

# OND reviewer's approach to the NDA/BLA Clinical Review and how analytical tools are used

Vaishali Popat MD, MPH

Associate Director of Biomedical Informatics  
and Regulatory Review Science

Office of New Drugs

# Disclosure

- No financial or commercial conflict of interest.
- The opinions and information in this presentation are those of the author/presenter, and do not represent the views and/or policies of the U.S. Food and Drug Administration.

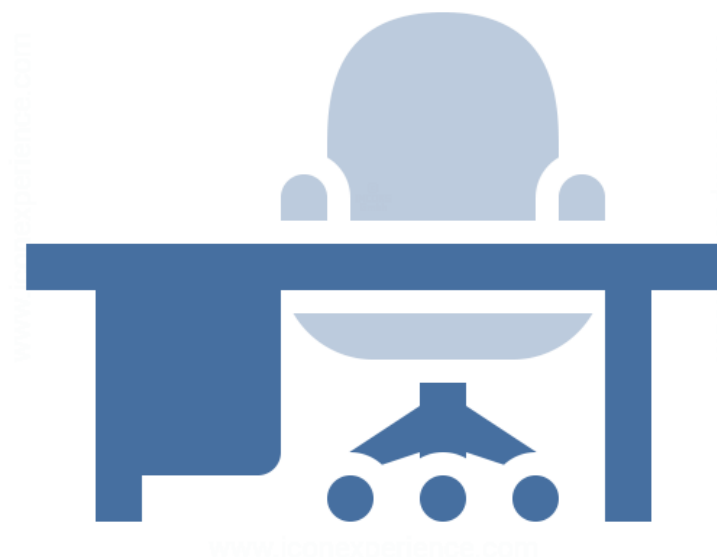
# Background: Clinical Reviewer's Role

- Most are physicians
- Responsible for reviewing all clinical data
- Examine all submission types – INDs, NDAs, meeting requests, safety reports



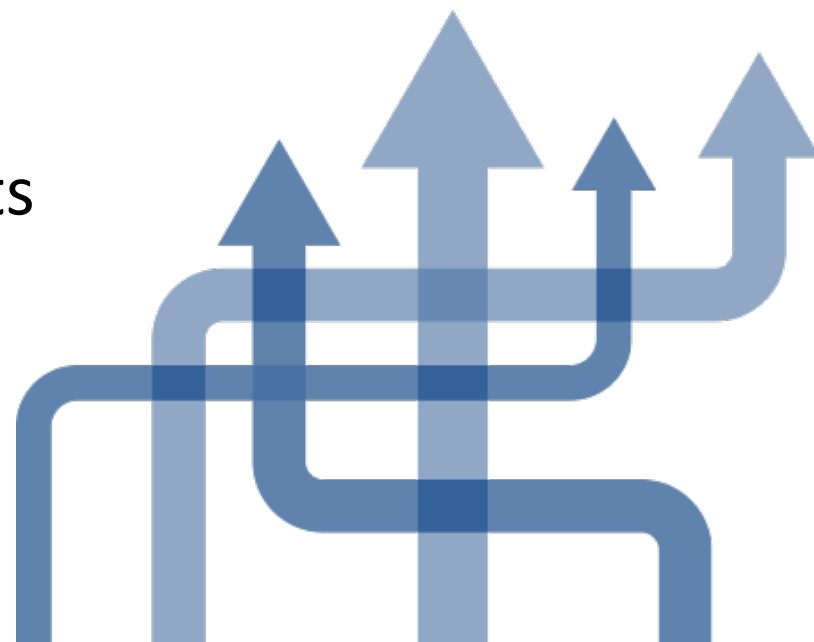
# My Experience as a Reviewer: From the Other Side of the Desk

- First NDA/BLA
  - Standard data

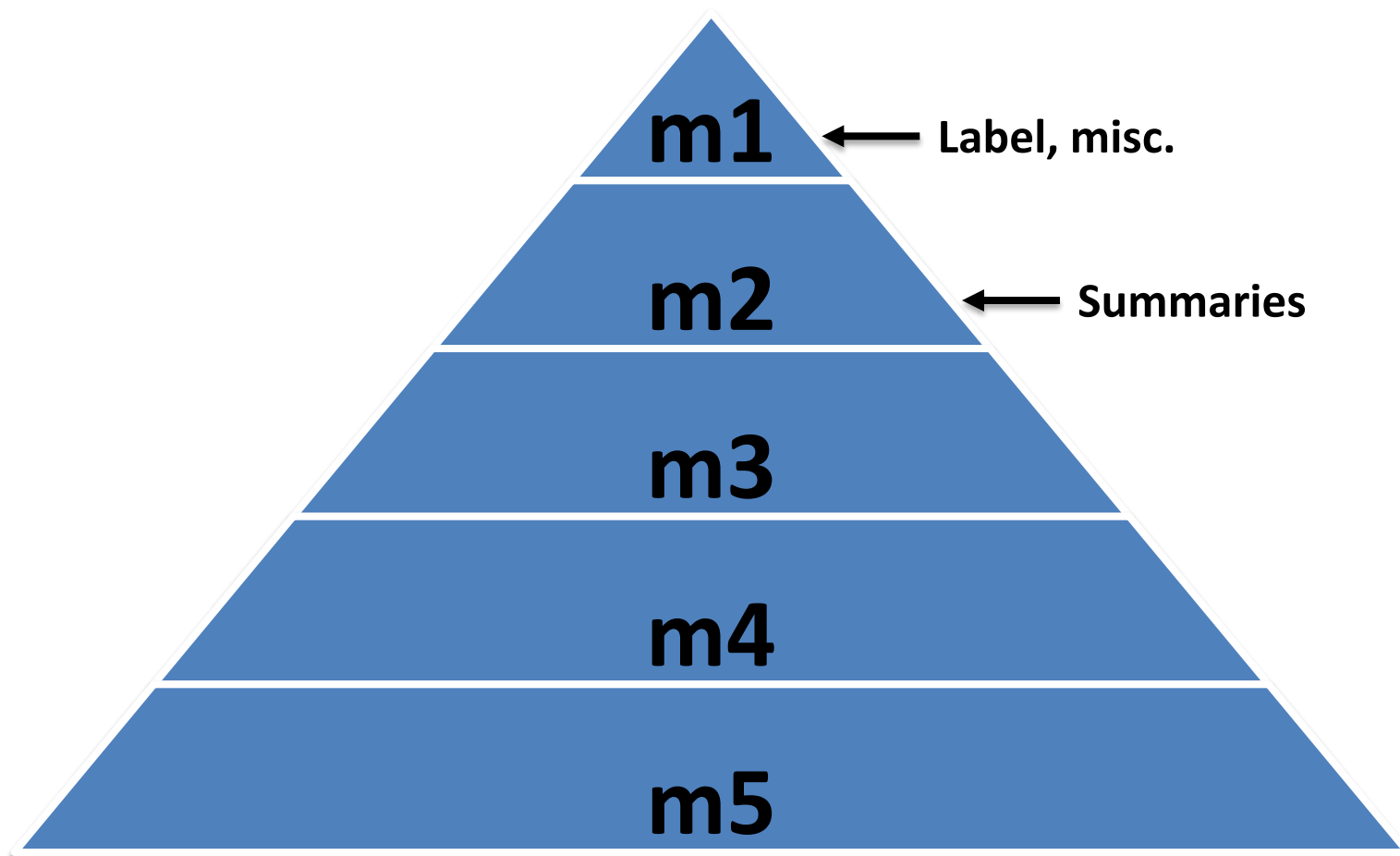


# Approach to NDA/BLA review

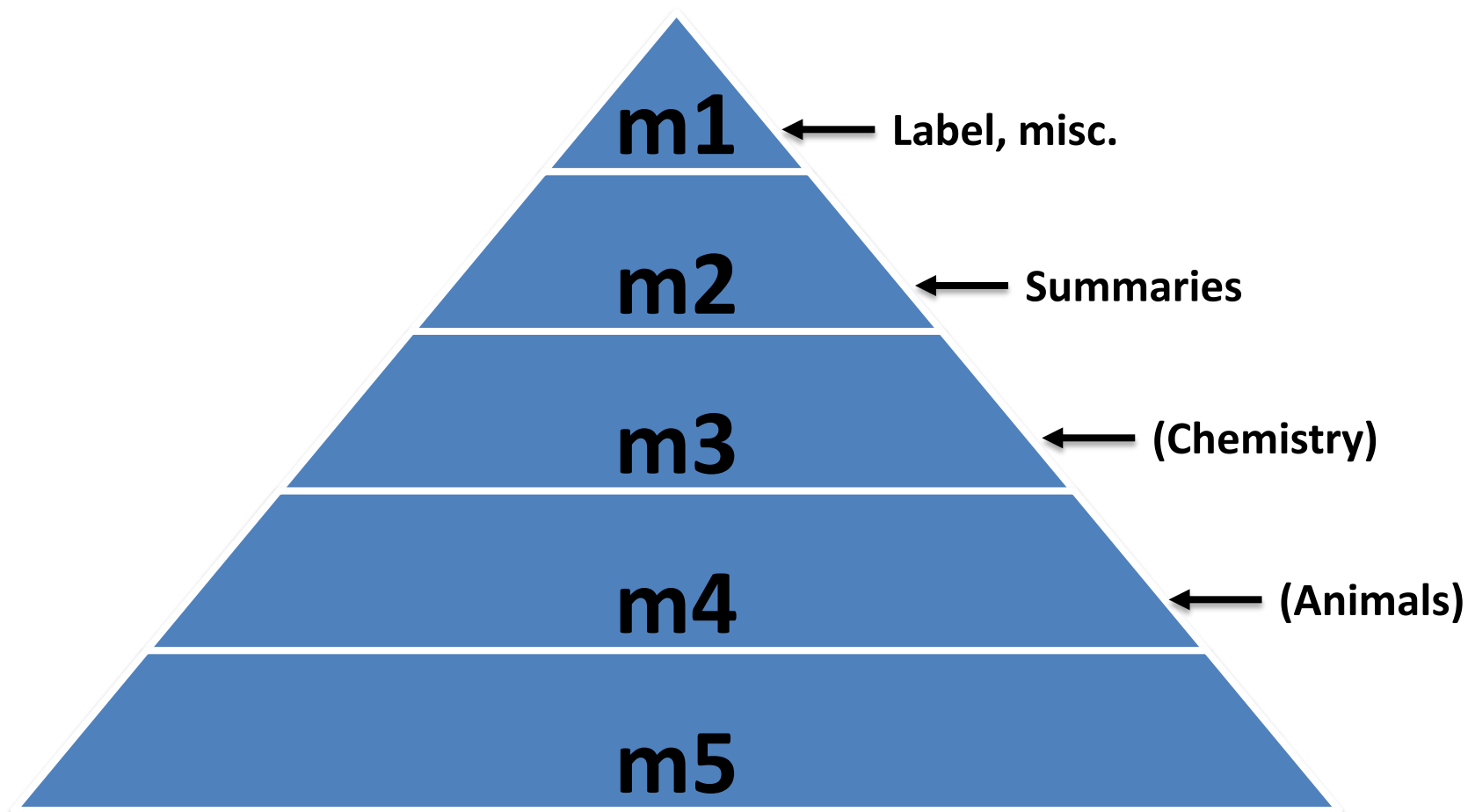
- Become familiar with application (mountain of information) presented
- Read the proposed PI
- Read summaries / overview
- Explore subject level datasets
- Write review



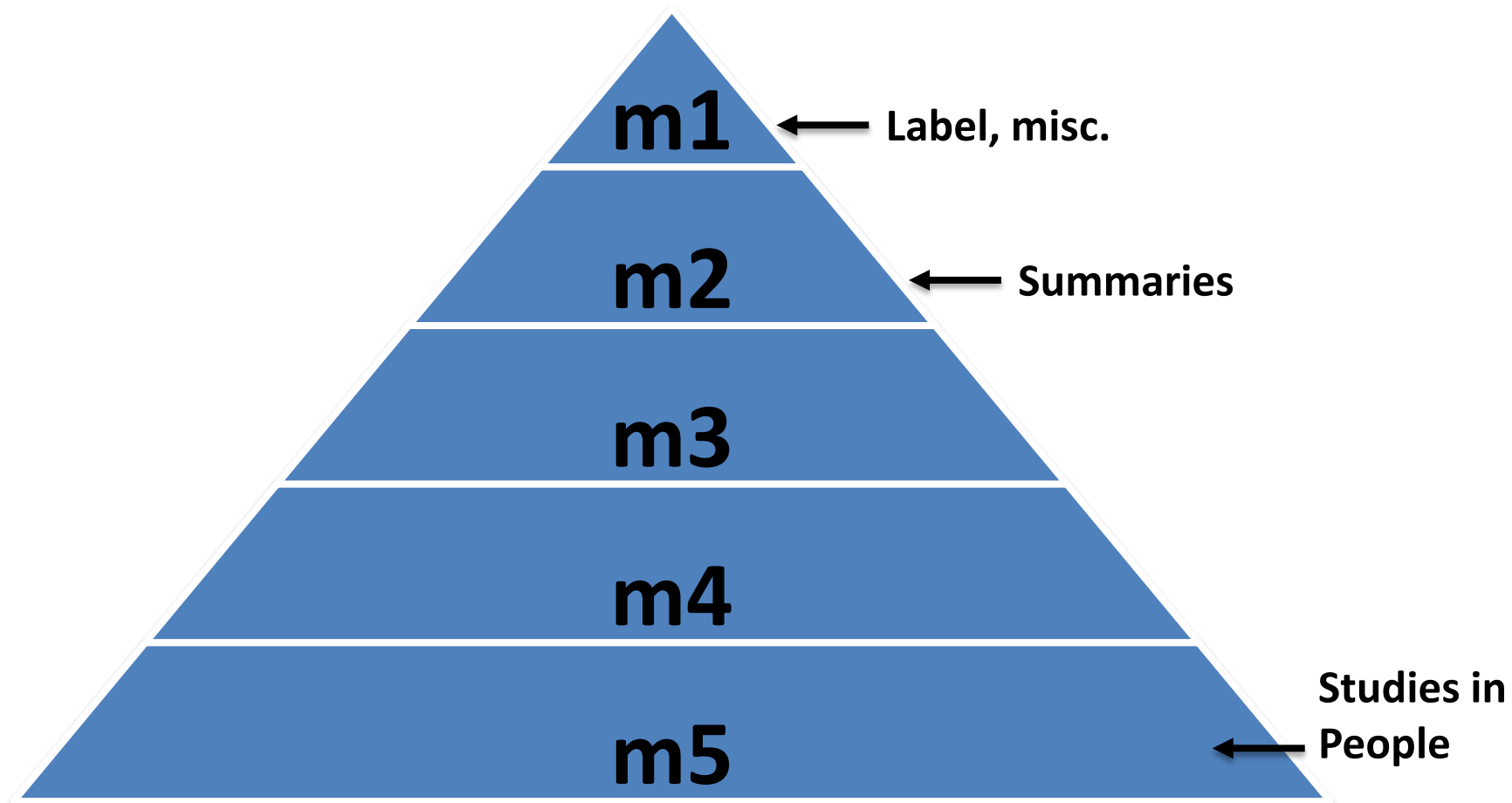
# Clinical Reviewer's CTD



# Clinical Reviewer's CTD

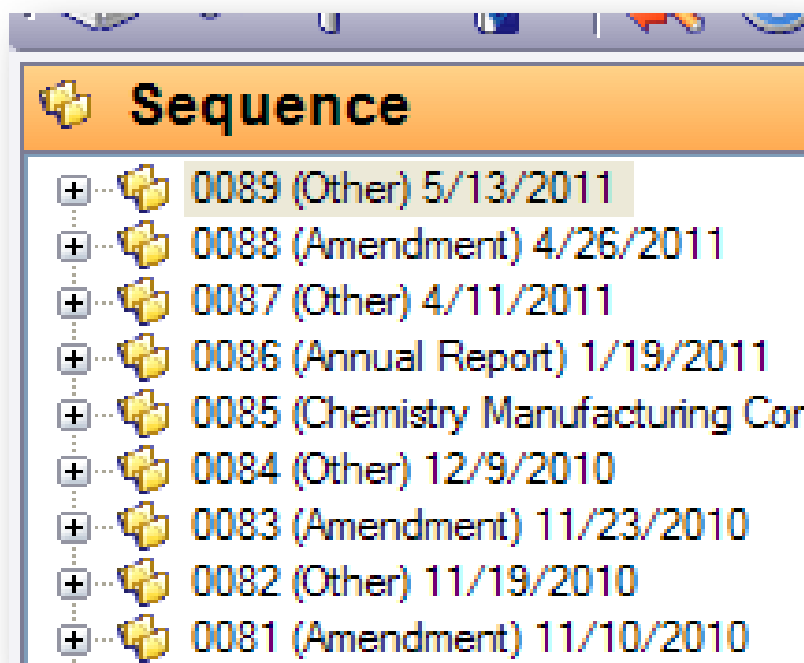
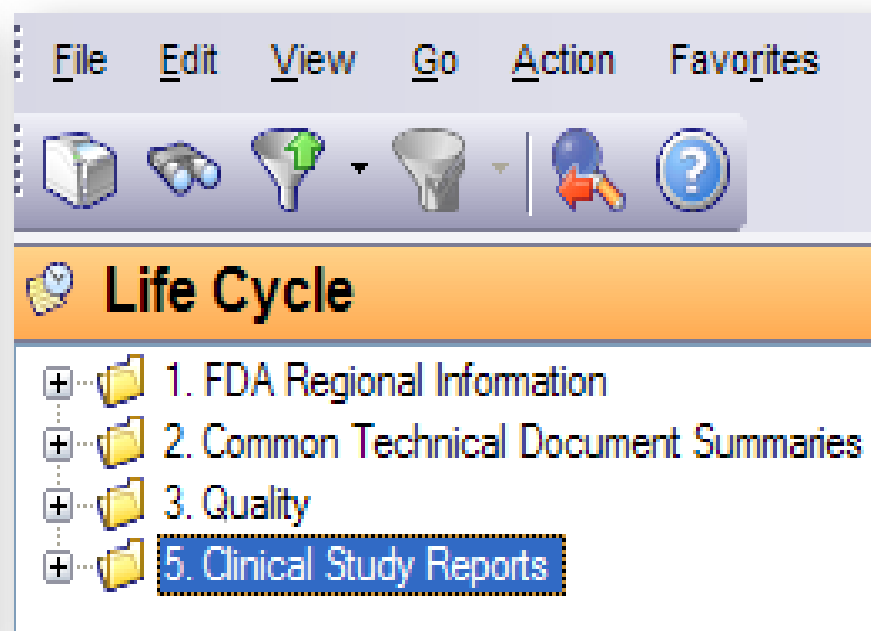


# Clinical Reviewer's CTD



# First Assignment

Common Views in Global Submit:

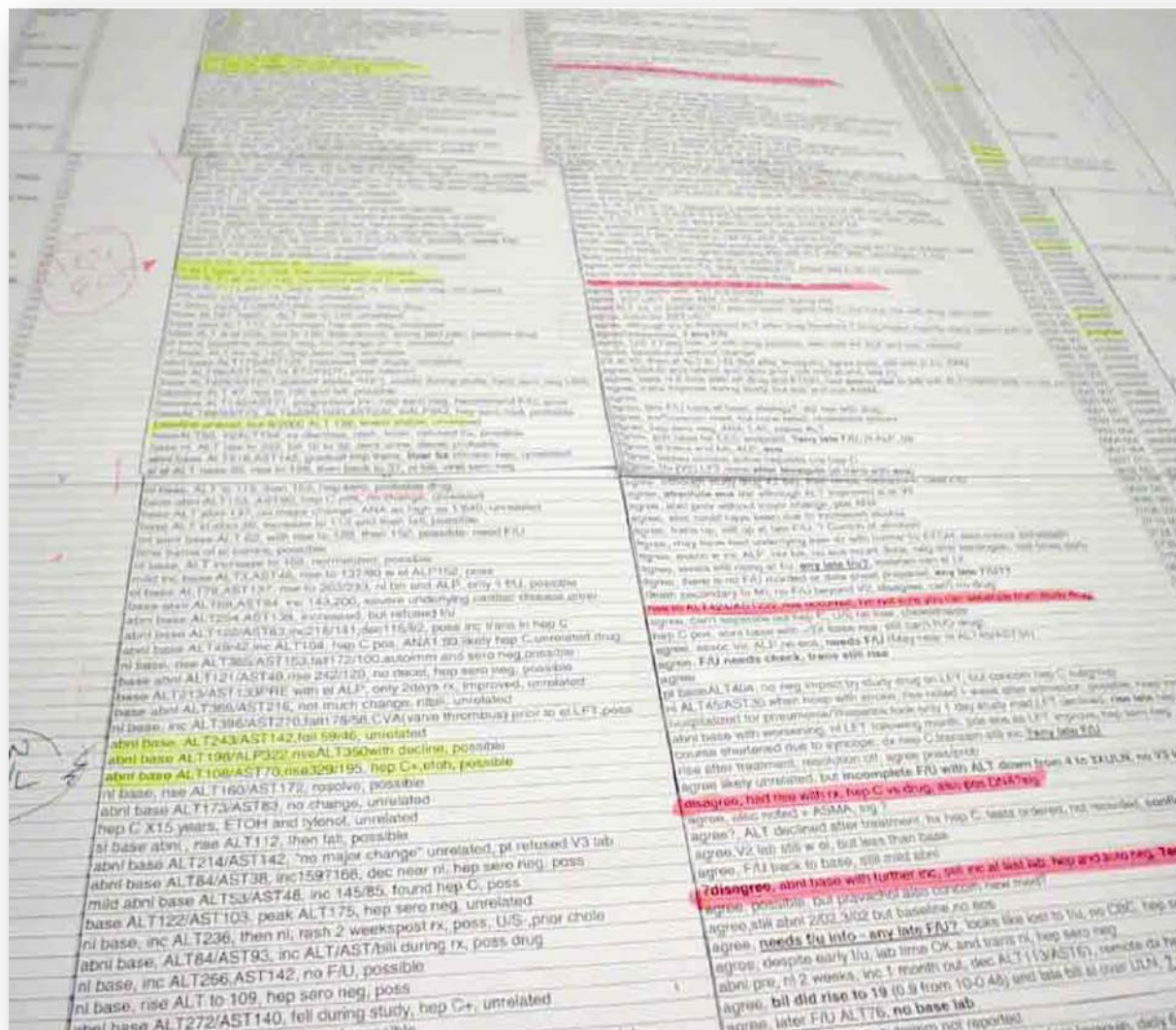




Back in  
the day...



Back in  
the day...



Back in  
the day...

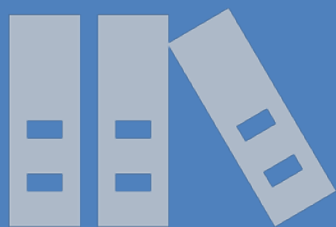
# Why We Like Electronic Submissions...

1. Eliminates lag time in FDA document room
2. Makes review process faster, more efficient
3. Eases searching through data
4. Makes documents easily accessible for years to come





# We Like Electronic Submissions, But...



## Paper Submission:

- Table of Contents of the ENTIRE SUBMISSION allows reviewer to see the magnitude of information at one glance



## Electronic Submission:

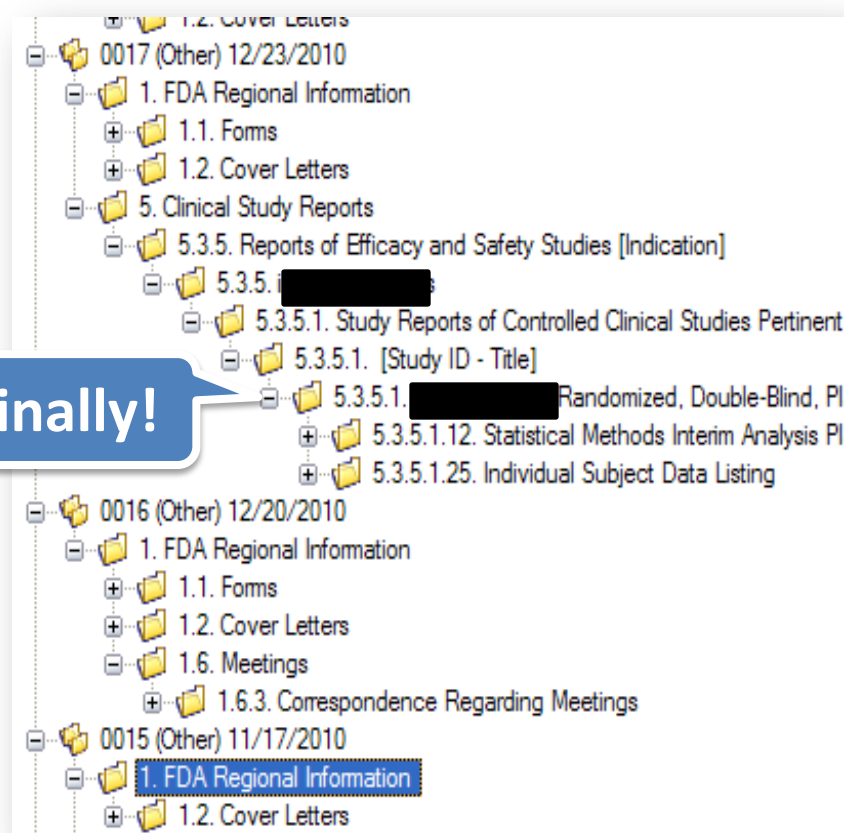
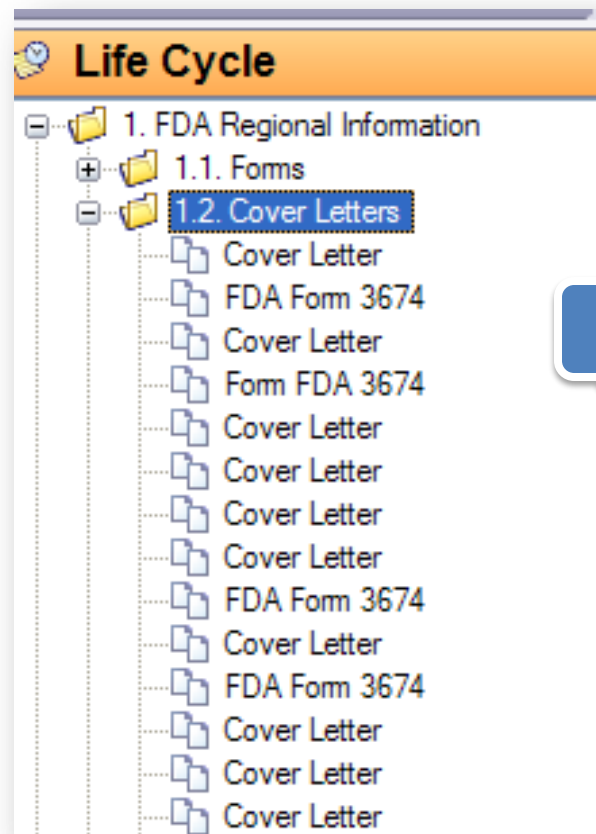
- Everything is “hidden”
- Most open and close many folders to see the whole submission

**Problem:** Can't easily find what is in the submission



**Danger:** NOT KNOWING that you are missing something

# Where's Waldo?



Yikes!



# Example of Useful Hyperlink

## In-text table

|                             |             |             |             |
|-----------------------------|-------------|-------------|-------------|
| Number of Patients n(%)     |             |             |             |
| Completed                   | 214 (93.9%) | 202 (86.7%) | 416 (90.2%) |
| Discontinued                | 14 (6.1%)   | 31 (13.3%)  | 45 (9.8%)   |
| Discontinuation due to:     |             |             |             |
| Adverse Event               | 6 (2.6%)    | 20 (8.6%)   | 26 (5.6%)   |
| Protocol Violation          | 3 (1.3%)    | 2 (0.9%)    | 5 (1.1%)    |
| Voluntary Withdrawal        | 4 (1.8%)    | 1 (0.4%)    | 5 (1.1%)    |
| Lack of Efficacy            | 0 (0.0%)    | 2 (0.9%)    | 2 (0.4%)    |
| Lost to Follow-up           | 0 (0.0%)    | 4 (1.7%)    | 4 (0.9%)    |
| Investigator Recommendation | 0 (0.0%)    | 1 (0.4%)    | 1 (0.2%)    |
| Other                       | 1 (0.4%)    | 1 (0.4%)    | 2 (0.4%)    |

Source: [Table 14.1-2](#)

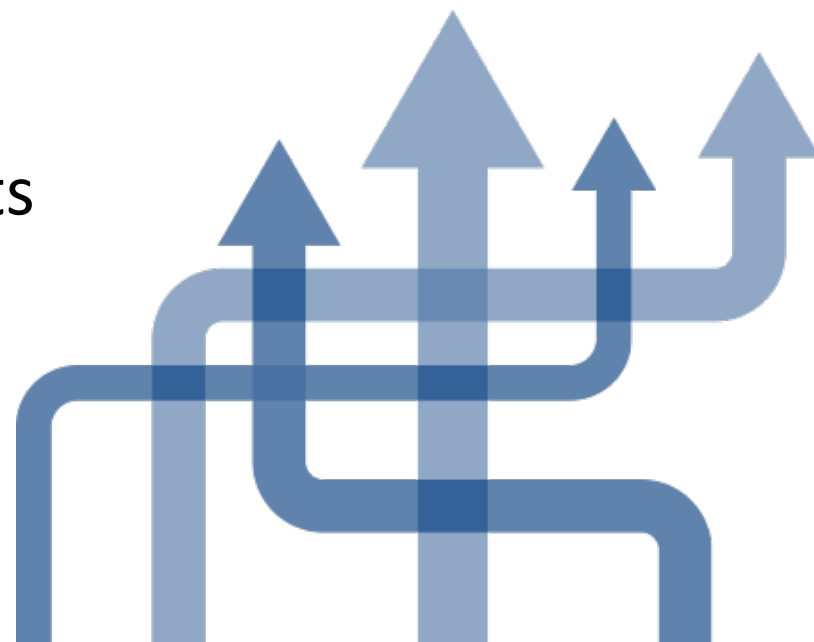
# Wish List

- Send submissions electronically
- Make submissions user-friendly
  - Hyperlinks
  - Bookmarks
  - Specific leaf titles
  - AVOID REPETITION – the same info (especially background, some data, conclusions) is repeated in multiple areas - parts of module 2 and 5 (and sometimes other areas)
- Hyperlink within patient narrative to CRF
  - Easy access to Case Report Forms (CRFs) from Patient Narratives



# Approach to NDA/BLA review

- Become familiar with application (mountain of information) presented
- Read the proposed PI
- Read summaries / overview
- Explore subject level datasets
- Write review





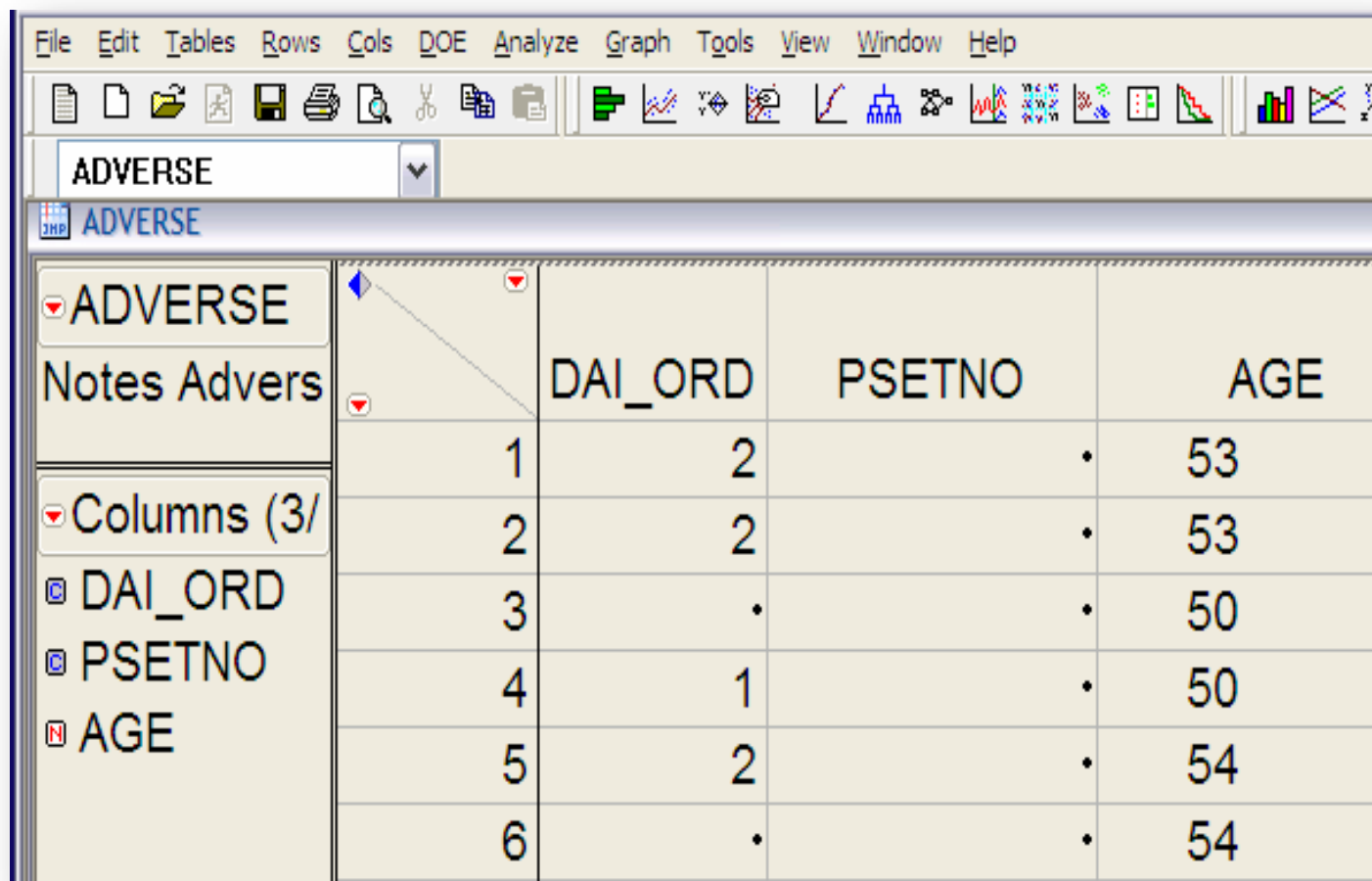
# What Do I Do with the Data?

- Understand what is in the datasets – walk through from left to right
- Check coding
- Verify definitions (e.g., TEAE)
- Look for answers to questions that arise
- Repeat some analyses or do them differently
- Look for outlier sites to advise inspectors for site selection



- Second NDA
  - Legacy data - Non standard format

# Obscure Datasets



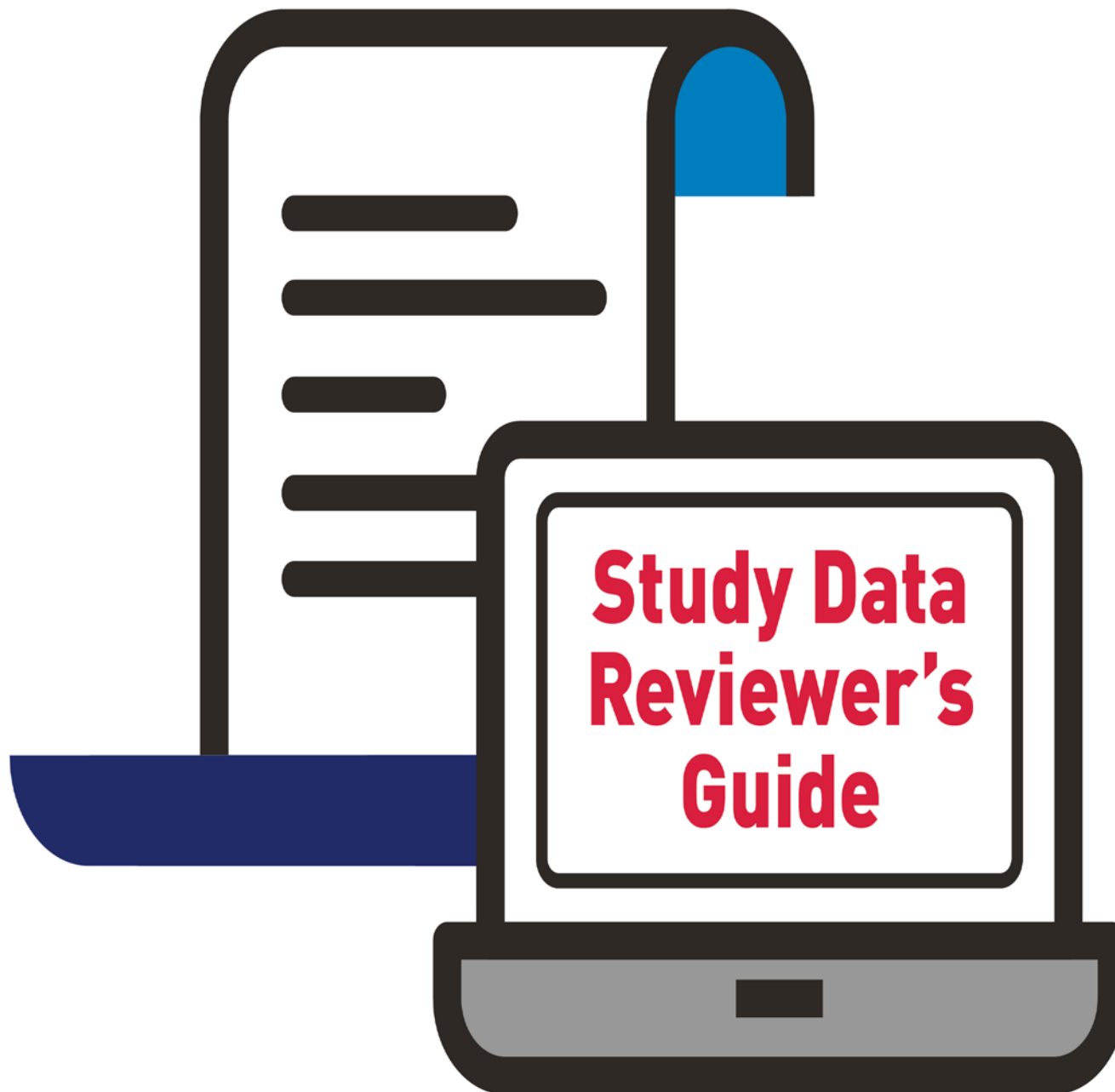
The screenshot shows the JMP software interface with the 'ADVERSE' dataset loaded. The table has columns for 'Notes Advers', 'DAI\_ORD', 'PSETNO', and 'AGE'. The data is as follows:

| Notes Advers | DAI_ORD | PSETNO | AGE |
|--------------|---------|--------|-----|
| 1            | 2       | •      | 53  |
| 2            | 2       | •      | 53  |
| 3            | •       | •      | 50  |
| 4            | 1       | •      | 50  |
| 5            | 2       | •      | 54  |
| 6            | •       | •      | 54  |

## Excerpt of “define.pdf”

| Column Header | Explanation                      |
|---------------|----------------------------------|
| AGE           | AGE                              |
| DAI_ORD       | Partitioning column - DA I Order |
| PSETNO        | PSETNO                           |







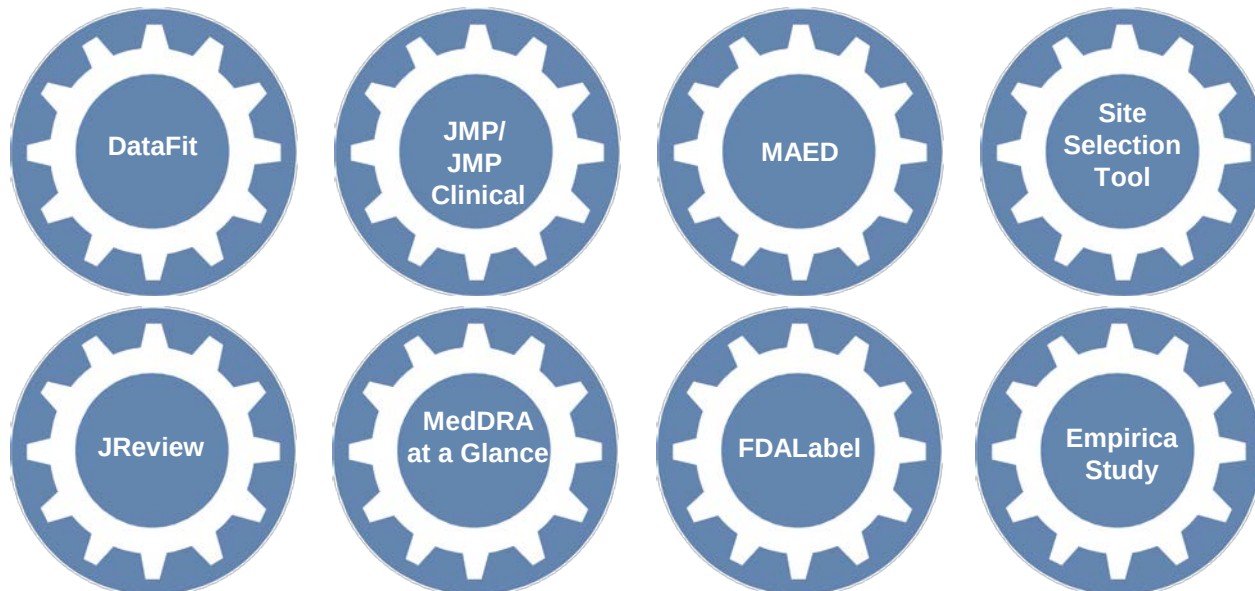
# Requests

- Write Reviewer's Guide (and maybe define file) in 'Plain English'
  - Majority of the reviewers are physicians, think of your PCP
- Think of traceability
- Be mindful of the size of the datasets
  - Columns with missing data for the entire dataset ???
- Clarify how you have pooled data
- **Data standards**
- Follow the [Study Data Technical Conformance Guide](#)



# We Have Come a Long Way

- New tools: We are constantly evaluating and using software programs (review tools) in a very collaborative effort



# Medical Informatics: science of learning from data



Decisions



Information

Data

|    | $x[n]$       | $r[n]$       | Solution at iteration $n$ |
|----|--------------|--------------|---------------------------|
| 4  | -2.139833188 | -3.195957170 | -1.945611656              |
| 5  | -1.884840650 | -1.173224163 | -2.002174399              |
| 6  | -2.102184058 | -1.221204184 | -2.004334698              |
| 7  | -1.924209391 | -1.169466973 | -2.006245518              |
| 8  | -2.076393823 | -1.201867210 | -2.007277742              |
| 9  | -1.949770490 | -1.168987472 | -2.008149496              |
| 10 | -2.058089301 | -1.191861309 | -2.008670658              |
| 11 | -1.967207241 | -1.169680559 | -2.009094541              |
| 12 | -2.044905429 | -1.186126702 | -2.009363945              |
| 13 | -1.979399621 | -1.170714188 | -2.009576697              |

Example 1: Solving  $\sin(x) - \frac{1}{2}x = 0.1$  by fixed-point iteration

# **How Analytical Tools are Used for the NDA/BLA Clinical Review**

Mary Doi, M.D., M.S.  
Deputy Director  
Office of Computational Science (OCS)



NONCLINICAL  
PHASE



INVESTIGATIONAL  
PHASE



APPLICATION  
REVIEW PHASE



POST-MARKETING  
PHASE



NONCLINICAL  
PHASE



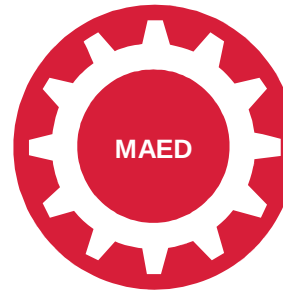
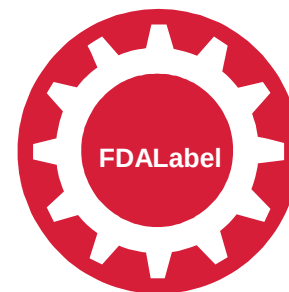
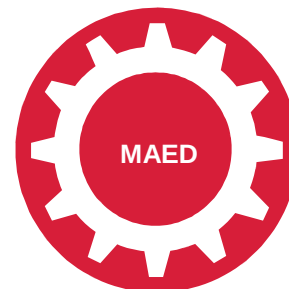
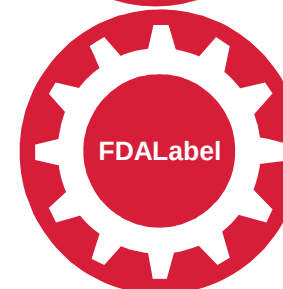
INVESTIGATIONAL  
PHASE



APPLICATION  
REVIEW PHASE



POST-MARKETING  
PHASE





NONCLINICAL  
PHASE



INVESTIGATIONAL  
PHASE



APPLICATION  
REVIEW PHASE



POST-MARKETING  
PHASE





NONCLINICAL  
PHASE



INVESTIGATIONAL  
PHASE



APPLICATION  
REVIEW PHASE



POST-MARKETING  
PHASE



# Training

- Data Standards
  - Training modules for nonclinical and clinical
  - Resources: TCG, Guidances, Catalogs
- MedDRA
  - Training modules
  - MedDRA Web-based browser
  - MedDRA Points to Consider document



NONCLINICAL  
PHASE



INVESTIGATIONAL  
PHASE



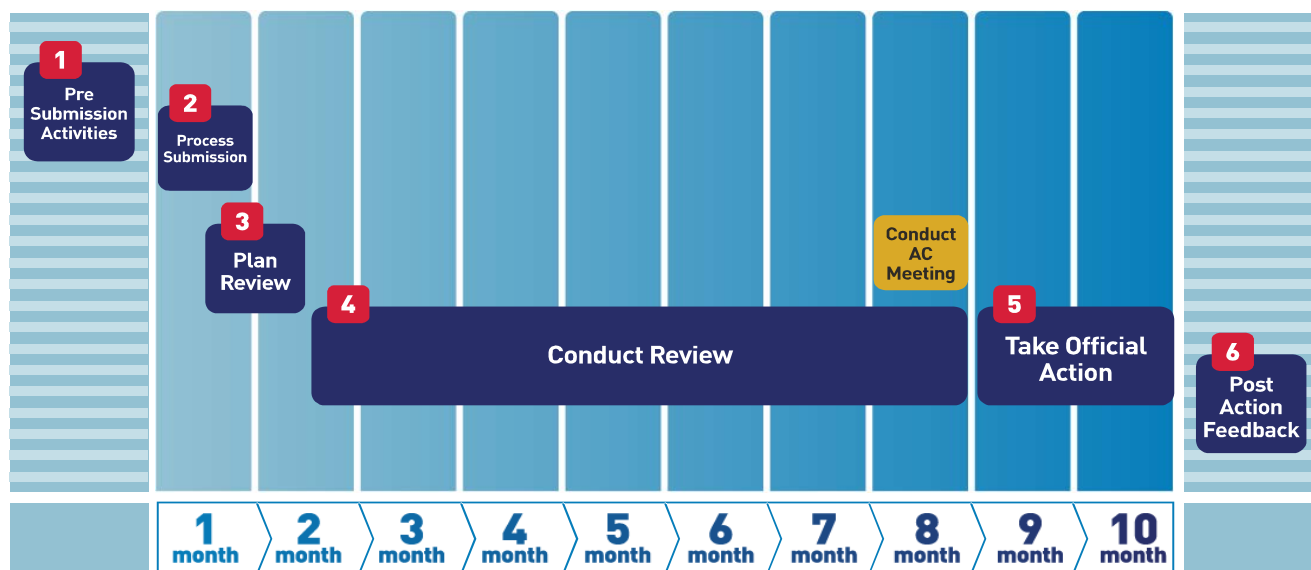
APPLICATION  
REVIEW PHASE



POST-MARKETING  
PHASE

# 21st Century Review

## CDER 21st Century Review Process Desk Reference Guide



New Drug Application and Biologics License Application Reviews  
NDA/BLA Review Process



NONCLINICAL  
PHASE



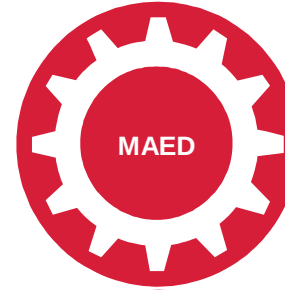
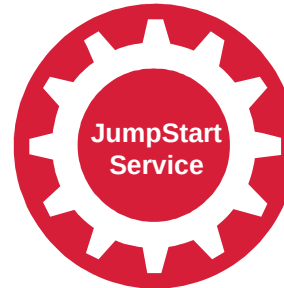
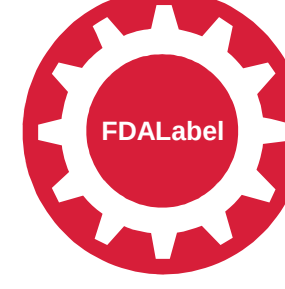
INVESTIGATIONAL  
PHASE



APPLICATION  
REVIEW PHASE



POST-MARKETING  
PHASE





NONCLINICAL  
PHASE



INVESTIGATIONAL  
PHASE



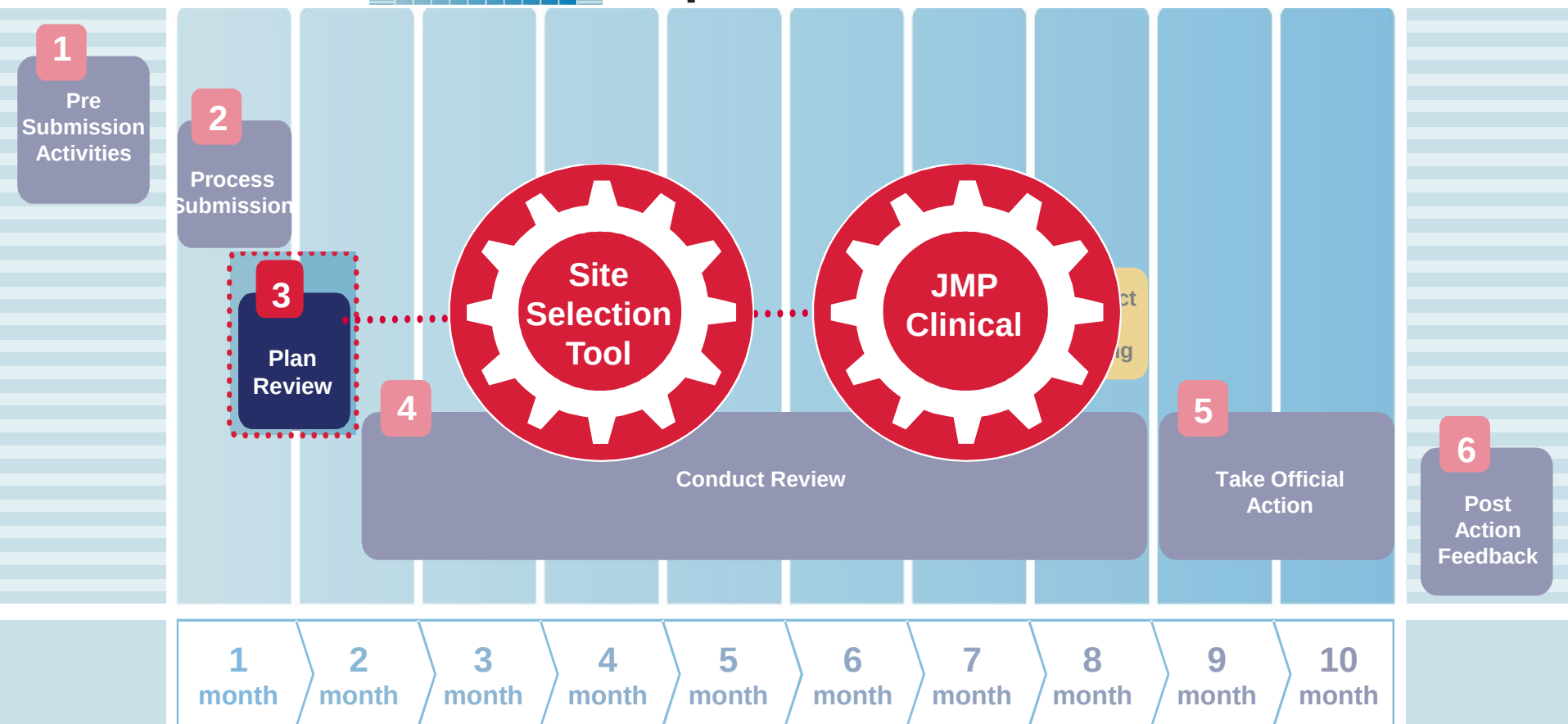
APPLICATION  
REVIEW PHASE



POST-MARKETING  
PHASE

21st Century  
Review

## 21st Century Review Process: Inspections





# CDER's Clinical Investigator Site Selection Tool

Displaying 1 to 20 of 28 Sites in Study (Page 1 to 1 of 2)

Application Risk: 0 out of 25

Study Risk: #VALUE! out of 25

Print Table

| MEMO              | SITEID              | UNDER IND | FRSTNAME | LASTNAME | CITY                | STATE | COUNTRY | REGION         | ICH     | RANK | TOTAL RISK | SITE RISK |
|-------------------|---------------------|-----------|----------|----------|---------------------|-------|---------|----------------|---------|------|------------|-----------|
| <a href="#">N</a> | <a href="#">181</a> | Y         |          |          | Central Hong Kong   | NA    | HKG     | Asia/Pacific   | Non-ICH | 1    | 26.9       | 26.9      |
| <a href="#">N</a> | <a href="#">121</a> | Y         |          |          | Rio de Janeiro      | NA    | BRA     | Latin America  | Non-ICH | 2    | 17.2       | 17.2      |
| <a href="#">N</a> | <a href="#">131</a> | Y         |          |          | Pardubice           | NA    | CZE     | Eastern Europe | ICH     | 3    | 15.2       | 15.2      |
| <a href="#">N</a> | <a href="#">161</a> | Y         |          |          | Bucharest           | NA    | ROU     | Eastern Europe | ICH     | 4    | 11.0       | 11.0      |
| <a href="#">N</a> | <a href="#">216</a> | Y         |          |          | Hialeah             | FL    | USA     | United States  | ICH     | 5    | 9.6        | 9.6       |
| <a href="#">N</a> | <a href="#">103</a> | Y         |          |          | Vejle               | NA    | DNK     | Western Europe | ICH     | 6    | 9.1        | 9.1       |
| <a href="#">N</a> | <a href="#">132</a> | Y         |          |          | Brno                | NA    | CZE     | Eastern Europe | ICH     | 7    | 7.7        | 7.7       |
| <a href="#">N</a> | <a href="#">102</a> | Y         |          |          | Aalborg             | NA    | DNK     | Western Europe | ICH     | 8    | 7.3        | 7.3       |
| <a href="#">N</a> | <a href="#">213</a> | Y         |          |          | Miami               | FL    | USA     | United States  | ICH     | 9    | 6.8        | 6.8       |
| <a href="#">N</a> | <a href="#">133</a> | Y         |          |          | Praha 3 – Vinohrady | NA    | CZE     | Eastern Europe | ICH     | 10   | 6.8        | 6.8       |



NONCLINICAL  
PHASE



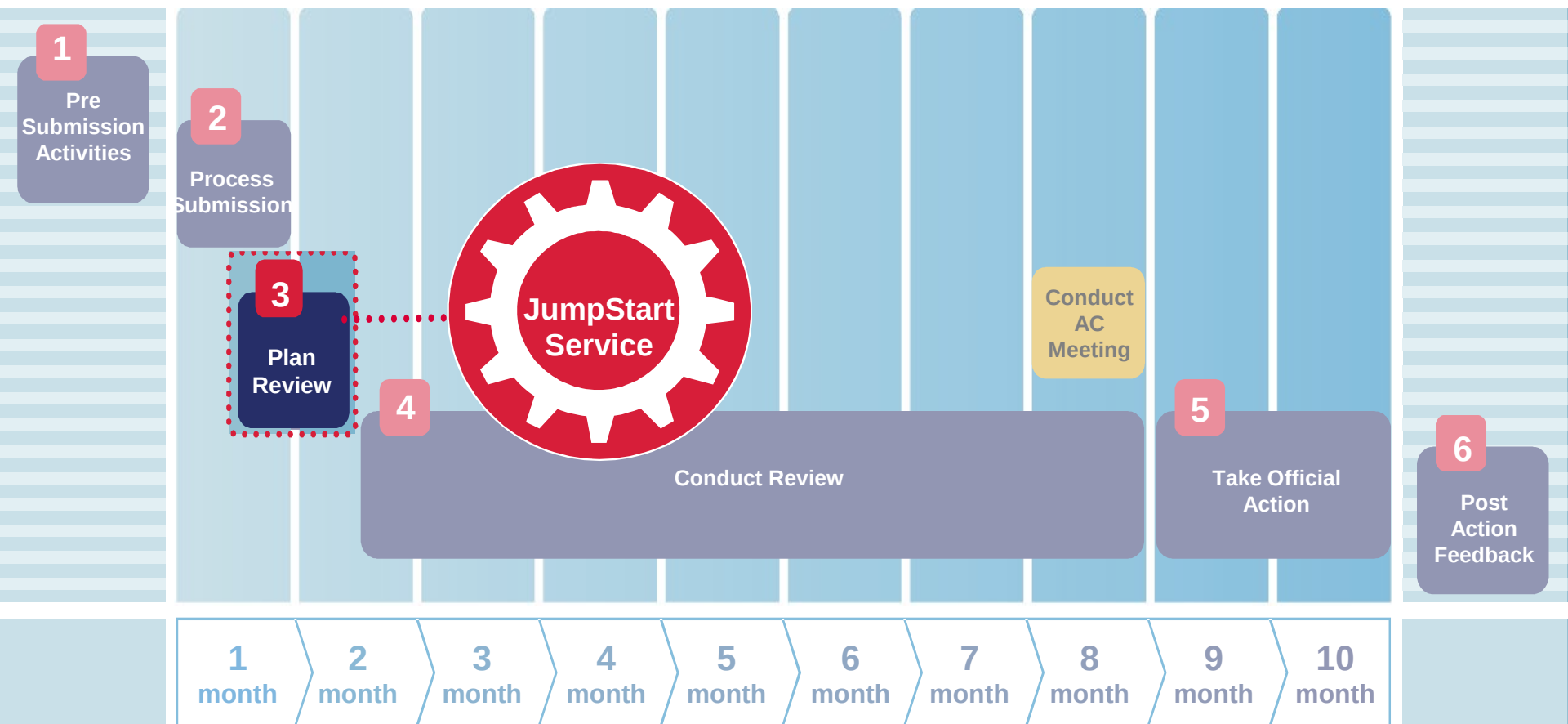
INVESTIGATIONAL  
PHASE



APPLICATION  
REVIEW PHASE



POST-MARKETING  
PHASE



# JumpStart Service

**U.S. FOOD & DRUG  
ADMINISTRATION**

A to Z Index | Follow FDA | En Español

Search FDA

Home | Food | Drugs | Medical Devices | Radiation-Emitting Products | Vaccines, Blood & Biologics | Animal & Veterinary | Cosmetics | Tobacco Products

## Drugs

Home > Drugs > Resources for You > Information for Consumers (Drugs)

**Information for Consumers (Drugs)**

- Educational Resources: Free Drug-Related Publications
- JumpStarting Drug Review**
- Questions & Answers
- Buying & Using Medicine Safely
- Tips for Seniors
- Tips for Parents
- En Español
- Prescription Drug Advertising

**Resources for You**

## JumpStarting Drug Review

[f SHARE](#) [TWEET](#) [in LINKEDIN](#) [PIN IT](#) [EMAIL](#) [PRINT](#)

- [The Need for JumpStart](#)
- [How JumpStart Works](#)
- [JumpStart Testimonials](#)
- [Future Directions](#)



The JumpStart service is modernizing the drug review process—medical reviewers are using this service to quickly and thoroughly assess data from drug clinical trials, ensuring safe and effective products are approved for public use.



NONCLINICAL  
PHASE



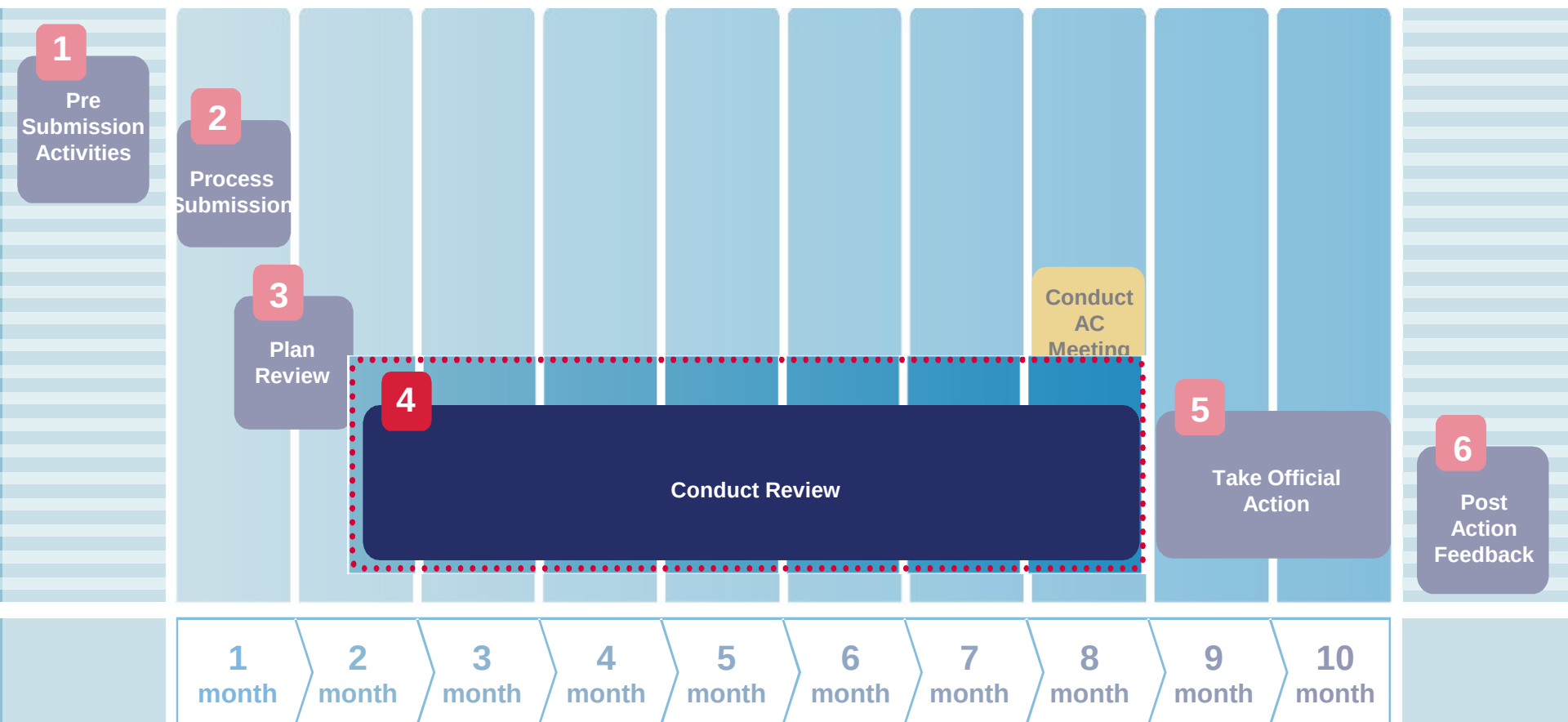
INVESTIGATIONAL  
PHASE



APPLICATION  
REVIEW PHASE



POST-MARKETING  
PHASE





# Demographic Service

Site Actions ▾

Browse

Page

Request Service

Explore Demographic Tool

Access Output Tables

## Demographic Service

Office of Computational Science

Better Data | Better Tools | Better Decisions

### Demographic Subgroup Analysis Service

Section 907 of the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA) directed the FDA to report on safety and effectiveness data by demographic subgroups including age, sex, race, and ethnicity. The Demographic Service provides targeted descriptive statistics and safety endpoint analysis for these subgroups.

Some of the tables and graphics we can assist in generating are:

Table 8.6 Subgroup Analysis for Primary Endpoint (SAFFL = 'Y')

| Subgroup                      | Treatment<br>N=144 |         | Placebo<br>N=140 |         | Odds Ratio<br>(95% CI) |
|-------------------------------|--------------------|---------|------------------|---------|------------------------|
|                               | n(%)               | Total,N | n(%)             | Total,N |                        |
| Safety Subgroup (TRTEMFL='Y') | 13 (9.0)           | 144     | 9 (6.4)          | 140     | 1.44 (0.60, 3.50)      |
| SEX                           |                    |         |                  |         |                        |
| Male                          | 7 (10.1)           | 69      | 4 (5.9)          | 68      | 1.81 (0.50, 6.48)      |
| Female                        | 6 (8.0)            | 75      | 5 (6.9)          | 72      | 1.17 (0.34, 4.00)      |
| AGE                           |                    |         |                  |         |                        |
| < 3                           | 0 (0.0)            | 12      | 1 (8.3)          | 12      | ---                    |
| >= 3 <= 6                     | 3 (9.7)            | 31      | 0 (0.0)          | 24      | 6.02 (0.30, 122.32)*   |
| >= 7 <= 16                    | 10 (9.9)           | 101     | 8 (7.7)          | 104     | 1.32 (0.50, 3.49)      |
| RACE                          |                    |         |                  |         |                        |
| White                         | 0 (0.0)            | 0       | 0 (0.0)          | 0       | ---                    |



# Demographic Service:

| Table 8.6 Subgroup Analysis for Primary Endpoint (SAFFL = 'Y') |                      |         |                   |         |                             |
|----------------------------------------------------------------|----------------------|---------|-------------------|---------|-----------------------------|
| Subgroup                                                       | [REDACTED]<br>N=1408 |         | Placebo<br>N=1408 |         | Risk Difference<br>(95% CI) |
|                                                                | n(%)                 | Total,N | n(%)              | Total,N |                             |
| <i>Safety Subgroup (TRTEMFL='Y')</i>                           | 1387 (98.5)          | 1408    | 1240 (88.1)       | 1408    | 10.44 (8.63, 12.25)         |
| <b>SEX</b>                                                     |                      |         |                   |         |                             |
| Male                                                           | 0 (0.0)              | 0       | 0 (0.0)           | 0       | --                          |
| Female                                                         | 1387 (98.5)          | 1408    | 1240 (88.1)       | 1408    | 10.44 (8.63, 12.25)         |
| <b>AGE</b>                                                     |                      |         |                   |         |                             |
| < 65                                                           | 1218 (98.5)          | 1236    | 1085 (87.9)       | 1235    | 10.69 (8.75, 12.63)         |
| >= 65                                                          | 169 (98.3)           | 172     | 155 (89.6)        | 173     | 8.66 (3.71, 13.61)          |
| <b>RACE</b>                                                    |                      |         |                   |         |                             |
| White                                                          | 1137 (98.4)          | 1156    | 991 (88.1)        | 1125    | 10.27 (8.24, 12.30)         |
| Black                                                          | 25 (100.0)           | 25      | 37 (82.2)         | 45      | 17.78 (6.61, 28.95)         |
| Asian                                                          | 186 (98.9)           | 188     | 174 (88.3)        | 197     | 10.61 (5.89, 15.33)         |
| American Indian                                                | 0 (0.0)              | 0       | 0 (0.0)           | 0       | --                          |
| Native Hawaiian                                                | 0 (0.0)              | 0       | 0 (0.0)           | 0       | --                          |
| Other                                                          | 39 (100.0)           | 39      | 38 (92.7)         | 41      | 7.32 (-0.65, 15.29)         |
| Missing Race                                                   | 0 (0.0)              | 0       | 0 (0.0)           | 0       | --                          |
| <b>ETHNICITY</b>                                               |                      |         |                   |         |                             |
| Hispanic                                                       | 22 (100.0)           | 22      | 27 (93.1)         | 29      | 6.90 (-2.33, 16.12)         |
| Non-Hispanic                                                   | 0 (0.0)              | 0       | 0 (0.0)           | 0       | --                          |
| Missing Ethnic                                                 | 1365 (98.5)          | 1386    | 1213 (88.0)       | 1379    | 10.52 (8.69, 12.36)         |
| <b>REGION</b>                                                  |                      |         |                   |         |                             |
| North America                                                  | 511 (99.0)           | 516     | 440 (92.8)        | 474     | 6.20 (3.73, 8.68)           |
| W. EUR, AUS and S. AFR                                         | 466 (97.3)           | 479     | 452 (86.3)        | 524     | 11.03 (7.74, 14.31)         |
| Asia, E. EUR and S. AME                                        | 410 (99.3)           | 413     | 348 (84.9)        | 410     | 14.40 (10.83, 17.96)        |
| Source: adsl, adae                                             |                      |         |                   |         |                             |
| Safety Subgroup (TRTEMFL='Y')                                  |                      |         |                   |         |                             |

# Check Coding

- Coding term
- Checking what patients said
  - Verbatim term to MedDRA Hierarchy
- Splitting and bundling
  - Hot flushes, hot flushes and sweating
- Labeling?





# AE Coding Report

| Reported Term (AETERM)                         | MedDRA PT (AEDECOD)           | Match Details                                       | Score | Record Count |
|------------------------------------------------|-------------------------------|-----------------------------------------------------|-------|--------------|
| ANXIETY ATTACK                                 | Anxiety                       | Direct match to LLT                                 | 100   | 2            |
| CLAMMINESS                                     | Cold sweat                    | Direct match to LLT                                 | 100   | 1            |
| DIZZINESS                                      | Dizziness                     | Direct match to PT                                  | 100   | 1            |
| HOARSENESS                                     | Dysphonia                     | Direct match to LLT                                 | 100   | 1            |
| NOSE BLEED                                     | Epistaxis                     | Direct match to LLT                                 | 100   | 2            |
| NOSEBLEED                                      | Epistaxis                     | Direct match to LLT                                 | 100   | 3            |
| FATIGUE                                        | Fatigue                       | Direct match to PT                                  | 100   | 1            |
| HEADACHE                                       | Headache                      | Direct match to PT                                  | 100   | 10           |
| NASAL CONGESTION                               | Nasal congestion              | Direct match to PT                                  | 100   | 1            |
| NASAL STUFFINESS                               | Nasal congestion              | Direct match to LLT                                 | 100   | 1            |
| NAUSEA                                         | Nausea                        | Direct match to PT                                  | 100   | 1            |
| NECK PAIN                                      | Neck pain                     | Direct match to PT                                  | 100   | 1            |
| SNEEZING                                       | Sneezing                      | Direct match to PT                                  | 100   | 1            |
| BLURRED VISION                                 | Vision blurred                | Direct match to LLT                                 | 100   | 1            |
| NOSE BLEED (EPISTAXIS)                         | Epistaxis                     | Alternate spelling of LLT Nose bleeds               | 99    | 1            |
| POST NASAL DRIP                                | Upper-airway cough syndrome   | Alternate spelling of LLT Postnasal drip            | 99    | 1            |
| CLAMMY/HOT                                     | Cold sweat                    | Alternate spelling of LLT Clammy                    | 96    | 1            |
| SWELLING RIGHT LIP                             | Lip swelling                  | Alternate spelling of LLT Swelling of lips          | 94    | 1            |
| BLEEDING OF THE NOSE                           | Epistaxis                     | Alternate spelling of LLT Bleeding nose             | 93    | 1            |
| HEADACHE - FRONTAL, ETHMOID                    | Headache                      | Alternate spelling of LLT Headache aggravated       | 86    | 1            |
| UNCONTROLLED HYPERTENSION WITH ARYTHMIAS       | Hypertension                  | Alternate spelling of LLT Uncontrolled hypertension | 85    | 1            |
| MILD DIZZINESS                                 | Dizziness                     | Partial word match to PT                            | 80    | 1            |
| ALLERGIC REACTION - RASH ON FACE, ARMS         | Dermatitis allergic           | Alternate spelling of LLT Allergic skin reaction    | 77    | 1            |
| FACIAL PAIN S/P BALLOON SINUPLASTY             | Facial pain                   | Alternate spelling of LLT Facial pain               | 77    | 1            |
| FEELING OF "SAND IN EYES"                      | Foreign body sensation in eye | Partial word match to PT                            | 11    | 1            |
| MIGRAINE                                       | Headache                      | Could not match                                     | 0     | 1            |
| PATIENT SWALLOWED 4X3 PLEDGET DURING TREATMENT | Medication error              | Could not match                                     | 0     | 1            |
| INCREASED POST NASAL DRAINAGE                  | Rhinorrhoea                   | Could not match                                     | 0     | 1            |



# Review Activity

Review the safety results of deaths, nonfatal serious adverse events, dropouts and/or discontinuations, TEAEs, and labs.

- Review individual patients
  - Use of Graphical Patient Profiles
  - Death reconciliation
- Perform exploratory adverse event analyses
  - Incidence tables of AEs along the MedDRA hierarchy
  - Forest plots
  - Analyze which PTs are driving the differences
  - Standardized MedDRA Queries
  - Custom MedDRA queries
- Identify important medical events (key preferred terms)
- Perform laboratory analyses that include Hy's Law laboratory criteria



# MAED: AE Incidence Table

|    | A                                                                                                | B      | C                  | D              | E      | F                  | G              | H               |
|----|--------------------------------------------------------------------------------------------------|--------|--------------------|----------------|--------|--------------------|----------------|-----------------|
| 1  | <b>WARNING: THIS IS ONLY AN EXPLORATORY ANALYSIS!</b>                                            |        |                    |                |        |                    |                |                 |
| 2  | Secondary preferred terms excluded.                                                              |        |                    |                |        |                    |                |                 |
| 3  | P-values should be used for ranking purposes only, not for determining statistical significance. |        |                    |                |        |                    |                |                 |
| 5  |                                                                                                  |        |                    |                |        | Placebo (N = 442)  |                |                 |
| 6  | SOC                                                                                              | Events | Number of subjects | Proportion (%) | Events | Number of subjects | Proportion (%) | RD (per hundred |
| 7  | Blood and lymphatic system disorders                                                             | 32     | 26                 | 2.5            | 5      | 5                  | 1.13           | 1.37            |
| 8  | Cardiac disorders                                                                                | 20     | 18                 | 1.73           | 11     | 10                 | 2.26           | -0.53           |
| 9  | Ear and labyrinth disorders                                                                      | 81     | 55                 | 5.3            | 8      | 8                  | 1.81           | 3.49            |
| 10 | Endocrine disorders                                                                              | 6      | 5                  | 0.48           | 1      | 1                  | 0.23           | 0.26            |
| 11 | Eye disorders                                                                                    | 77     | 64                 | 6.17           | 22     | 16                 | 3.62           | 2.55            |
| 12 | Gastrointestinal disorders                                                                       | 272    | 179                | 17.24          | 123    | 82                 | 18.55          | -1.31           |
| 13 | General disorders and administration site conditions                                             | 325    | 235                | 22.64          | 61     | 51                 | 11.54          | 11.1            |
| 14 | Hepatobiliary disorders                                                                          | 4      | 4                  | 0.39           | 0      | 0                  | 0              | 0.39            |
| 15 | Immune system disorders                                                                          | 6      | 5                  | 0.48           | 6      | 6                  | 1.36           | -0.88           |
| 16 | Infections and infestations                                                                      | 281    | 212                | 20.42          | 120    | 94                 | 21.27          | -0.84           |
| 17 | Injury, poisoning and procedural complications                                                   | 270    | 149                | 14.35          | 83     | 53                 | 11.99          | 2.36            |
| 18 | Investigations                                                                                   | 131    | 103                | 9.92           | 38     | 32                 | 7.24           | 2.68            |
| 19 | Metabolism and nutrition disorders                                                               | 69     | 61                 | 5.88           | 16     | 15                 | 3.39           | 2.48            |
| 20 | Musculoskeletal and connective tissue disorders                                                  | 155    | 121                | 11.66          | 57     | 45                 | 10.18          | 1.48            |
| 21 | Neoplasms benign, malignant and unspecified (incl cysts and polyps)                              | 2      | 2                  | 0.19           | 3      | 2                  | 0.45           | -0.26           |
| 22 | Nervous system disorders                                                                         | 1094   | 528                | 50.87          | 252    | 137                | 31             | 19.87           |
| 23 | Pregnancy, puerperium and perinatal conditions                                                   | 1      | 1                  | 0.1            | 0      | 0                  | 0              | 0.1             |
| 24 | Psychiatric disorders                                                                            | 261    | 159                | 15.32          | 80     | 55                 | 12.44          | 2.87            |
| 25 | Renal and urinary disorders                                                                      | 21     | 19                 | 1.83           | 7      | 5                  | 1.13           | 0.7             |
| 26 | Reproductive system and breast disorders                                                         | 25     | 22                 | 2.12           | 6      | 6                  | 1.36           | 0.76            |
| 27 | Respiratory, thoracic and mediastinal disorders                                                  | 86     | 68                 | 6.55           | 50     | 39                 | 8.82           | -2.27           |
| 28 | Skin and subcutaneous tissue disorders                                                           | 103    | 82                 | 7.9            | 40     | 31                 | 7.01           | 0.89            |

Introduction

Groups

SOC

HLGT

HLT

PT

Broad

Algorithmic

Narrow

SOC

HLGT

HLT

PT



# MAED: SMQ, Custom MedDRA Queries

|    |                                                                                                  |          |                      |                  |                   |                      |                  |                    |
|----|--------------------------------------------------------------------------------------------------|----------|----------------------|------------------|-------------------|----------------------|------------------|--------------------|
| 1  | <b>WARNING: THIS IS ONLY AN EXPLORATORY ANALYSIS!</b>                                            |          |                      |                  |                   |                      |                  |                    |
| 2  | * after SMQ name indicates SMQ with narrow terms only. Broad search will yield the same results. |          |                      |                  |                   |                      |                  |                    |
| 3  | Number in parenthesis before SMQ name represents SMQ level.                                      |          |                      |                  |                   |                      |                  |                    |
| 4  | P-values should be used for ranking purposes only, not for determining statistical significance. |          |                      |                  |                   |                      |                  |                    |
| 6  |                                                                                                  |          |                      |                  | Placebo (N = 442) |                      |                  |                    |
| 7  | SMQ (Narrow Search) ▾                                                                            | Events ▾ | Number of subjects ▾ | Proportion (%) ▾ | Events ▾          | Number of subjects ▾ | Proportion (%) ▾ | RD (per hundred ▾) |
| 8  | (1) Hostility/aggression                                                                         | 47       | 31                   | 2.99             | 4                 | 3                    | 0.68             | 2.31               |
| 9  | (2) Vestibular disorders                                                                         | 64       | 40                   | 3.85             | 4                 | 4                    | 0.9              | 2.95               |
| 10 | (1) Hearing and vestibular disorders                                                             | 74       | 48                   | 4.62             | 5                 | 5                    | 1.13             | 3.49               |
| 11 | (1) Biliary disorders                                                                            | 4        | 4                    | 0.39             | 0                 | 0                    | 0                | 0.39               |
| 12 | (2) Functional, inflammatory and gallstone related biliary disorders                             | 4        | 4                    | 0.39             | 0                 | 0                    | 0                | 0.39               |
| 13 | (1) Hyponatraemia/SIADH                                                                          | 12       | 9                    | 0.87             | 1                 | 1                    | 0.23             | 0.64               |
| 14 | (2) Hearing impairment                                                                           | 10       | 9                    | 0.87             | 1                 | 1                    | 0.23             | 0.64               |
| 15 | (1) Torsade de pointes/QT prolongation                                                           | 3        | 3                    | 0.29             | 0                 | 0                    | 0                | 0.29               |
| 16 | (1) Shock                                                                                        | 3        | 3                    | 0.29             | 0                 | 0                    | 0                | 0.29               |
| 17 | (2) Torsade de pointes, shock-associated conditions                                              | 3        | 3                    | 0.29             | 0                 | 0                    | 0                | 0.29               |
| 18 | (3) Gallbladder related disorders *                                                              | 3        | 3                    | 0.29             | 0                 | 0                    | 0                | 0.29               |
| 19 | (3) Gallstone related disorders *                                                                | 3        | 3                    | 0.29             | 0                 | 0                    | 0                | 0.29               |
| 20 | (1) Dyslipidaemia *                                                                              | 19       | 18                   | 1.73             | 3                 | 3                    | 0.68             | 1.06               |
| 21 | (1) Ischaemic heart disease                                                                      | 2        | 2                    | 0.19             | 0                 | 0                    | 0                | 0.19               |
| 22 | (2) Other ischaemic heart disease                                                                | 2        | 2                    | 0.19             | 0                 | 0                    | 0                | 0.19               |
| 23 | (1) Drug abuse, dependence and withdrawal                                                        | 2        | 2                    | 0.19             | 0                 | 0                    | 0                | 0.19               |
| 24 | (2) Drug abuse                                                                                   | 2        | 2                    | 0.19             | 0                 | 0                    | 0                | 0.19               |
| 25 | (1) Haemodynamic oedema, effusions and fluid overload *                                          | 16       | 14                   | 1.35             | 4                 | 3                    | 0.68             | 0.67               |
| 26 | (1) Hepatic disorders                                                                            | 16       | 12                   | 1.16             | 3                 | 3                    | 0.68             | 0.48               |
| 27 | (2) Drug related hepatic disorders - comprehensive search                                        | 16       | 12                   | 1.16             | 3                 | 3                    | 0.68             | 0.48               |
| 28 | (3) Liver related investigations, signs and symptoms                                             | 16       | 12                   | 1.16             | 3                 | 3                    | 0.68             | 0.48               |

Algorithmic SMQ

Broad SMQ      Narrow SMQ



# JumpStart: MedDRA at a Glance

## MedDRA at a Glance Comparison Analysis

Treatment arm:

Control arm:

Risk difference threshold (%):

Relative risk threshold:

Negative log p-value threshold:

Choose your arms and type in your thresholds in the yellow input cells  
Look below to see which terms have signals; you may have to scroll down  
The colors in the signal columns tell you about the signal:

 This term shows a signal

 A term above or below in MedDRA shows a signal

| Level | System Organ Class         | High-Level Group Term                                 | High-Level Term                                      | Preferred Term       | DME | Signal | Signal At |      |     |    |               | Treatment: |               | Control: |      | Risk Difference | Relative Risk* | Cont Corr | Negative Log P-value | Sort Order |
|-------|----------------------------|-------------------------------------------------------|------------------------------------------------------|----------------------|-----|--------|-----------|------|-----|----|---------------|------------|---------------|----------|------|-----------------|----------------|-----------|----------------------|------------|
|       |                            |                                                       |                                                      |                      |     |        | SOC       | HLGT | HLT | PT |               |            |               |          |      |                 |                |           |                      |            |
|       |                            |                                                       |                                                      |                      |     |        |           |      |     |    |               |            |               |          |      |                 |                |           |                      |            |
|       |                            |                                                       |                                                      |                      |     |        |           |      |     |    | Subject Count | %          | Subject Count | %        |      |                 |                |           |                      |            |
| 1     | Gastrointestinal disorders |                                                       |                                                      |                      |     |        |           |      |     |    | 270           | 32.7       | 82            | 19.9     | 12.8 | 1.6             |                | 13.2      |                      |            |
| 2     | Gastrointestinal disorders | Abdominal hernias and other abdominal wall conditions |                                                      |                      |     |        |           |      |     |    | 3             | 0.4        | 0             | 0.0      | 0.4  | 3.5 *           |                | 0.6       |                      |            |
| 3     | Gastrointestinal disorders | Abdominal hernias and other abdominal wall conditions | Abdominal hernias, site unspecified                  |                      |     |        |           |      |     |    | 0             | 0.0        | 0             | 0.0      | 0.0  | 0.5 *           |                | .         |                      |            |
| 4     | Gastrointestinal disorders | Abdominal hernias and other abdominal wall conditions | Abdominal hernias, site unspecified                  | Abdominal hernia     |     |        |           |      |     |    | 0             | 0.0        | 0             | 0.0      | 0.0  | 0.5 *           |                | .         |                      |            |
| 3     | Gastrointestinal disorders | Abdominal hernias and other abdominal wall conditions | Diaphragmatic hernias                                |                      |     |        |           |      |     |    | 3             | 0.4        | 0             | 0.0      | 0.4  | 3.5 *           |                | 0.6       |                      |            |
| 4     | Gastrointestinal disorders | Abdominal hernias and other abdominal wall conditions | Diaphragmatic hernias                                | Hiatus hernia        |     |        |           |      |     |    | 3             | 0.4        | 0             | 0.0      | 0.4  | 3.5 *           |                | 0.6       |                      |            |
| 3     | Gastrointestinal disorders | Abdominal hernias and other abdominal wall conditions | Umbilical hernias                                    |                      |     |        |           |      |     |    | 0             | 0.0        | 0             | 0.0      | 0.0  | 0.5 *           |                | .         |                      |            |
| 4     | Gastrointestinal disorders | Abdominal hernias and other abdominal wall conditions | Umbilical hernias                                    | Umbilical hernia     |     |        |           |      |     |    | 0             | 0.0        | 0             | 0.0      | 0.0  | 0.5 *           |                | .         |                      |            |
| 2     | Gastrointestinal disorders | Anal and rectal conditions NEC                        |                                                      |                      |     |        |           |      |     |    | 1             | 0.1        | 1             | 0.2      | -0.1 | 0.5             |                | 0.0       |                      |            |
| 3     | Gastrointestinal disorders | Anal and rectal conditions NEC                        | Anal and rectal disorders NEC                        |                      |     |        |           |      |     |    | 1             | 0.1        | 1             | 0.2      | -0.1 | 0.5             |                | 0.0       |                      |            |
| 4     | Gastrointestinal disorders | Anal and rectal conditions NEC                        | Anal and rectal disorders NEC                        | Anal fissure         |     |        |           |      |     |    | 1             | 0.1        | 1             | 0.2      | -0.1 | 0.5             |                | 0.0       |                      |            |
| 3     | Gastrointestinal disorders | Anal and rectal conditions NEC                        | Anal and rectal signs and symptoms                   |                      |     |        |           |      |     |    | 1             | 0.1        | 0             | 0.0      | 0.1  | 1.5 *           |                | 0.0       |                      |            |
| 4     | Gastrointestinal disorders | Anal and rectal conditions NEC                        | Anal and rectal signs and symptoms                   | Anorectal discomfort |     |        |           |      |     |    | 1             | 0.1        | 0             | 0.0      | 0.1  | 1.5 *           |                | 0.0       |                      |            |
| 2     | Gastrointestinal disorders | Benign neoplasms gastrointestinal                     |                                                      |                      |     |        |           |      |     |    | 2             | 0.2        | 1             | 0.2      | 0.0  | 1.0             |                | 0.0       |                      |            |
| 3     | Gastrointestinal disorders | Benign neoplasms gastrointestinal                     | Benign neoplasms gastrointestinal (excl oral cavity) |                      |     |        |           |      |     |    | 2             | 0.2        | 1             | 0.2      | 0.0  | 1.0             |                | 0.0       |                      |            |
| 4     | Gastrointestinal disorders | Benign neoplasms gastrointestinal                     | Benign neoplasms gastrointestinal                    | Colonic polyp        |     |        |           |      |     |    | 1             | 0.1        | 1             | 0.2      | -0.1 | 0.5             |                | 0.0       |                      |            |
| 4     | Gastrointestinal disorders | Benign neoplasms gastrointestinal                     | Benign neoplasms gastrointestinal                    | Gastric polyps       |     |        |           |      |     |    | 0             | 0.0        | 0             | 0.0      | 0.0  | 0.5 *           |                | .         |                      |            |
| 4     | Gastrointestinal disorders | Benign neoplasms gastrointestinal                     | Benign neoplasms gastrointestinal                    | Polyp colorectal     |     |        |           |      |     |    | 1             | 0.1        | 0             | 0.0      | 0.1  | 1.5 *           |                | 0.0       |                      |            |
| 2     | Gastrointestinal disorders | Dental and gingival conditions                        |                                                      |                      |     |        |           |      |     |    | 37            | 4.5        | 10            | 2.4      | 2.1  | 1.9             |                | 2.5       |                      |            |



# JumpStart: MedDRA at a Glance

## Adverse Events Data Validation

Data validation is performed on all adverse events experienced by validated subjects, of which there were 41 in this study. Adverse events can be excluded for the following reasons:

- 1. The start date of the adverse event was missing or could not be interpreted as a date with at least month and year
- 2. The start date of the adverse event was not between the subject's first exposure date and last exposure date + 999 days
- 3. The body system or organ class (AEBODSYS) or dictionary-derived term (AEDECOD) was blank

No adverse events were excluded during data validation.

## MedDRA Matching

MedDRA matching is performed on all adverse events which passed data validation, of which there were 41 in this study.

| MedDRA Matching Summary<br>N=41 |                |                        |            |
|---------------------------------|----------------|------------------------|------------|
| MedDRA Version                  | Match<br>Count | Non-<br>Match<br>Count | Match<br>% |
| MedDRA hierarchy version 18.0   | 41             | 0                      | 100.0      |



# JumpStart:



## Preferred Term Analysis by Toxicity Grade

NDA/BLA: [REDACTED]

Study: pooled

Analysis run date: 2016-08-12 8:51:44 AM

Where subject count is the number of subjects experiencing at least one adverse event at the stated toxicity grade using the maximum toxicity grade per subject, organ class, and term

| Adverse Event                                     | [REDACTED] N=378 |      |               |      |               |     |
|---------------------------------------------------|------------------|------|---------------|------|---------------|-----|
|                                                   | All Grades       |      | Grades 3/4    |      | Grade 5       |     |
|                                                   | Subject Count    | %    | Subject Count | %    | Subject Count | %   |
| <b>Blood and lymphatic system disorders</b>       |                  |      |               |      |               |     |
| Anaemia                                           | 157              | 41.5 | 85            | 22.5 | 0             | 0.0 |
| Febrile neutropenia                               | 4                | 1.1  | 4             | 1.1  | 0             | 0.0 |
| Granulocytopenia                                  | 1                | 0.3  | 1             | 0.3  | 0             | 0.0 |
| Increased tendency to bruise                      | 1                | 0.3  | 0             | 0.0  | 0             | 0.0 |
| Leukocytosis                                      | 1                | 0.3  | 0             | 0.0  | 0             | 0.0 |
| Leukopenia                                        | 9                | 2.4  | 3             | 0.8  | 0             | 0.0 |
| Lymphadenopathy                                   | 2                | 0.5  | 0             | 0.0  | 0             | 0.0 |
| Lymphopenia                                       | 7                | 1.9  | 0             | 0.0  | 0             | 0.0 |
| Macrocytosis                                      | 1                | 0.3  | 0             | 0.0  | 0             | 0.0 |
| Neutropenia                                       | 27               | 7.1  | 18            | 4.8  | 0             | 0.0 |
| Normochromic normocytic anaemia                   | 1                | 0.3  | 0             | 0.0  | 0             | 0.0 |
| Thrombocytopenia                                  | 48               | 12.7 | 10            | 2.6  | 0             | 0.0 |
| <b>Cardiac disorders</b>                          |                  |      |               |      |               |     |
| Angina pectoris                                   | 1                | 0.3  | 0             | 0.0  | 0             | 0.0 |
| Cardiac failure                                   | 1                | 0.3  | 0             | 0.0  | 0             | 0.0 |
| Myocardial ischaemia                              | 1                | 0.3  | 1             | 0.3  | 0             | 0.0 |
| Palpitations                                      | 11               | 2.9  | 0             | 0.0  | 0             | 0.0 |
| Pericardial effusion                              | 1                | 0.3  | 1             | 0.3  | 0             | 0.0 |
| Sinus tachycardia                                 | 1                | 0.3  | 0             | 0.0  | 0             | 0.0 |
| Tachycardia                                       | 2                | 0.5  | 1             | 0.3  | 0             | 0.0 |
| <b>Congenital, familial and genetic disorders</b> |                  |      |               |      |               |     |
| Long QT syndrome congenital                       | 1                | 0.3  | 1             | 0.3  | 0             | 0.0 |
| <b>Ear and labyrinth disorders</b>                |                  |      |               |      |               |     |
| Deafness                                          | 1                | 0.3  | 0             | 0.0  | 0             | 0.0 |
| Ear discomfort                                    | 1                | 0.3  | 0             | 0.0  | 0             | 0.0 |
| Ear pain                                          | 3                | 0.8  | 0             | 0.0  | 0             | 0.0 |
| Tinnitus                                          | 7                | 1.9  | 0             | 0.0  | 0             | 0.0 |
| Vertigo                                           | 8                | 2.1  | 0             | 0.0  | 0             | 0.0 |



# JumpStart: Liver Analyses

## *Liver Lab Tests Greater Than Upper Limit of Normal*

NDA/BLA [REDACTED]

Study: [REDACTED]

Analysis run date: 2016-07-29 1:01:58 PM

| Liver Lab Test | [REDACTED]  |               |               |
|----------------|-------------|---------------|---------------|
|                | N = 204     |               |               |
| ALT ≥ ULN      | Event Count | Subject Count | % of Subjects |
| 2x ULN         | 406         | 107           | 52.45         |
| 3x ULN         | 163         | 71            | 34.80         |
| 5x ULN         | 42          | 28            | 13.73         |
| 10x ULN        | 7           | 6             | 2.94          |
| 20x ULN        | 1           | 1             | 0.49          |
| AST ≥ ULN      | Event Count | Subject Count | % of Subjects |
| 2x ULN         | 183         | 78            | 38.24         |
| 3x ULN         | 64          | 39            | 19.12         |
| 5x ULN         | 17          | 11            | 5.39          |
| 10x ULN        | 4           | 1             | 0.49          |
| 20x ULN        | 0           | 0             | 0.00          |
| ALP ≥ ULN      | Event Count | Subject Count | % of Subjects |
| 2x ULN         | 35          | 13            | 6.37          |
| 3x ULN         | 15          | 7             | 3.43          |
| 5x ULN         | 10          | 3             | 1.47          |
| 10x ULN        | 3           | 1             | 0.49          |
| 20x ULN        | 0           | 0             | 0.00          |
| TB ≥ ULN       | Event Count | Subject Count | % of Subjects |
| 1.5x ULN       | 56          | 16            | 7.84          |
| 2x ULN         | 24          | 12            | 5.88          |
| 3x ULN         | 12          | 7             | 3.43          |

Notes: All scores are post-baseline. Subject scores may be counted more than once in that th



NONCLINICAL  
PHASE



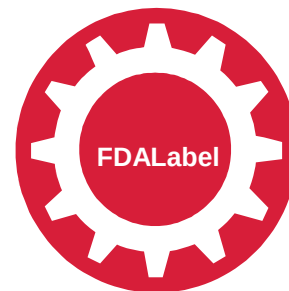
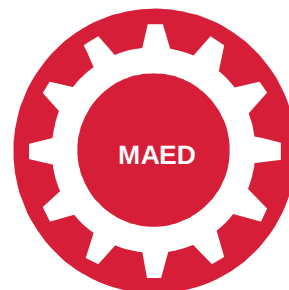
INVESTIGATIONAL  
PHASE



APPLICATION  
REVIEW PHASE



POST-MARKETING  
PHASE





# FDALabel



**U.S. FOOD & DRUG**  
ADMINISTRATION

[A to Z Index](#) | [Follow FDA](#) | [En Español](#)

Home | Food | Drugs | Medical Devices | Radiation-Emitting Products | Vaccines, Blood &amp; Biologics | Animal &amp; Veterinary | Cosmetics | Tobacco Products

**Science & Research**

Home &gt; Science &amp; Research &gt; Bioinformatics Tools

**Bioinformatics Tools**

[Gene Ontology for Functional Analysis \(GOFFA\)](#)

**FDALabel: Full-Text Search of Drug Labeling**

[NCTR Liver Cancer Database \(NCTRlodb\)](#)

[atBioNet](#)

ArrayTrack™

▼

[Decision Forest](#)

Endocrine Disruptor Knowledge Base (EDKB)

▼

Estrogenic Activity Database (EADB)

▼

MicroArray Quality Control (MAQC)

▼

Mold2

▼

Liver Toxicity Knowledge Base (LTKB)

▼

SNPTrack

▼

## FDALabel: Full-Text Search of Drug Labeling

[SHARE](#) [TWEET](#) [LINKEDIN](#) [PIN IT](#) [EMAIL](#) [PRINT](#)

[Click to subscribe for e-mail updates.](#)



To use FDALabel (version 1.0) enter the following URL into your Google Chrome or Firefox browser (the database will not work properly with Internet Explorer):

**<https://rm2.scinet.fda.gov/druglabel/#simsearch-0>**

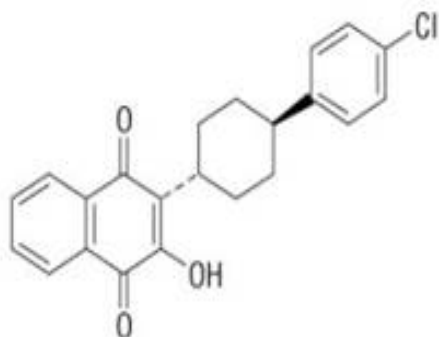
[Overview of FDALabel Database](#)  
[Potential Users](#)  
[What is Included in Drug Labeling?](#)  
[Database Features](#)  
[Updates and Statistics](#)  
[User Guides](#)  
[References](#)  
[Contact Information](#)  
[Disclaimer](#)



# FDA Label: Output

## 11 DESCRIPTION

MEPRON (atovaquone) is a quinone antimicrobial drug for **oral** administration. The chemical name of atovaquone is *trans*-2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthalenedione. Atovaquone is a yellow crystalline solid that is practically insoluble in water. It has a molecular weight of 366.84 and the molecular formula  $C_{22}H_{19}ClO_3$ . The compound has the following structural formula:



MEPRON **suspension** is a formulation of micro-fine particles of atovaquone.

Each 5 mL of MEPRON **suspension** contains 750 mg of atovaquone and the inactive ingredients **benzyl alcohol**, flavor, poloxamer 188, purified water, saccharin sodium, and xanthan gum.



# MAED: Database Analysis of FAERS



Office of Computational Science  
Better Data | Better Tools | Better Decisions



U.S. Food and Drug Administration  
**MAED**  
MedDRA-Based Adverse  
Event Diagnostics

HomeMy FilesUsers Activity LogClean-Up Users FilesUpdate MedDRA VersionLogout

Page 2: Select Analysis Type and File(s)

Page 2 of 6 ?

Select the type of Analysis

☐ Clinical Trial Analysis  
☒ Database (numerator) Analysis

Input SAS Datasets (SAS7BDAT or XPT file)

Adverse Event File :  Browse...

PreviousNextCancel



NONCLINICAL  
PHASE



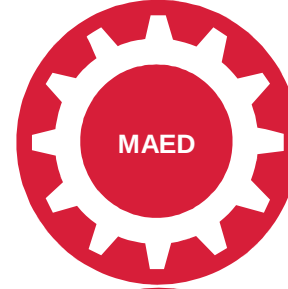
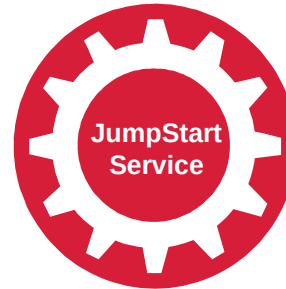
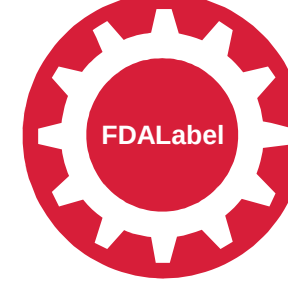
INVESTIGATIONAL  
PHASE



APPLICATION  
REVIEW PHASE



POST-MARKETING  
PHASE



# Medical Informatics: science of learning from data



Decisions



Information

Data

|    | $x[n]$       | $r[n]$       | Solution at iteration $n$ |
|----|--------------|--------------|---------------------------|
| 4  | -2.139833188 | -3.195957170 | -1.945611656              |
| 5  | -1.884840650 | -1.173224163 | -2.002174399              |
| 6  | -2.102184058 | -1.221204184 | -2.004334698              |
| 7  | -1.924209391 | -1.169466973 | -2.006245518              |
| 8  | -2.076393823 | -1.201867210 | -2.007277742              |
| 9  | -1.949770490 | -1.168987472 | -2.008149496              |
| 10 | -2.058089301 | -1.191861309 | -2.008670658              |
| 11 | -1.967207241 | -1.169680559 | -2.009094541              |
| 12 | -2.044905429 | -1.186126702 | -2.009363945              |
| 13 | -1.979399621 | -1.170714188 | -2.009576697              |

Example 1: Solving  $\sin(x) - \frac{1}{2}x = 0.1$  by fixed-point iteration

# Conclusions

- Subject level datasets help us understand and do better reviews
- Data standards help us automate standard analyses using review tools
- Better reviews serve everyone
- Standards serve everyone

