FDA

Office of Computational Science

BETTER DATA | BETTER TOOLS | BETTER DECISIONS

The Background

1. Not All Applicants' reviews to be Audited Service

2. Set of Jumpstart analyses are included in this

3. What we need "dummy" data to generate the reports

The Premise

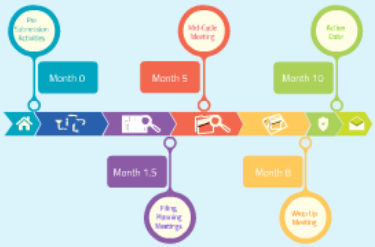
Let's Interact

We'll ask questions, you respond, using either:

1. Poll Everywhere - PollEv.com/jessej511

2. Microphone

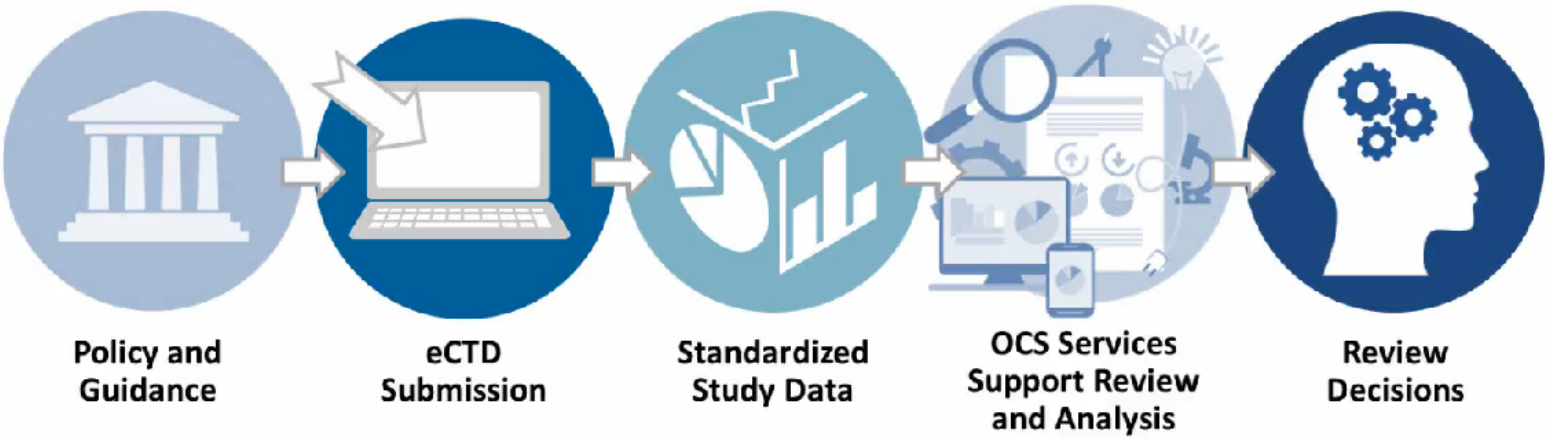
21st Century Review



Office of Computational Science

BETTER DATA | BETTER TOOLS | BETTER DECISIONS

From Policy to Review



The Premise

You're a Clinical Reviewer - You Have To make a Filing Determination

The Background

1. Not All Applications receive a JumpStart Service

2. Not all JumpStart analyses are included today

3. We've used "dummy" data to generate the reports

Let's Interact

We'll ask questions, you respond, using either:

1. Poll Everywhere - PollEv.com/jessej511

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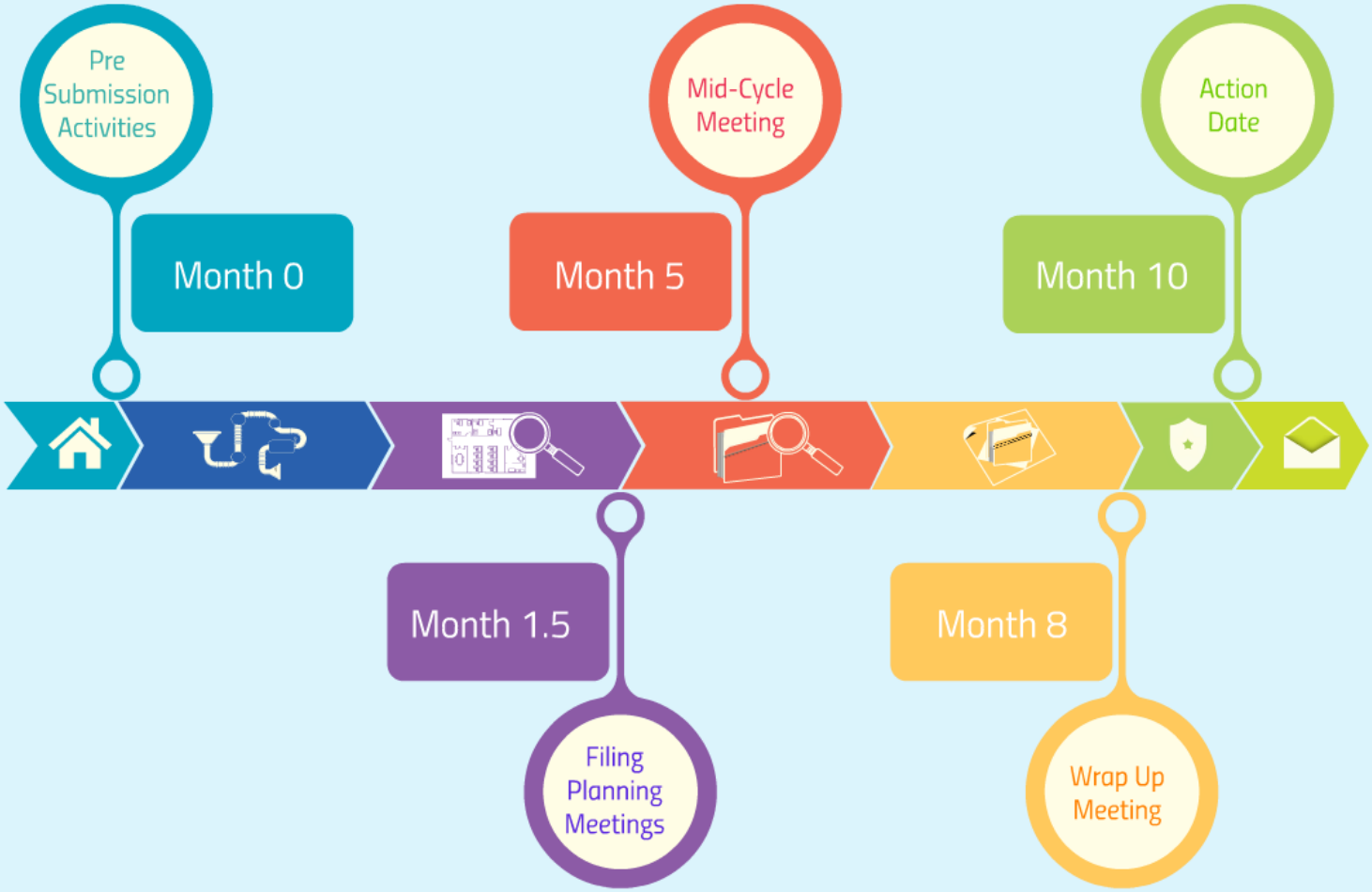
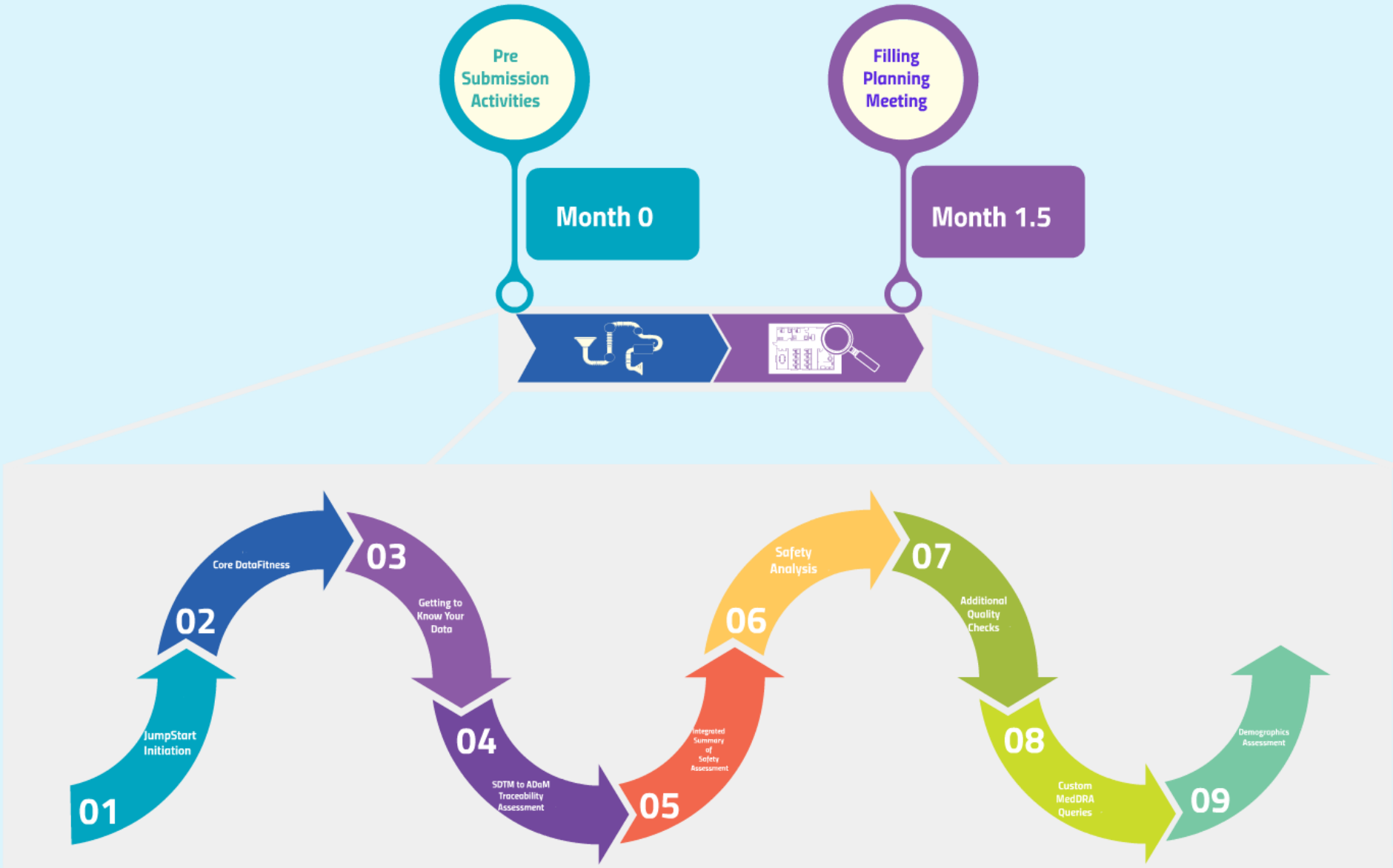
21st Century Review




Pre Submission Activities
Month 0
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Month 1.5
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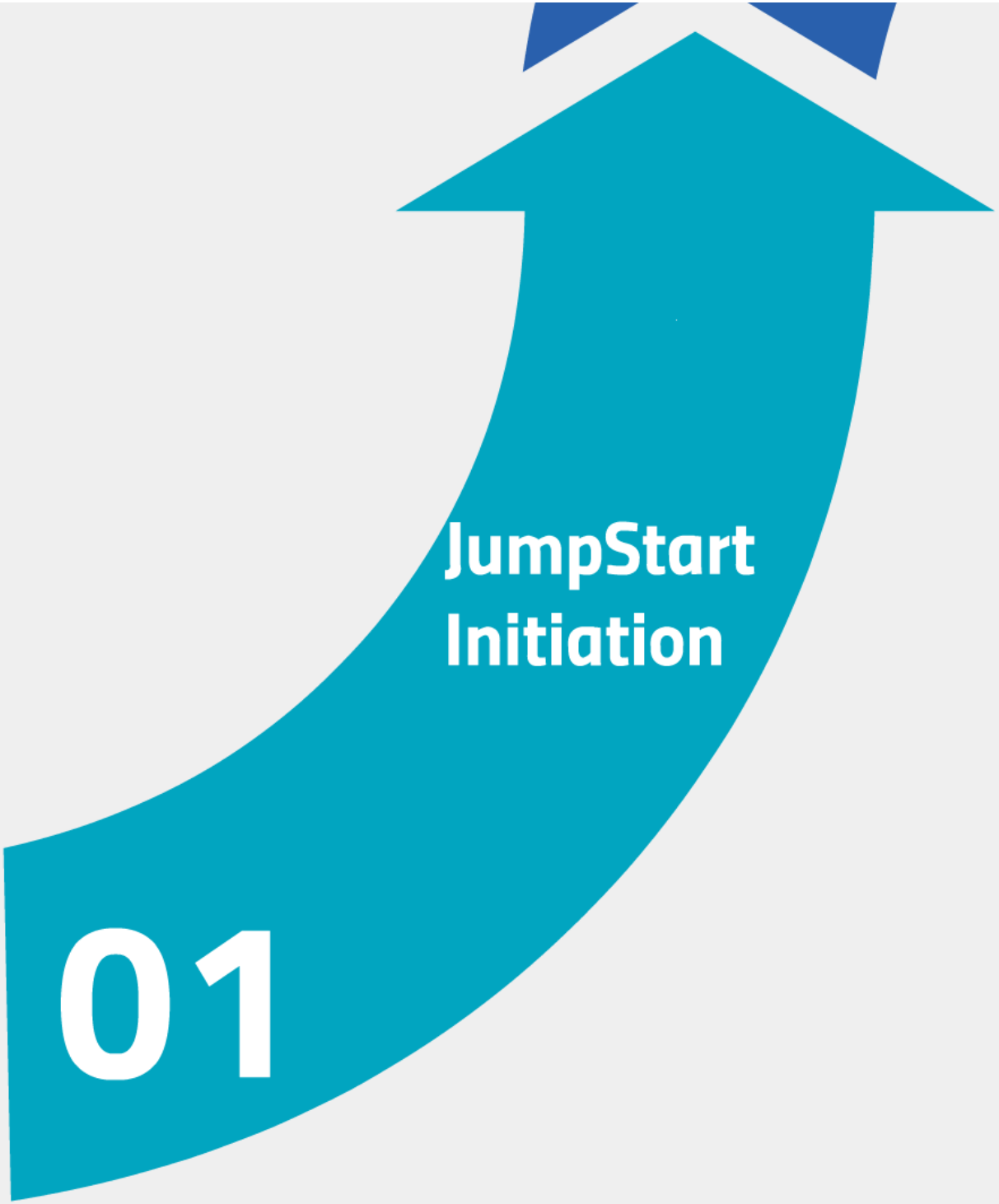
JumpStart
Initiation
01

JumpStart uses SDTM and ADaM data

- **Study Data Tabulation Model – SDTM** is a representation of data collected on subjects in a clinical trial. Sources include Case Report Forms (CRF), Electronic Data Capture (EDC), Electronic transfers (e.g., lab, ECG), and Electronic Health Records (EHR)
- **Analysis Data Model – ADaM** datasets are typically built on/derivable from SDTM domains and provide the data elements and derived data needed for a specific analyses

SDTM Assessment

- Assessment of the Define file, SDRG, and all **SDTM** domains
- Identification of potential information requests for the applicant

SDTM to ADaM Traceability

- Comparison of key variables between **SDTM** and **ADaM** datasets

ISS Assessment

- Summary of ISS documents and **ADaM** datasets provided

Core DataFitness

02

Core DataFitness Assessments (Core DF)

- Core DataFitness Assessments (CoreDF) are a set of automated reports
  - Data Quality information for clinical reviewers
  - Early in the review process.
  - Common data quality errors
  - Standalone
  - Self-explanatory
- Approximately 75% of data quality information previously provided only through a JumpStart Service.
- **Pilot**

AE Term Matching Report

Description

This report will help you compare verbatim terms in the variable AETERM to the MedDRA terms (LLT or PT) they were coded to in the variable AEDECOD. The uderlying logic uses a keystroke by keystroke match of the two phrases, and puts a score to how similar each term is. ***It does not use any medical context*** . A score of 100 means the two terms are identical. Case does not impact score. A low score does not mean that data was poorly coded.

Adverse Events Coding of Verbatim Terms				
Verbatim Term (AETERM)	MedDRA PT (AEDECOD)	Match Details	Score	Rows Impacted
WEAK AND SHAKY - HYPOGLYCEMIC EPISODE	Asthenia	Could not match	0	1
SYMPTOMATIC HYPOGLYCEMIA (BS=46MG/DL)	Blood glucose decreased	Could not match	0	1
SYMPTOMATIC HYPOGLYCEMIA (BS=47MG/DL)	Blood glucose decreased	Could not match	0	1
SYMPTOMATIC HYPOGLYCEMIA (BS=70MG/DL)	Blood glucose decreased	Could not match	0	1
HYPOGLYCEMIA - SHAKY, SWEATY	Hyperhidrosis	Could not match	0	1
HYPOGLYCEMIA, SHAKY, SWEATY	Hyperhidrosis	Could not match	0	3
SYMPTOMATIC HYPOGLYCEMIA (BS=73MG/DL)	Impaired healing	Could not match	0	1
HYPOGLYCEMIA - SHAKY, SWEATY	Tremor	Could not match	0	1
HYPOGLYCEMIA, SHAKY, SWEATY	Tremor	Could not match	0	3
HYPOGLYCEMIC "SHAKE"	Tremor	Could not match	0	1
HYPOGLYCEMIC EVENT - SHAKING	Tremor	Could not match	0	1
WEAK AND SHAKY - HYPOGLYCEMIC EPISODE	Tremor	Could not match	0	1
OCCASIONAL SYMPTOMATIC HYPOGLYCEMIA	Hypoglycaemia	Partial word match to PT	35	1
SYMPTOMATIC HYPOGLYCEMIA (BS=46MG/DL)	Hypoglycaemia	Partial word match to PT	35	1
SYMPTOMATIC HYPOGLYCEMIA (BS=47MG/DL)	Hypoglycaemia	Partial word match to PT	35	1
SYMPTOMATIC HYPOGLYCEMIA (BS=70MG/DL)	Hypoglycaemia	Partial word match to PT	35	1

Question: Is a hypoglycemic events signal being diluted?

Description

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Look how all these terms don't align under a single clinical concept

Supplemental Datasets Report

Application: OCS Data

Generated: 2018-02-15T22:59:06

Study: PhUSE CSS 2018

Back to Summary

Description

Here is a list of variables available in supplemental datasets (starts with SUPP) - a place where applicants put information that does not fit well into an existing SDTM structure. These variables may be useful for analysis.

Supplemental Contents

Dataset	Variable Name	Variable Label (QLABEL)	Count
SUPPEG	INFARD	Infarction Detail	50

Question: Wouldn't you want to know more about these 50 infarctions?

Application: OCS Data
Generated: 2018-02-15T22:59:06
Study: PhUSE CSS 2018
Back to Summary

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SUPPEG	INFARD	Infarction Detail	50

AESTCTC after DSSTDTC Report

Application: OCS Data

Generated: 2018-02-15T22:59:06

Study: PhUSE CSS 2018

Back to Summary

Finding

324 (10.3%) of adverse events started after the last disposition date in the DS dataset

Impact

This usually occurs in ongoing studies or if subject discontinuation date is not collected.

AE start date is after the latest Disposition date

--SEQ	USUBJID	AEDECOD	AESTDTC
286	017	Blood creatine phosphokinase increase	2001-02-01
287	017	Lower respiratory tract infection	2001-03-25
288	017	Proteinuria	2001-03-29
289	017	Diverticulitis	2001-06-08
290	017	Cardiac failure congestive	2001-06-08
291	017	Left ventricular dysfunction	2001-06-08
292	017	Ventricular tachycardia	2001-06-24

Question: This subject was having a lot of problems – what's their story? What arm were they in?

Application: OCS Data
Study: PhUSE CSS 2018
Generated: 2018-02-15T22:59:06

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291	017	Left ventricular dysfunction	2001-06-08
292	017	Ventricular tachycardia	2001-06-24

Potential duplicate AEs Report

Application: OCS Data
Generated: 2018-02-15T22:59:06
Study: PhUSE CSS 2018
Back to Summary

Finding

48 (1.5%) of adverse events are potential duplicates

Impact

Potential duplicates are any adverse events with the same Unique Subject Identifier (USUBJID), Reported Term (AETERM), Dictionary-Derived Term (AEDECOD), Category (AECAT), Subcategory (AESCAT), Severity (AESEV), Toxicity Grade (AETOXGR), and Start Date/Time (AESTDTC). ***Data manipulation may be required to avoid double counting.***

Duplicate records in AE domain

USUBJID	AESEQ	AEGRP	AESPID	AETERM	AEDECOD	AEBODSYS	AESEV	AESER	AEACN	AEREL	A
027	3.1	3	2	VOMITING	Vomiting	Gastrointestinal disorders	SEVERE	N	DOSE NOT CHANGED	POSSIBLE, REASONABLE PC	2
027	3.2	3	2	VOMITING	Vomiting	Gastrointestinal disorders	SEVERE	N	DOSE NOT CHANGED	POSSIBLE, REASONABLE PC	2
044	4.1	4	2	VOMITING	Vomiting	Gastrointestinal disorders	SEVERE	Y	DRUG WITHDRAWN	NO, NOT RELATED, NOT SL	2
044	4.2	4	2	VOMITING	Vomiting	Gastrointestinal disorders	SEVERE	Y	DRUG WITHDRAWN	NO, NOT RELATED, NOT SL	2

Question: The overall amount of potential duplicates is small – but these two sets are classified as severe. Is that enough to skew a signal?

Application: OCS Data — Generated: 2018-02-15T22:59:06

Study: PhUSE CSS 2018

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Duplicate records in AE domain

USUBJID	AESEQ	AEGRP	AESPID	AETERM	AEDECOD	AEBODSYS	AESEV	AESER	AEACN	AEREL	A
027	3.1	3	2	VOMITING	Vomiting	Gastrointestinal disorders	SEVERE	N	DOSE NOT CHANGED	POSSIBLE, REASONABLE PC	2
027	3.2	3	2	VOMITING	Vomiting	Gastrointestinal disorders	SEVERE	N	DOSE NOT CHANGED	POSSIBLE, REASONABLE PC	2
044	4.1	4	2	VOMITING	Vomiting	Gastrointestinal disorders	SEVERE	Y	DRUG WITHDRAWN	NO, NOT RELATED, NOT SU	2
044	4.2	4	2	VOMITING	Vomiting	Gastrointestinal disorders	SEVERE	Y	DRUG WITHDRAWN	NO, NOT RELATED, NOT SU	2

DS Coding Report

Application: OCS Data
Study: PhUSE CSS 2018
Back to Summary

Description

This report will help you compare verbatim terms in the variable DSTERM to the terms they were coded to in the variable DSDE keystroke match of the two phrases, and puts a score to how similar each term is. ***It does not use any medical context*** . A score does not impact score. A low score does not mean that data was poorly coded.

Disposition Coding Quality

Reported Term (DSTERM)	Standardized Ter (DSDECOD)
CONTINUED HYPERGLYCEMIA	OTHER
D/C PER TAKEDA DUE TO LACK OF ADEQUATE DOUBLE BLIND DRUG SUPPLY	OTHER
DETERIORATING GLYCEMIC CONTROL PER DAILY FBG CHECKS ON HOME GLUCOMETER	OTHER
DISCONTINUED DUE TO INSUFFICIENT DRUG SUPPLY	OTHER
DISCONTINUED DUE TO INSUFFICIENT DRUG SUPPLY.	OTHER
DISCONTINUED DUE TO PENDING SURGERY OF PRE EXISTING CONDITION	OTHER
DROPPED PER SPONSOR REQUEST - PATIENT DISCONTINUED DUE TO INSUFFICIENT DRUG SUPPLY	OTHER
DROPPED PER SPONSOR REQUEST DUE TO INSUFFICIENT DRUG SUPPLY.RE-SCREENED UNDER NEW NUMBER	OTHER
HYPERTRIGLYCERIDEMIA DIABETIC LIPEMIA	OTHER
INVESTIGATOR OPINION: EXCLUDE PT DUE TO ELEVATED ALKALINE PHOSPHATASE FOUND AT V-1, V-1 RETEST & V-2	OTHER
PATIENT #88136 WAS DISCONTINUED DUE TO INSUFFICIENT DRUG SUPPLY. RE-SCREENED UNDER NEW NUMBER	OTHER
PATIENT DISCONTINUED DUE TO INSUFFICIENT DRUG SUPPLY. PATIENT WAS RE-SCREENED UNDER A NEW NUMBER	OTHER

Question: why do so many verbatim terms that could be easily coded to the designated controlled terminology get coded instead to 'OTHER'?

keystroke match of the two phrases, and puts a score to how similar each term is. ***It does not use any medical context***. A score does not impact score. A low score does not mean that data was poorly coded.

Disposition Coding Quality

Reported Term (DSTERM)	Standardized Term (DSDECOD)
CONTINUED HYPERGLYCEMIA	OTHER
D/C PER TAKEDA DUE TO LACK OF ADEQUATE DOUBLE BLIND DRUG SUPPLY	OTHER
DETERIORATING GLYCEMIC CONTROL PER DAILY FBG CHECKS ON HOME GLUCOMETER	OTHER
DISCONTINUED DUE TO INSUFFICIENT DRUG SUPPLY	OTHER
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DROPPED PER SPONSOR REQUEST DUE TO INSUFFICIENT DRUG SUPPLY.RE-SCREENED UNDER NEW NUMBER	OTHER
HYPERTRIGLYCERIDEMIA DIABETIC LIPEMIA	OTHER
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PATIENT DISCONTINUED DUE TO INSUFFICIENT DRUG SUPPLY. PATIENT WAS RE-SCREENED UNDER A NEW NUMBER	OTHER

Inconsistent Units Report

Application: OCS Data

Generated: 2018-02-15T22:59:06

Study: PhUSE CSS 2018

Back to Summary

Finding

4,702 (2.6%) of observations use inconsistent values for Standard Units (LBSTRESU)

Impact

Manipulation or sub-setting may be needed before the effected records are analyzed.

Inconsistent value for Standard Units

LBTESTCD	LBTEST	LBCAT	LBSCA	LBSPE	LBMET	LBSTRESU	Row Count
CREAT	Creatinine	CHEMISTRY				IU/L	4677
CREAT	Creatinine	CHEMISTRY				mg/dL	4649
FATACFR	Free Fatty Acid	CHEMISTRY				mg/dL	3270
FATACFR	Free Fatty Acid	CHEMISTRY				MG/DL	19
TSH	Thyrotropin	CHEMISTRY				uIU/mL	1512
TSH	Thyrotropin	CHEMISTRY				UIU/ML	6

Question: Why does this happen?

Application: OCS Data

Generated: 2018-02-15T22:59:06

Study: PhUSE CSS 2018

Back to Summary

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4,702 (2.6%) of observations use inconsistent values for Standard Units (LBSTRESU)

Impact

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LBTESTCD	LBTEST	LBCAT	LBSCA	LBSPE	LBME	LBSTRESU	Row Count
CREAT	Creatinine	CHEMISTRY				IU/L	4677
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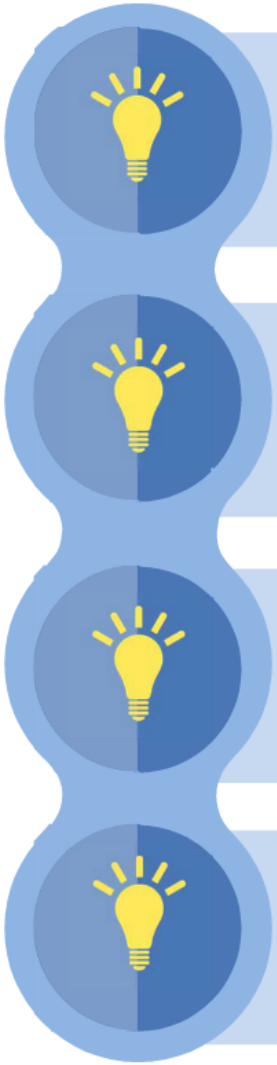
FATACFR	Free Fatty Acid	CHEMISTRY				mg/dL	3270
FATACFR	Free Fatty Acid	CHEMISTRY				MG/DL	19
TSH	Thyrotropin	CHEMISTRY				uIU/mL	1512
TSH	Thyrotropin	CHEMISTRY				UIU/ML	6

And these two sets *are* the same

03

Getting to Know Your Data

Know Your Data



Accessing Your Data

- Data sets can be accessed through the EDR or GS Review,
- All of the data sets are located in Module 5, within the Tabulations folder

Types of Data

- SDTM and/or ADaM vs. Legacy
- ISS vs. Individual Study

Learning About Your Data

- Define.xml lists the names/descriptions of data sets
- Examples data sets include AE, DM, ADSL, or ADAD
- The SDRG serves as the roadmap to the study data

Selecting Studies and Subject Population

- Efficacy population limited to studies used for primary efficacy analysis
- Safety population should include all studies conducted regardless of indication
- Subset out subjects within datasets using different variables

04

SDTM to ADaM Traceability Assessment

SDTM to ADaM Traceability Assessment

- JumpStart's SDTM to AdaM traceability assessment helps answer questions such as:
  - Can you trace data from ADaM back to SDTM?
  - Are there data inconsistencies that may impact analyses?
  - Are data missing?

- The main datasets compared are:
  - DM vs ADSL
  - AE vs ADAE
  - LB vs ADLB
  - VS vs ADVS

Example Methodology

- Datasets:
  - DM (SDTM) vs ADSL (ADaM)
- Comparison:
  - Counts of subjects, Demographic characteristics, Reference dates, and Treatment variables
- Records are joined by USUBJID and the following variables are compared:

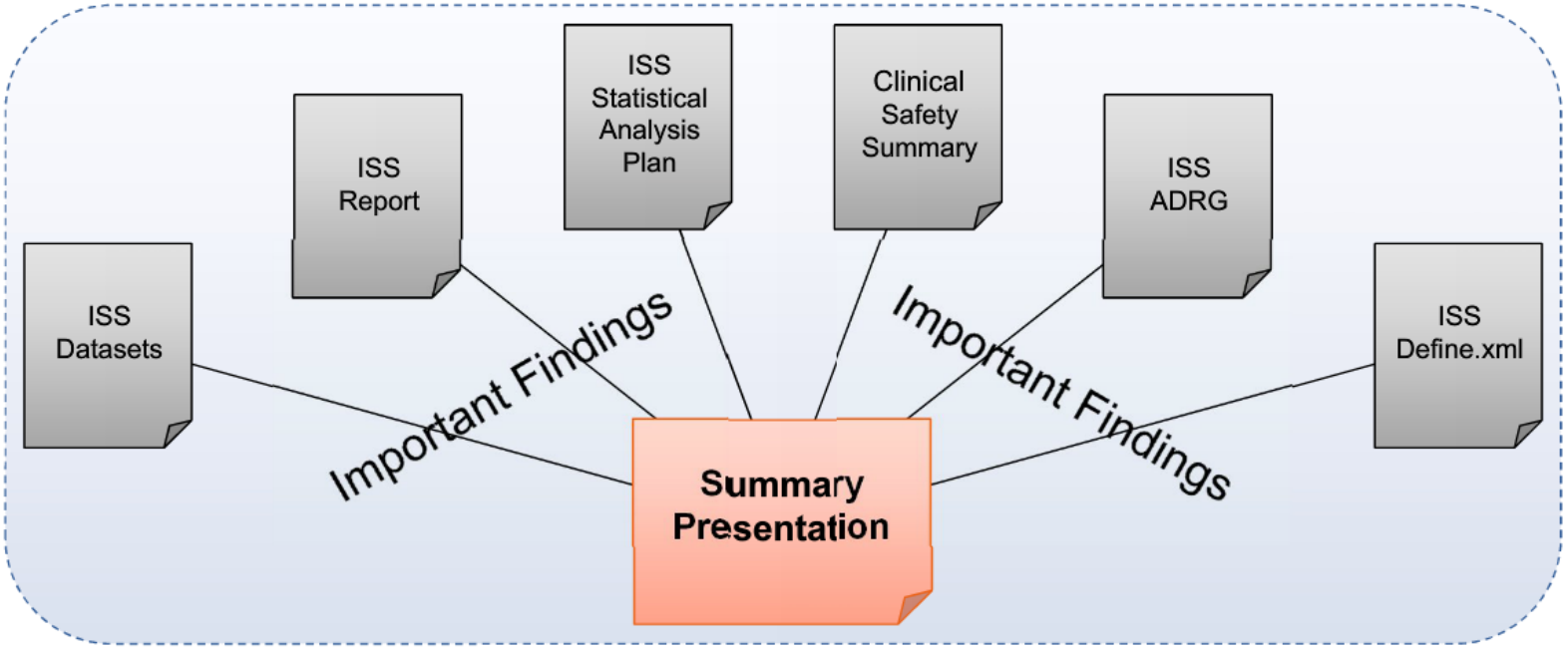
Characteristic	DM Variable	ADSL Variable
Age	AGE	AGE
Age Unit	AGEU	AGEU
Sex	SEX	SEX
Race	RACE	RACE
Ethnicity	ETHNIC	ETHNIC
Treatment Start Date	RFXSTDTC	TRTSDT
Treatment End Date	RFXENDTC	TRTEDT
Planned Treatment	ARM	TRT01P
Actual Treatment	ACTARM	TRT01A

Integrated Summary of Safety Assessment

05

ISS Assessment

- Provide reviewers with information on how the ISS was constructed and highlight potential issues that can influence the overall assessment of safety.
- Includes review of ISS reports, ISS datasets, Clinical Summaries, and other supporting documents



ISS Assessment

- The four topic areas covered in an ISS assessment are:

Submission Datasets/Documents and Integrated Studies	Analysis Sets, Treatment Arms, and Safety Population	Important Analysis Variables	MedDRA Analysis
A summary of the integrated datasets/documents that have been submitted and a listing of the studies which have been pooled into the ISS datasets.	An overview of the analysis sets the applicant used when performing safety analyses, as well as highlighting any treatment arm pooling that was done.	Important variables that support the reviewer's safety review are highlighted. These include analysis set population flags and treatment emergent flags.	A summary of the MedDRA versions used for individual studies and the version used for integrated data showing any MedDRA inconsistencies.

Safety Analysis

06

Safety Analyses Overview

Tool	Analyses	Strengths
Clinical Study Data Analyses Tools	• Adverse Events • Patient Profiles • Laboratory Results • Identify Hy's Law Candidates • Vital Signs	• Drill down to specific subjects for which a potential signal exists • Determine if an AE coincides with any other events/exposures • View Venn Diagrams and Forest Plots for AEs of interest
Liver Lab Panel	• Labs Greater than ULN • Possible Hy's Law • Maximum Lab Values Compared to Baseline	• Identify subjects with potential drug induced liver injury
MedDRA at a Glance	• Adverse Events	• Easily follow a potential signal across multiple levels of the hierarchy in a combined view
Severity/Toxicity Panel	• Adverse Events	• View adverse events by maximum severity/toxicity for each subject
MAED	• Adverse Events • SMQs	• Identify possible safety signals by looking at risk difference and relative risks at each level of the MedDRA hierarchy • Drill down to specific subjects Use SMQs to identify specific medical conditions or areas of interest that are not seen through comparing SOCs and compare potential findings across arms • Determine the PTs that are driving each SMQ

Analyses to Identify Potential Hy's Law Candidates

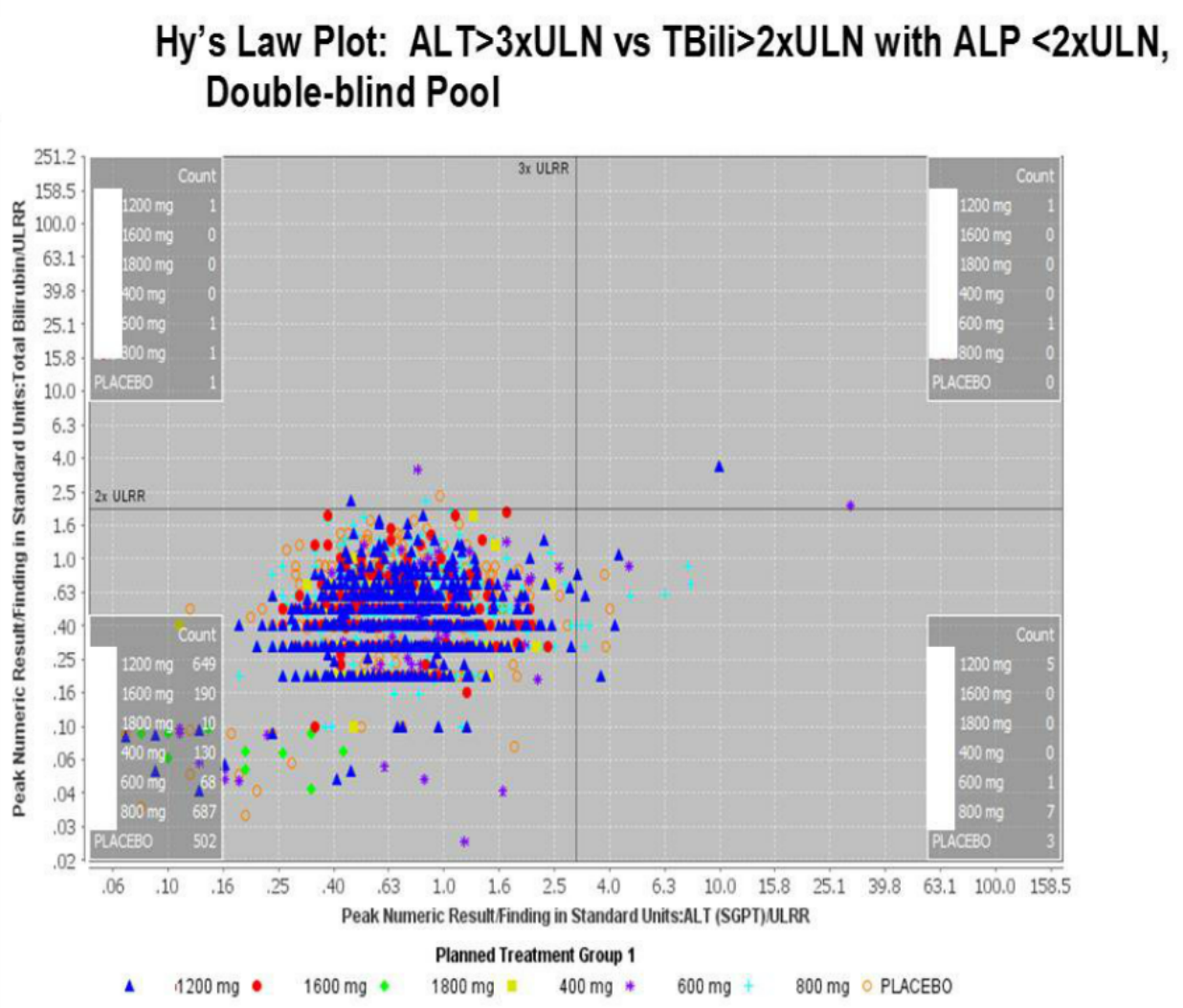
Possible Hy's Law Cases

Combinations for Possible Hy's Law Cases: At the Same Visit

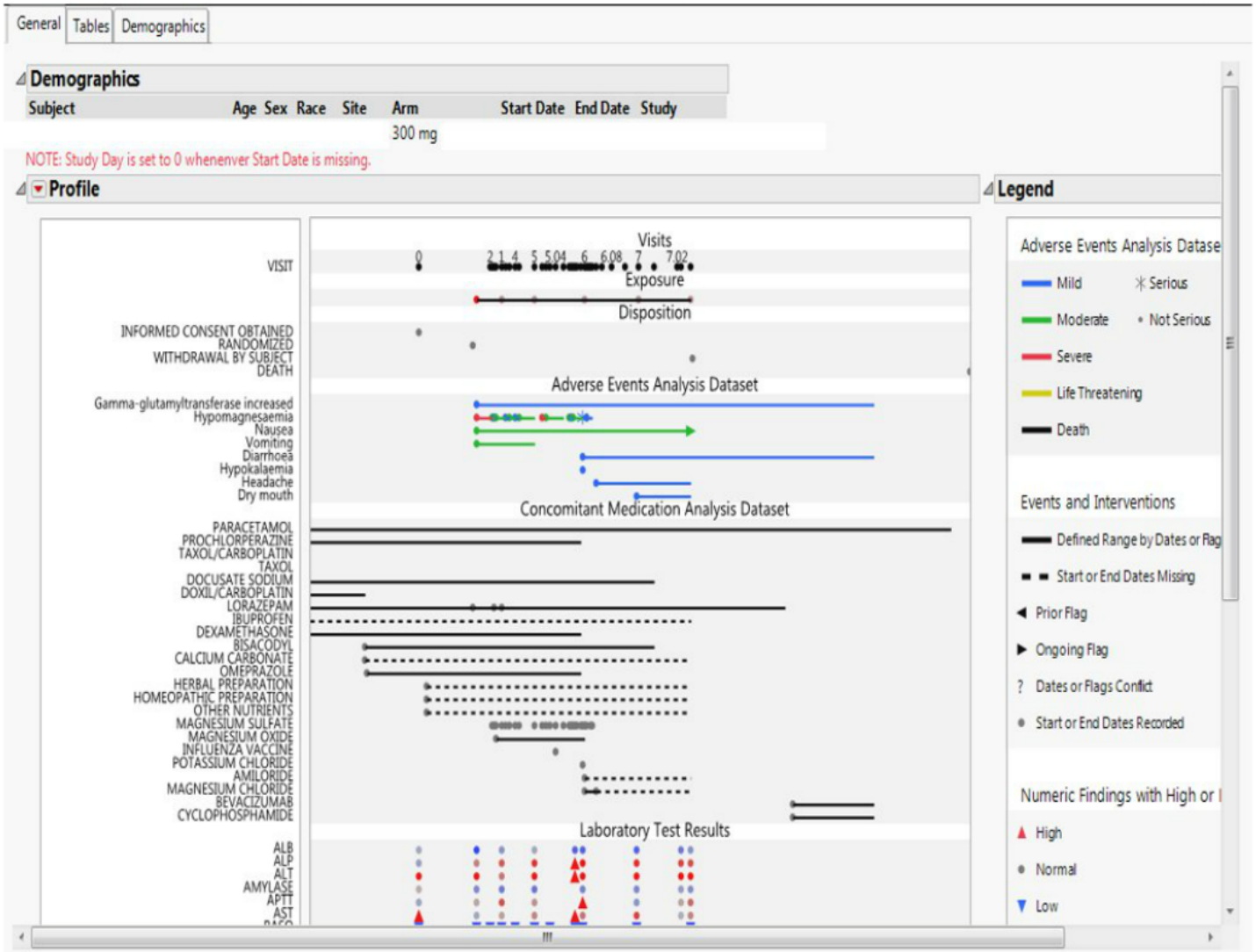
Liver Lab Test At Same Visit	[redacted] 600 mg BID N = 204		
	Event Count	Subject Count	% of Subjects
ALT or AST ≥ 3 ULN, TB ≥ 1.5 ULN & ALP normal	1	1	0.49
ALT or AST ≥ 3 ULN, TB ≥ 2 ULN & ALP normal	0	0	0.00
ALT or AST ≥ 5 ULN, TB ≥ 3 ULN & ALP normal	0	0	0.00
ALT or AST ≥ 3 ULN, TB ≥ 1.5 ULN & ALP > normal	9	3	1.47
ALT or AST ≥ 3 ULN, TB ≥ 2 ULN & ALP > normal	7	3	1.47
ALT or AST ≥ 5 ULN, TB ≥ 3 ULN & ALP > normal	6	2	0.98
Total Subjects	0	3	1.47
ALT or AST ≥ 3 ULN, TB ≥ 1.5 ULN	10	3	1.47
ALT or AST ≥ 3 ULN, TB ≥ 2 ULN	7	3	1.47
ALT or AST ≥ 5 ULN, TB ≥ 3 ULN	6	2	0.98
Total Subjects	0	3	1.47

Notes: All scores are post-baseline. Cases that have the lab combinations occurring at the same visit.

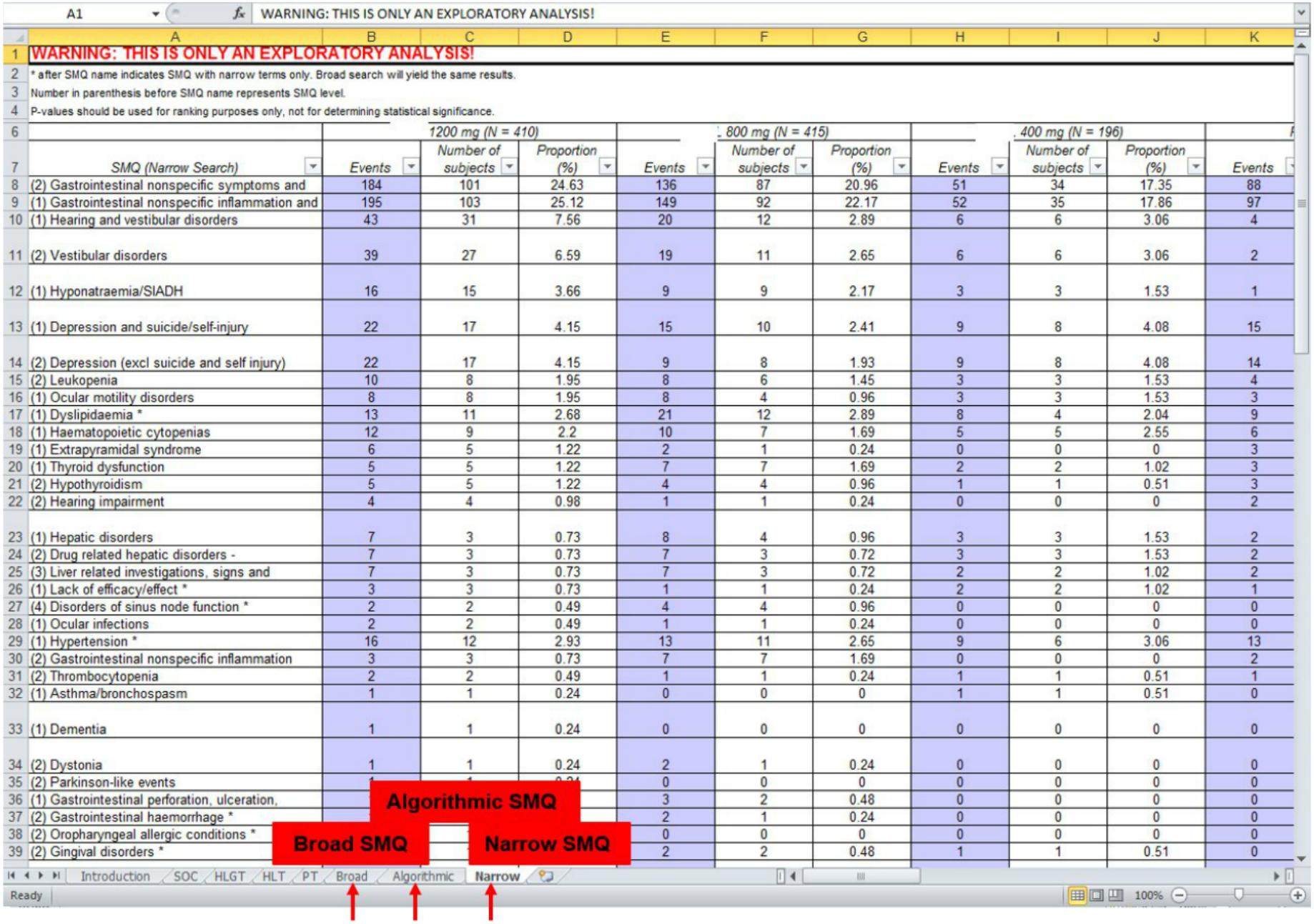
Plot to Identify Potential Hy's Law Candidates



Graphical Patient Profiles



Analyze Structured MedDRA Queries (SMQs) with MAED

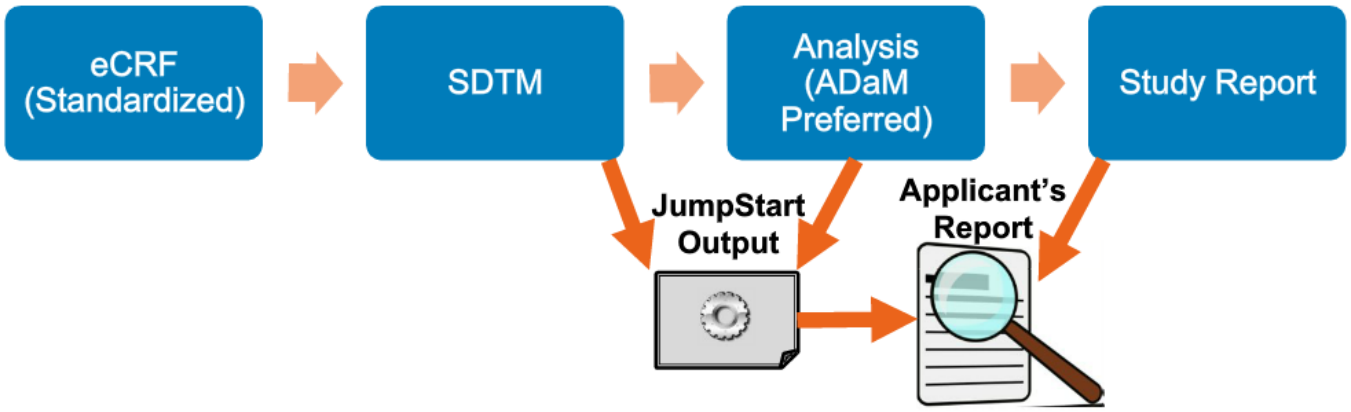


07

Additional Quality Checks

Quality Checks

- JumpStart validates its analyses against the applicant's study report and differences are communicated



Quality Checks

Analysis	Check Type	CSR Page #	Differences Found
Demographic Tool	Spot Check Counts	25	No
Demographics by Disposition	Spot Check Counts	26	No
Disposition Events by Arm	All Counts Verified	30	No
Clinical Review Tools	Spot Check Counts	35	No
Liver Labs	All Counts Verified	42	Yes, slight difference in methodology due to applicant excluding tests done at local labs
MedDRA at a Glance	Spot Check Counts	35	No
AE Severity/Toxicity	Spot Check Counts	35	No

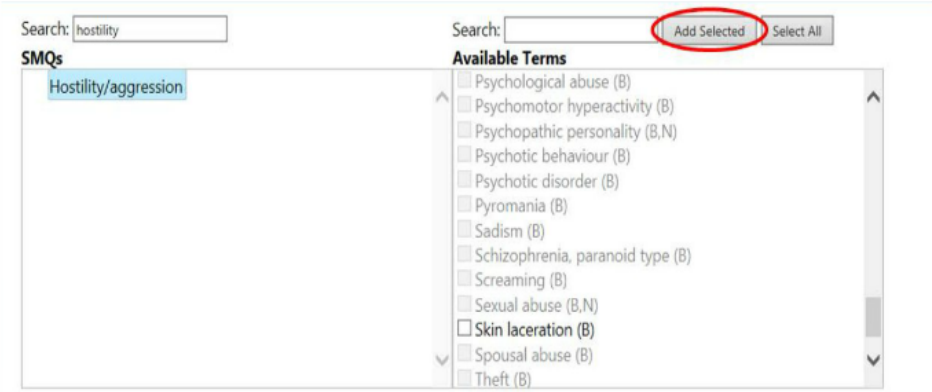
Adverse events matched to MedDRA version 18.0.

08

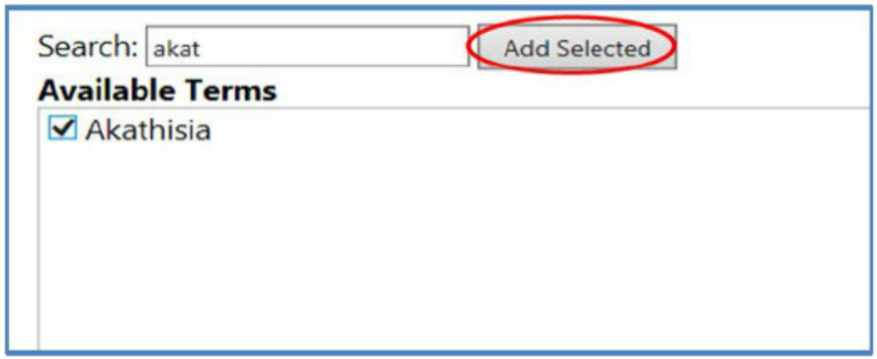
Custom MedDRA Queries

Custom MedDRA Queries Using the MAED Tool

- In this example, the Hostility/Aggression SMQ was modified to only include terms of interest to the reviewer
  - Terms from the Hostility/Aggression SMQ were used as the basis for this modified SMQ. “Skin laceration” was excluded from the list of included terms

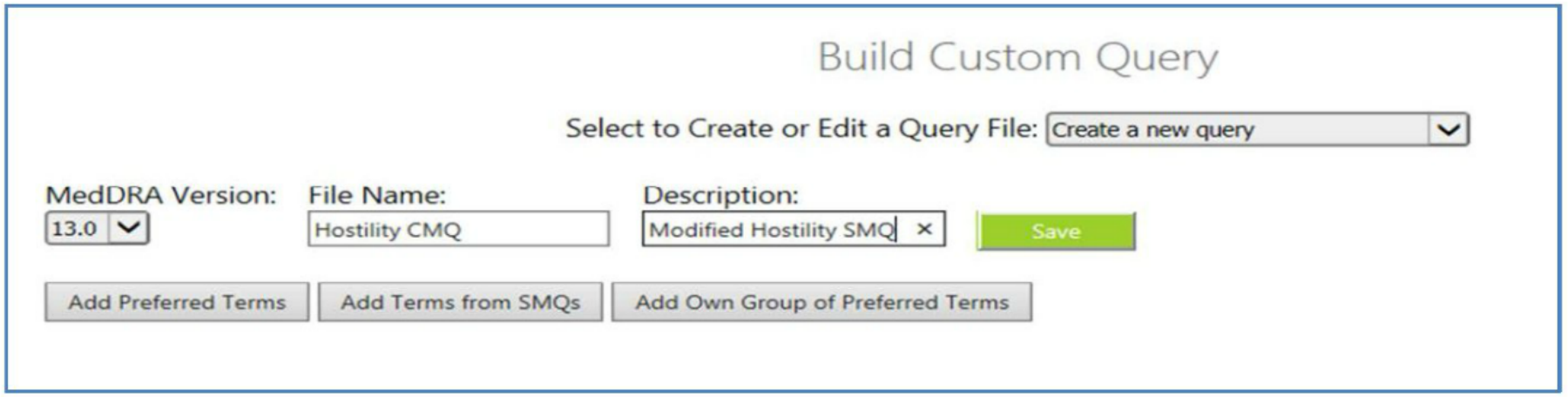


  - Terms such as “Akathisia” were added to the modified SMQ



Custom MedDRA Queries Using the MAED Tool

- MAED provides a user-friendly way to create CMQs
- JumpStart provides instructions on how to create a Custom MedDRA Query (CMQ) in the MAED tool



Demographics Assessment

09

Demographic Tool with R Shiny User Interface

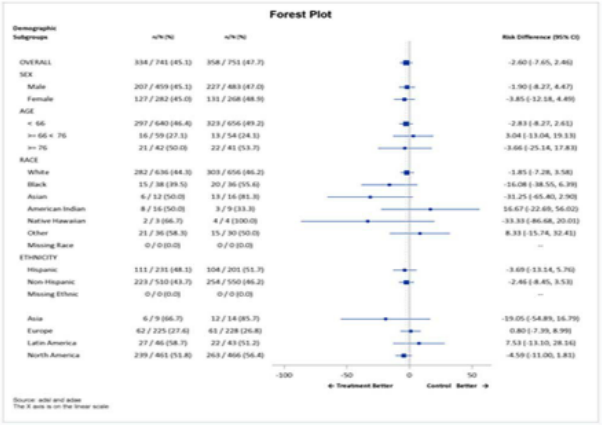
- Provides targeted descriptive statistics and safety endpoint analysis for demographic subgroups, including age, sex, race, and ethnicity, as required by Section 907 of the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA)

- Demographic tables extracted from completed product reviews are published in FDA's **Drug Trial Snapshots**, an initiative of the Professional Affairs and Stakeholder Engagement (PASE) Staff in the CDER Office of the Center Director

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

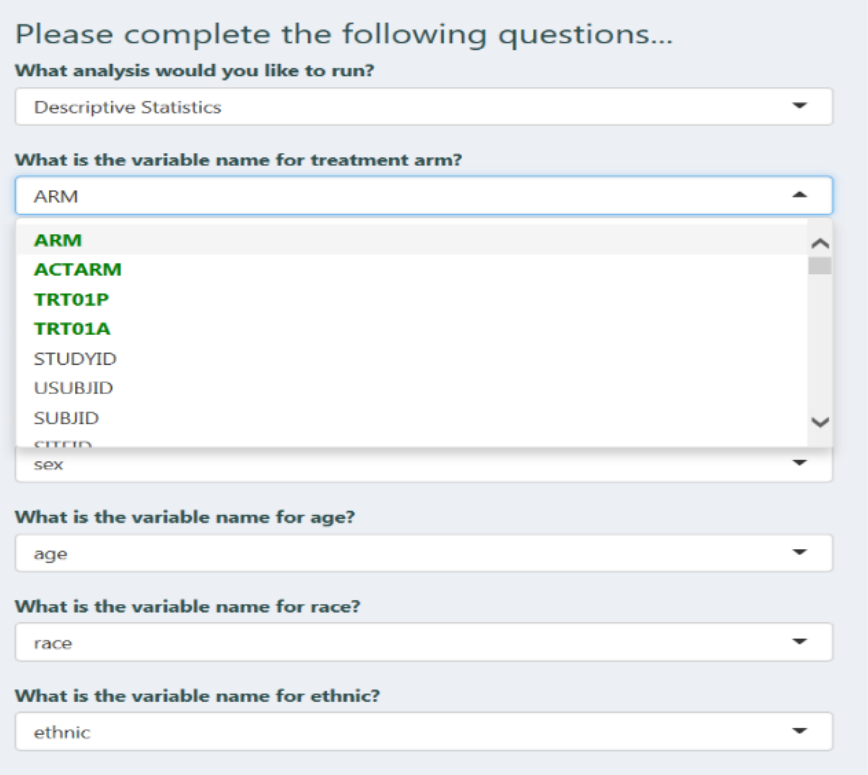
Subgroup	Treatment N=741		Placebo N=751		Risk Difference (95% CI)
	n(%)	Total,N	n(%)	Total,N	
Safety Subgroups (??/??/????) = ???	334 (45.1)	741	358 (47.7)	751	-2.60 (-7.65, 2.46)
SEX					
Male	207 (45.1)	459	227 (47.0)	483	-1.90 (-8.27, 4.47)
Female	127 (45.0)	282	131 (48.9)	268	-3.85 (-12.18, 4.49)
AGE					
< 65	297 (46.4)	640	323 (49.2)	656	-2.83 (-8.27, 2.61)
>= 65 < 75	16 (27.1)	59	13 (24.1)	54	3.04 (-13.04, 19.13)
>= 75	21 (50.0)	42	22 (53.7)	41	-3.66 (-25.14, 17.83)
RACE					
White	282 (44.3)	636	303 (46.2)	656	-1.85 (-7.28, 3.58)
Black	15 (39.5)	38	20 (55.6)	36	-16.08 (-38.55, 6.39)
Asian	6 (50.0)	12	13 (81.3)	16	-31.25 (-65.40, 2.90)
American Indian	8 (50.0)	16	3 (33.3)	9	16.67 (-22.69, 56.02)
Native Hawaiian	2 (66.7)	3	4 (100.0)	4	-33.33 (-86.88, 20.01)
Other	21 (58.3)	36	15 (50.0)	30	8.33 (-15.74, 32.41)
Missing Race	0 (0.0)	0	0 (0.0)	0	---
ETHNICITY					
Hispanic	111 (46.1)	231	104 (51.7)	201	-5.59 (-13.14, 5.76)
Non-Hispanic	223 (43.7)	510	254 (46.2)	550	-2.46 (-8.45, 3.53)
Missing Ethnic	0 (0.0)	0	0 (0.0)	0	---
REGION					
Asia	6 (66.7)	9	12 (85.7)	14	-19.05 (-54.89, 16.79)
Europe	62 (27.6)	225	61 (26.8)	228	0.80 (-7.39, 8.99)
Latin America	27 (60.7)	46	22 (51.2)	43	7.53 (-13.10, 28.16)
North America	239 (51.6)	461	263 (56.4)	466	-4.59 (-11.00, 1.81)

Source: adsl.adae



Demographic Tool with R Shiny User Interface

- Reviewers select variables for analyses using drop-down menus
- Easy way to customize groupings for characteristics such as age



FDA

Office of Computational Science

BETTER DATA | BETTER TOOLS | BETTER DECISIONS

The Background

1. Not All Applications receive a Substantive Review
2. Not all Complete Analyses are included in the
3. We've used "Survey" data to generate the reports

The Premise

You're a Clinical Reviewer - You Have To make a Filing Determination

Let's Interact

We'll ask questions, you respond, using either:

1. Poll Everywhere - PollEv.com/jessej511
2. Microphone

21st Century Review