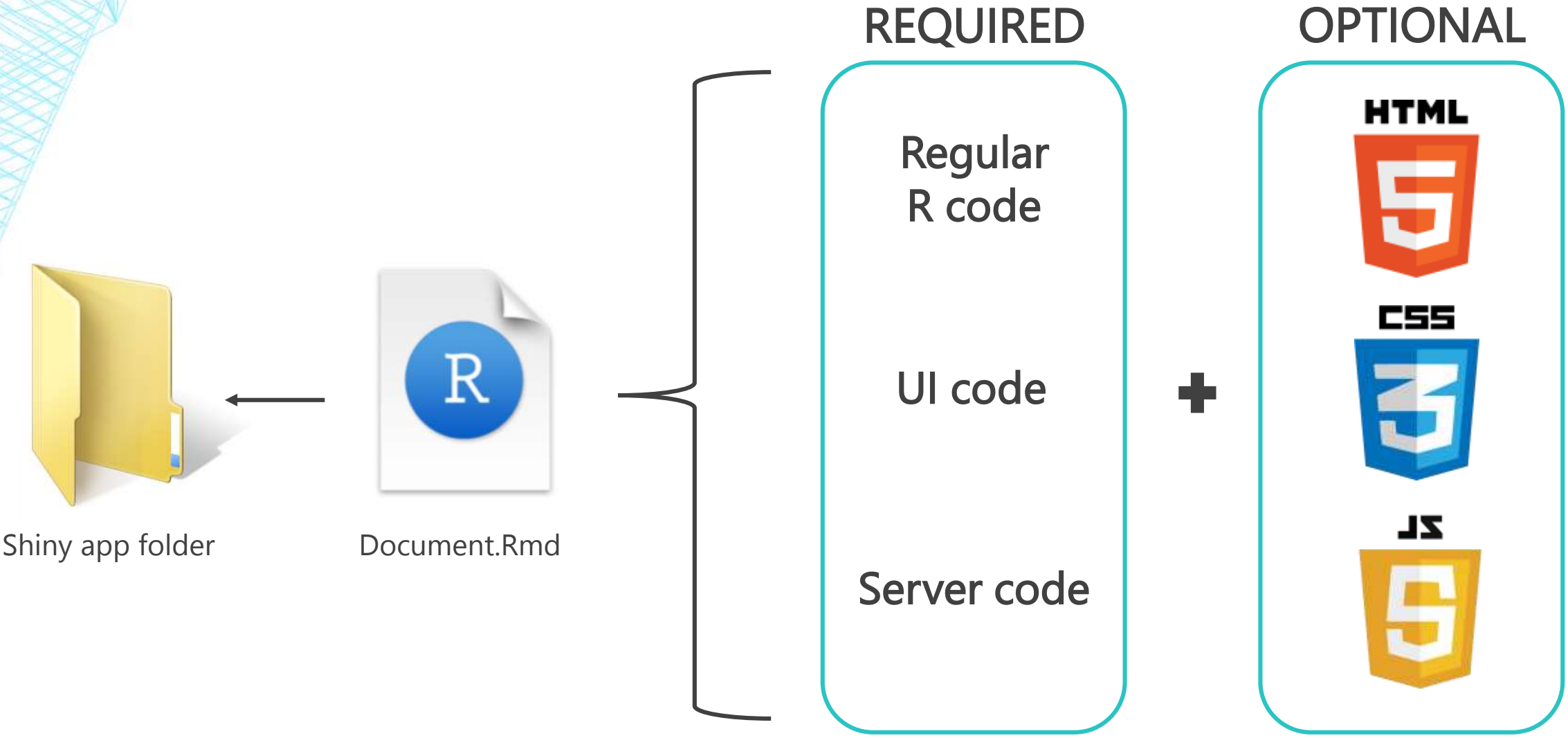
WHY WE WENT WITH SHINY

- 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



2. A SHINY DOCUMENT



ShinyDoc.Rmd

Run Document | Run | Chunks

```
---
title: "Interactive Document"
runtime: shiny
output: html_document
---

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, 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")
})
```
```

26:1 (Top Level) R Markdown

Specifications

UI code

Server code

Reference: R Markdown Tutorial http://rmarkdown.rstudio.com/authoring_shiny.html

PRO SHINY APP SCREENSHOTS

Patient-Reported Outcome Visualizations (Beta) | OVERVIEW | DATA | EXPLORATORY ANALYSIS | SCORE/CHANGE (CATEGORICAL) | SCORE/CHANGE (NUMERIC) | FEEDBACK

*This app requires to be opened in an internet browser.

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:

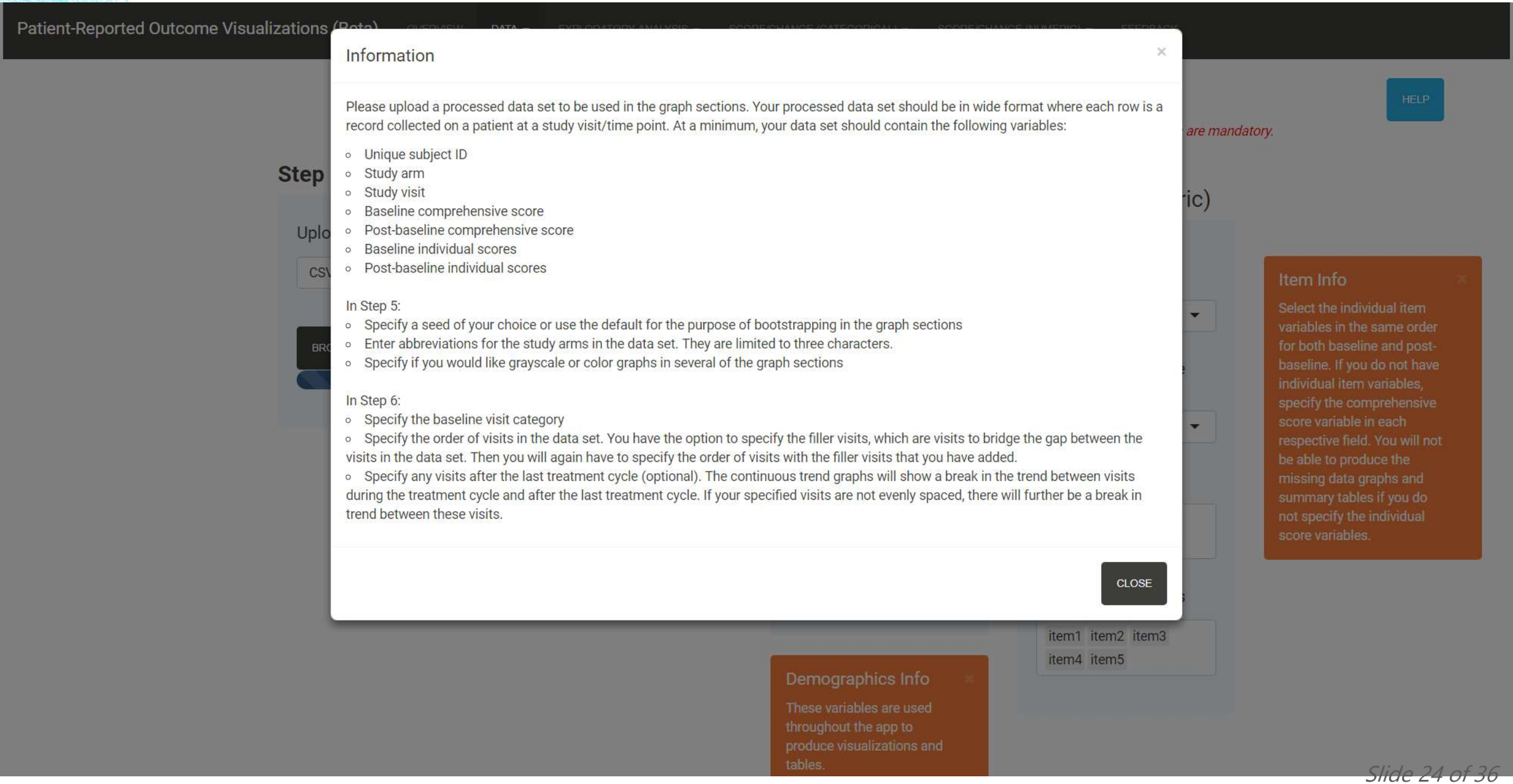
Color palettes using the 'wesanderson' R package

	A	B	C			F	G	H	I
1	USUBJID	VISIT2	TRT			BASE1	BASE2	ITEM1	ITEM2
2	00001	Baseline	Placebo			3	2	3	2
3	00001	C3D1	Placebo			3	2	3	3
4	00001	C5D1	Placebo	42.30782	73.33333	3	2	3	3
5	00001	C7D1	Placebo	38.46617	73.33333	3	2	3	4
6	00001	C9D1	Placebo	38.09605	73.33333	3	2	4	3
7	00001	C10D1	Placebo	50.44665	73.33333	3	2	3	3
8	00001	C11D1	Placebo	37.05395	73.33333	3	2	4	3
9	00001	C12D1	Placebo	38.36494	73.33333	3	2	3	3
10	00002	Baseline	Placebo	66.66667	66.66667	4	3	4	3
11	00002	C3D1	Placebo	86.69294	66.66667	4	3	3	2
12	00002	C5D1	Placebo	80.84118	66.66667	4	3	3	1
13	00002	C7D1	Placebo	86.92022	66.66667	4	3	2	1
14	00002	C9D1	Placebo	90.09377	66.66667	4	3	2	2
15	00002	C10D1	Placebo	63.56239	66.66667	4	3	4	2
16	00002	C11D1	Placebo	67.43886	66.66667	4	3	3	2
17	00002	C12D1	Placebo	81.93712	66.66667	4	3	3	2
18	00001	Baseline	Treatment	58.82824	66.66667	4	2	4	2
19	00002	Baseline	Treatment	70	70	1	1	1	1
20	00002	C3D1	Treatment	82.26395	70	1	1	1	1
21	00002	C5D1	Treatment	93.8185	70	1	1	1	1
22	00002	C7D1	Treatment	75.23211	70	1	1	1	1
23	00002	C10D1	Treatment	84.98729	70	1	1	1	1
24	00002	C11D1	Treatment	88.51938	70	1	1	1	1

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.



Information

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

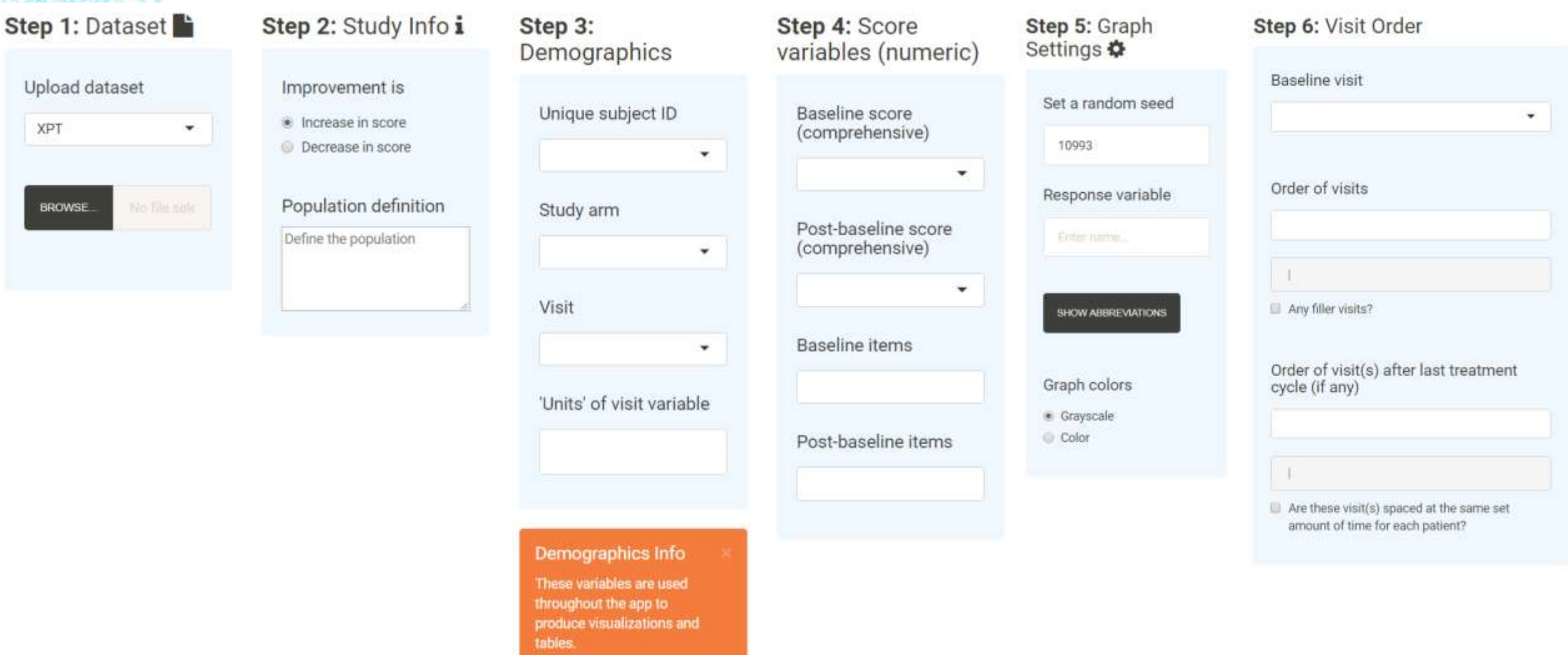
In Step 5:

- 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.

CLOSE


Step 1: Dataset
Upload dataset
XPT
BROWSE...
No file sele
Step 2: Study Info
Improvement is
Increase in score
Decrease in score
Population definition
Define the population
Step 3: Demographics
Unique subject ID
Study arm
Visit
'Units' of visit variable
Demographics Info
These variables are used throughout the app to produce visualizations and tables.
Step 4: Score variables (numeric)
Baseline score (comprehensive)
Post-baseline score (comprehensive)
Baseline items
Post-baseline items
Step 5: Graph Settings
Set a random seed
10993
Response variable
Enter name...
SHOW ABBREVIATIONS
Graph colors
Grayscale
Color
Step 6: Visit Order
Baseline visit
Order of visits
1
Any filler visits?
Order of visit(s) after last treatment cycle (if any)
1
Are these visit(s) spaced at the same set amount of time for each patient?

Patient-Reported Outcome Visualizations (Beta) | OVERVIEW | DATA | EXPLORATORY ANALYSIS | SCORE/CHANGE (CATEGORICAL) | SCORE/CHANGE (NUMERIC) | FEEDBACK

- SAMPLE SIZE OVER TIME
- MISSINGNESS (INPUTTED SAMPLE SIZES)
- MISSINGNESS (NA'S)
- TABLES OF COUNTS AND PERCENTAGES

HELP

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:

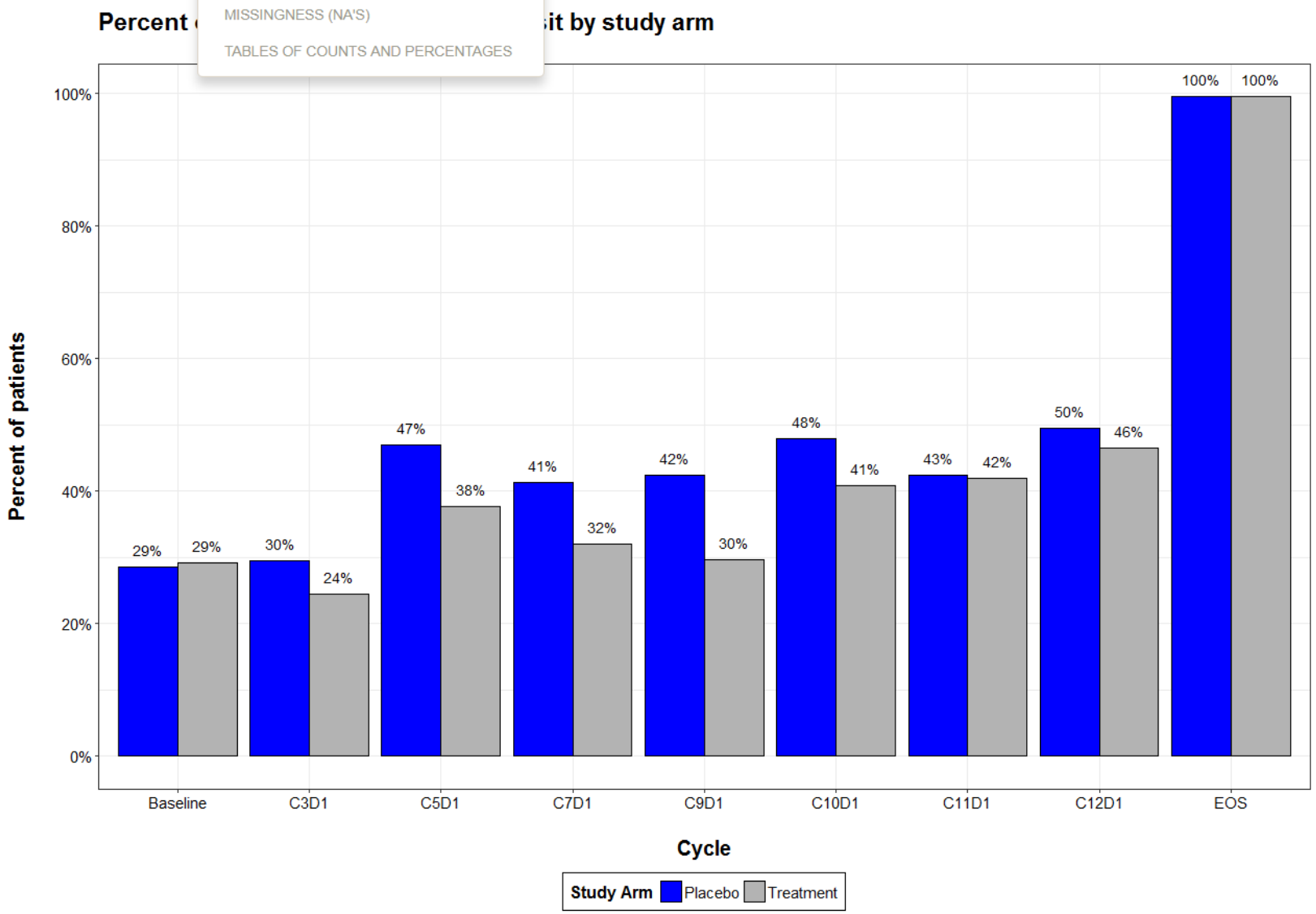
500,400,400,300,250,250,200,200,200

Outcome measure

Percent of missing

GENERATE GRAPH

DOWNLOAD GRAPH



Patient-Reported Outcome Visualizations (Beta) OVERVIEW DATA EXPLORATORY ANALYSIS SCORE/CHANGE (CATEGORICAL) SCORE/CHANGE (NUMERIC) FEEDBACK

HELP

Response measure

Raw change

Statistic of interest

Mean

Type of bootstrap CI

Bias-corrected and accelerated (BCa)

Confidence level

80 95 99

80 82 84 86 88 90 92 94 96 98 99

Number of bootstrap replicates

1,000 10,000 50,000

1,000 6,000 11,000 16,000 21,000 26,000 31,000 36,000 41,000 46,000 50,000

GENERATE

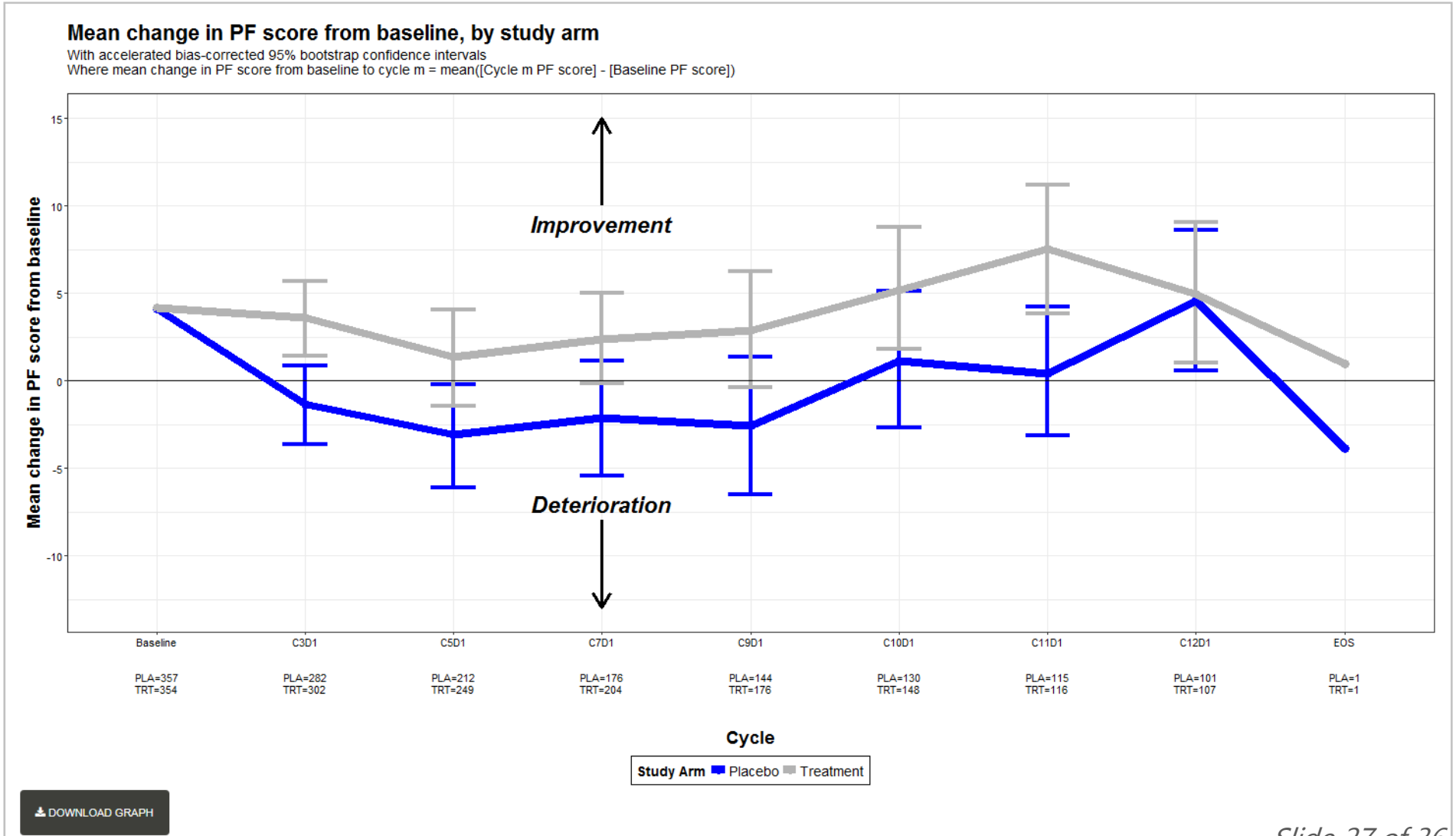
Add top text and arrow

Top text y-position:

9

Top arrow y-position:

10



DOWNLOAD GRAPH

- [x] Add top text and arrow

Top text y-position:

9

Top arrow y-position:

10

Top arrow length

5

- [x] Add bottom text and arrow

Bottom text y-position:

-7

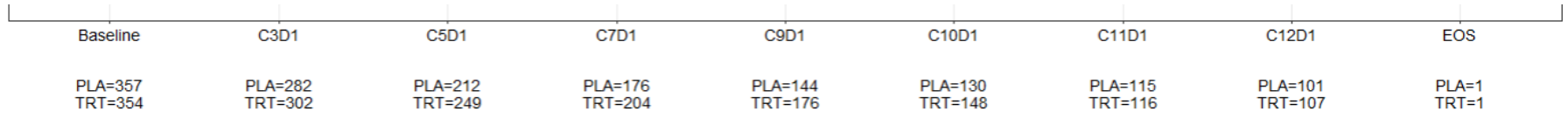
Bottom arrow y-position:

-8

Bottom arrow length

5

- [ ] Adjust graph elements
- [ ] Adjust y-axis limits



Cycle

Study Arm Placebo Treatment

DOWNLOAD GRAPH

Sample interpretation language:

[redacted]

Condition for using sample interpretation language: [redacted]

Note: [redacted]

Cautionary Note: [redacted]

Example (tolerability data for an approved drug): [redacted]

Patient-Reported Outcome Visualizations (Beta) OVERVIEW DATA EXPLORATORY ANALYSIS SCORE/CHANGE (CATEGORICAL) SCORE/CHANGE (NUMERIC) FEEDBACK

TREND IN SCORE OVER TIME
TREND IN SCORE CHANGE OVER TIME
PLOTS CONDITIONED ON STUDY VISITS
GREATEST IMPROVEMENT/DETERIORATION DISTRIBUTION
PATIENTS MEETING CRITERIA OVER TIME
PERCENT OF IMPROVEMENT/DETERIORATION OVER TIME
CONDITIONAL IMPROVEMENT/DETERIORATION DISTRIBUTION AND CIS

HELP

Variable

Score change

Outcome name

score change

Plot

ECDF

Time points

C3D1 C5D1 C7D1 C9D1

Change grouping variable?

GENERATE

Add left text and arrow

Left text y-position:

0.75

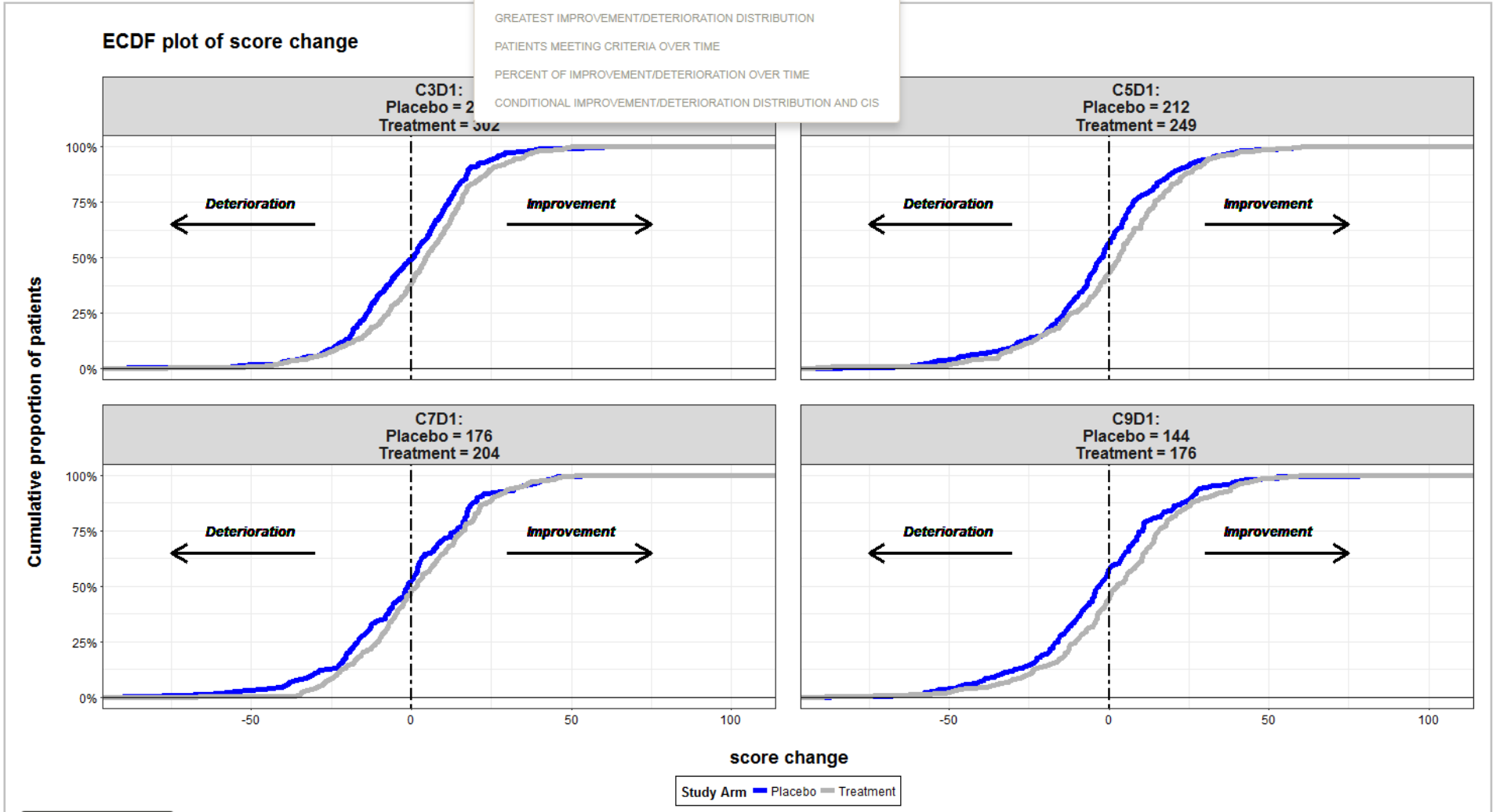
Left text x-position:

-50

Left arrow y-position:

0.65

Left arrow x-position:



DOWNLOAD GRAPH

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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?

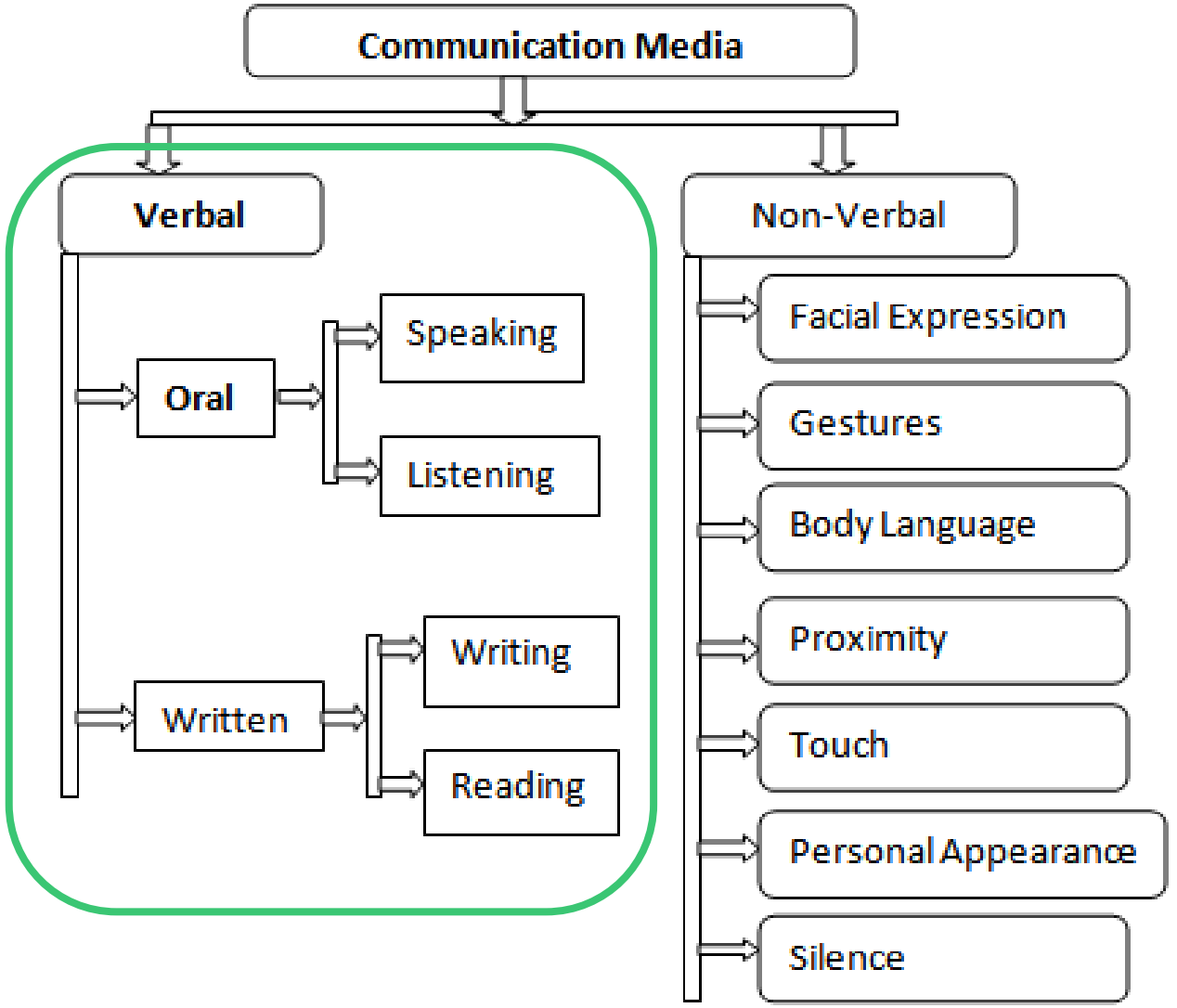
Advantages

- 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

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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

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THANK YOU!

QUESTIONS?

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