



Computational Science Symposium

March 15th–17th 2015

Silver Spring Civic Center | Silver Spring, Maryland, USA



JumpStarting the Regulatory Review Process: The Review Perspective

JumpStart Overview

Disclaimer: This speech reflects the views of the speakers and should not be construed to represent FDA's views or policies

JumpStart seeks to directly benefit the FDA reviewer in the review of this application

Purpose

1

Assess and report on whether data is fit for purpose

- Quality
- Tool loading ability
- Analysis ability

2

Load data into tools for reviewer use and run automated analyses that are universal or common (e.g., demographics, simple AE)

3

Provide analyses to highlight areas that may need a focus for review

Benefits for the Reviewer

1

Understand your data, analyses that can be performed, and identify potential information requests for the sponsor

2

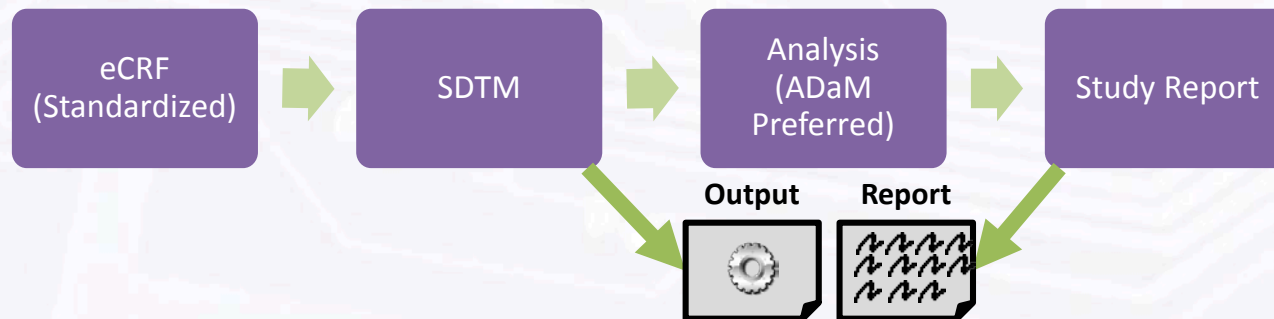
Improves the efficiency of your review by setting up tools and performing common analyses, which provides you with time to focus on more complex analyses

3

Points you to a possible direction for deeper analysis

JumpStart uses SDTM tabulation data as the basis for exploratory analysis

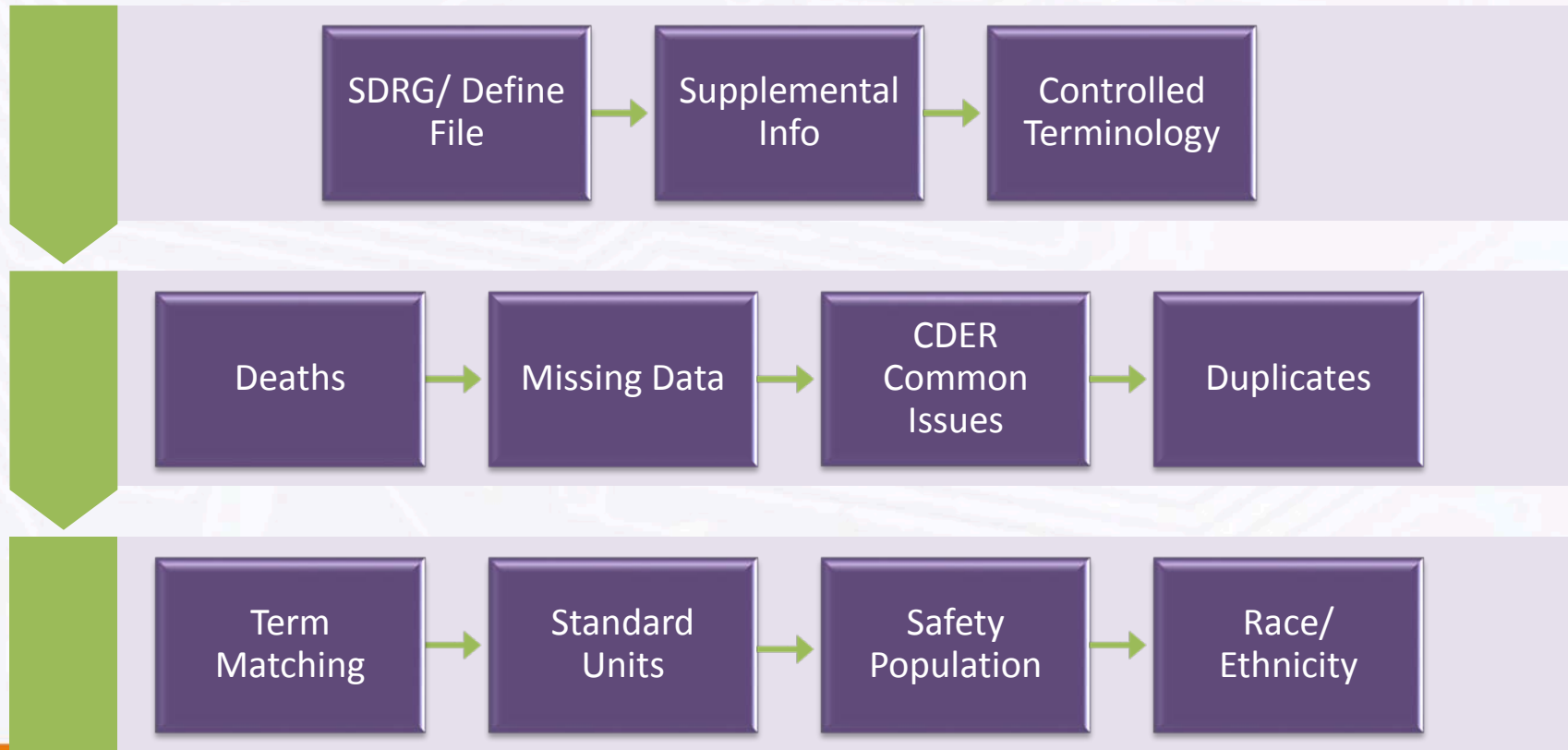
- ▶ **JumpStart using the following domains during its analysis:**
 - The Data Fitness session analyzes all datasets submitted for a trial
 - The Safety Analysis session focuses primarily on DM, DS, EX, AE, LB, and VS
- ▶ **What is the best practice for data submissions?**
 - SDTM data should represent the data that was actually collected during the trial with minimal data derivations or imputations
 - SDTM should then be used to create Analysis data
 - The results from outputs may not exactly match the sponsor's analyses but are valid for methods chosen



JumpStart uses the SDTM data to run automated analyses, create any derived variables that are needed, and check them against the sponsor's study report

We will walk you through an approach used by the CSC to navigate the data fitness findings

Data Fitness Findings Discussion Flow



The team will present the information in the following format to assist you with possible questions and identify the impact for each finding

Review Questions:

We will walk through each finding and point out questions you may have that can be answered using the highlighted findings group

Findings:

We will then outline how the data fitness findings may impact your analyses and ultimately your review

JumpStart has analyzed 10 submissions in FY2015 so far. All statistics around findings in this presentation are based on this set of 10 submissions.

Study Data Reviewer's Guide (SDRG) Content and Review of Define File

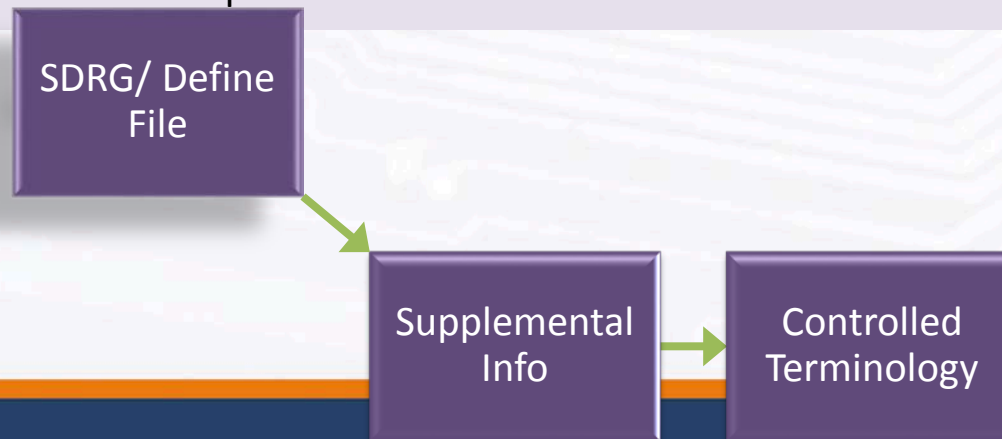
Review Questions:

SDRG

- ▶ Were the SDTM datasets used as sources for the analysis datasets?
- ▶ If there are issues with the data, why did the sponsor choose not to fix them?
- ▶ What version of MedDRA/WHODRUG did the sponsor use?
- ▶ Where is the efficacy data located?

Define File

- ▶ How does the information in the annotated CRFs map to the datasets?
- ▶ Does the sponsor provide an explanation of the codes used?



Supplemental Information

Review Questions:

- ▶ What information is available in the supplemental domains?
- ▶ How does the information contained in these domains map to the parent domains?
- ▶ What information from the supplemental domains could be useful for analysis?

FY2015 Findings:

For every application that goes through JumpStart, the team analyses the content of the Supplemental domains to highlight useful information as well as uncover inconsistencies.



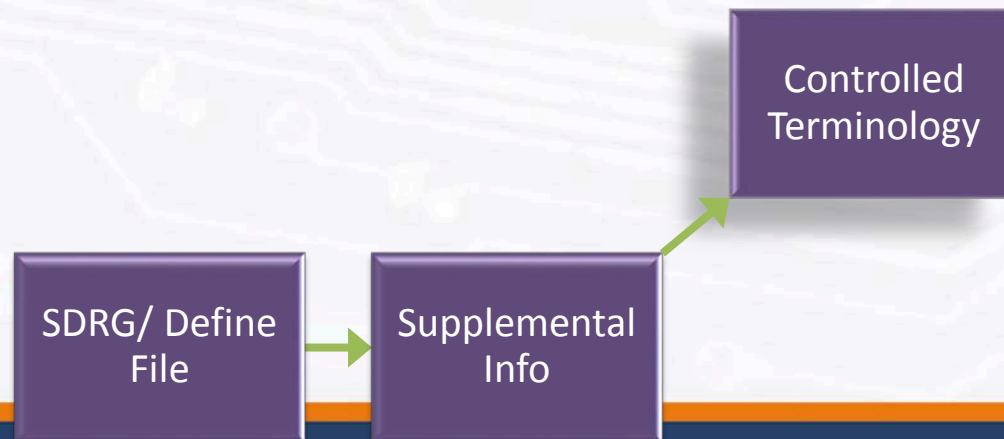
Controlled Terminology

Review Questions:

- ▶ How does the sponsor's terminology map to controlled terminology?
- ▶ Which domains do not use controlled terminology?
- ▶ Did a lack of controlled terminology cause ambiguity in the data?

FY2015 Findings:

60% of applications have had issues with controlled terminology



Controlled Terminology Findings and Impact

Findings

- ▶ Adverse Event Action Taken (AEACN) is not populated with controlled terminology

Impact

- ▶ Actual values provided in the data may be difficult to interpret and cause uncertainty during review

Illustrative Example:



USUBJ	AEDECOD	AEACN
001-123-551	Palpitations	DOSE ALTERED OR WITHHELD
001-123-552	Nausea	DOSE ALTERED OR WITHHELD

Examples from AEACN Codelist



DOSE INCREASED	DOSE NOT CHANGED	DRUG WITHDRAWN
DOSE REDUCED	DRUG INTERRUPTED	UNKNOWN

Deaths

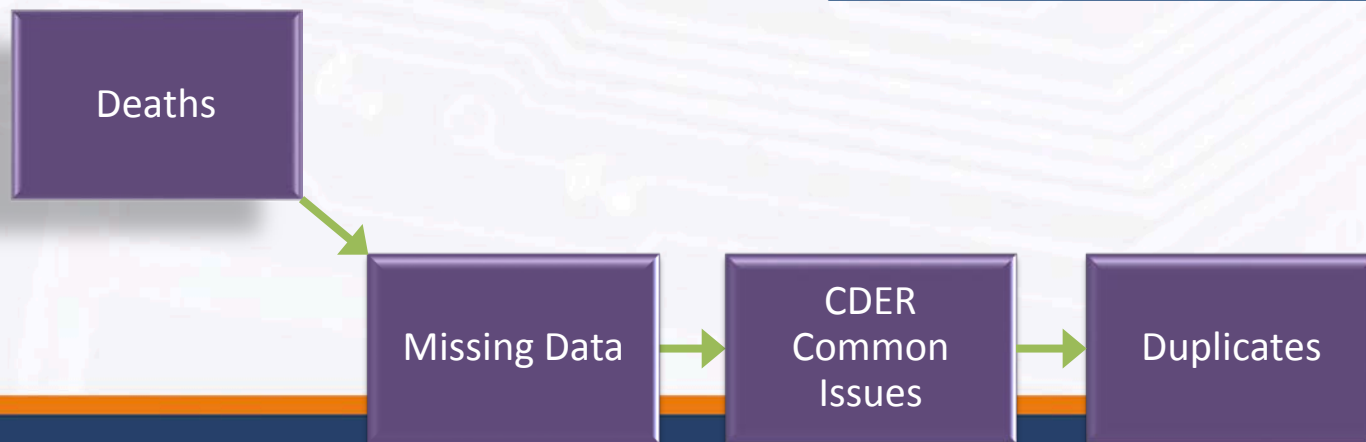
Review Questions:

- ▶ How many deaths occurred during the study?
- ▶ Where is information about deaths located?
- ▶ Was the death information represented consistently across domains?

FY2015 Findings:

100% of studies that go through JumpStart are provided a summary of death information. The summary highlights issues such as:

- DM death flags are not consistent with DS and AE records
- Potential death information located only in the CO domain



Death Findings and Impact

Findings

- ▶ Death information not represented consistently across DM, AE, DS, and CO domains.

Impact

- ▶ You may miss pertinent death information if relying on certain flags or indicators

Illustrative Example:

USUBJID	DM Death Flag	DM Death Date	DSDECOD	DSSTDTC	FATAL AE	FATAL AE End Date	Death Info in Comments
001-123-551	Y	2011-12-21	DEATH	2011-12-21	Acute Renal Failure	2011-12-21	N
001-123-672	Y	2010-06-05	DEATH	2010-06-05	Cardiac Arrest	2010-06-03	N
001-123-241			ADVERSE EVENT	2010-04-15	Cerebral Haemorrhage	2010-04-15	Y
001-123-456							Y

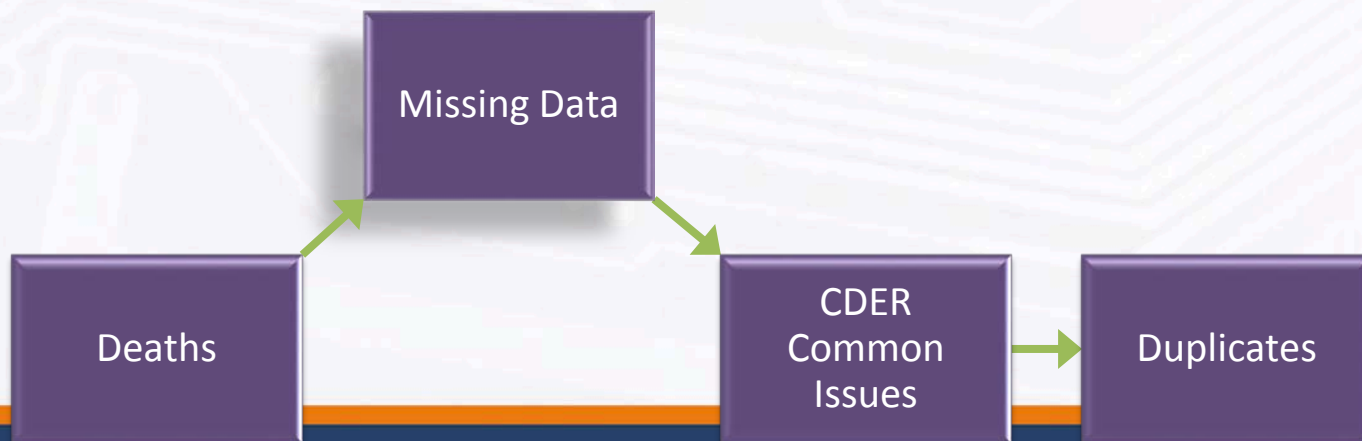
Missing Data

Review Questions:

- ▶ What data is missing?
- ▶ How will the missing data impact analyses?
- ▶ Are there other variables that can be used in lieu of the missing data?

FY2015 Findings:

60% of applications are missing AE Seriousness Criteria or have inconsistencies between AE Serious Flag and Seriousness Criteria



Missing Data Findings and Impact

Findings

- ▶ A portion of Serious AEs are missing AE Seriousness Criteria

Impact

- ▶ Cannot independently verify whether an adverse event was serious or not

Illustrative Example:

	DOMAIN	USUBJID	AEDECOD	AEBODSYS	AESER	AESCONG	AESDISAB	AESDTH	AESHOSP	AESLIFE	AESMIE
	AE	123101	Headache	Nervous system disorders	N						
	AE	123101	Neutropenia	Blood and lymphatic system disorders	Y						
	AE	123101	Pulmonary embolism	Vascular disorders	Y				Y	Y	
	AE	123101	Stroke	Nervous system disorders	N		Y				
	AE	123101	Chest Pain	General Disorders and Administrative Site Conditions	N						

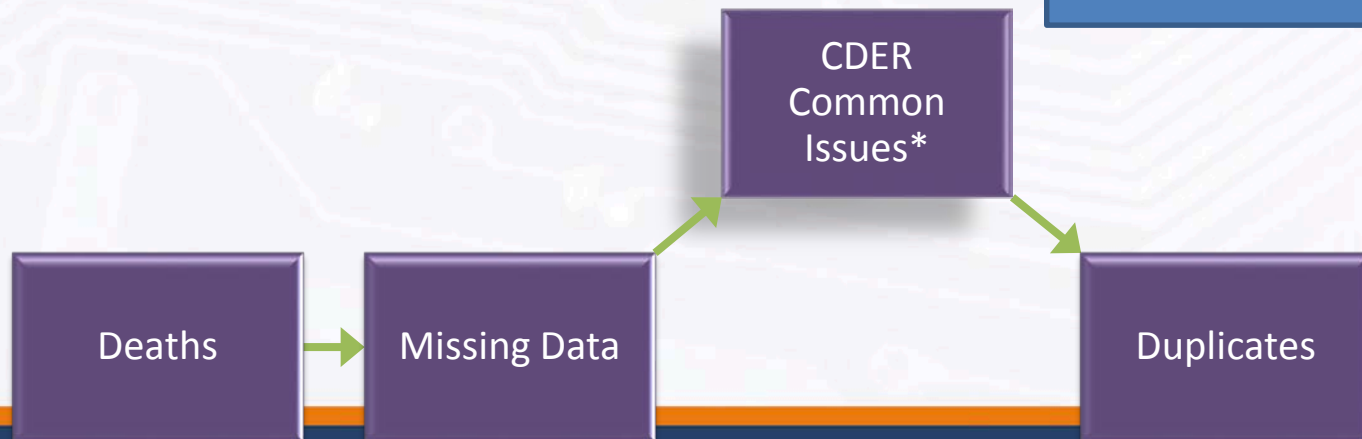
CDER Common Issues

Review Questions:

- ▶ Does the DM domain include start and end dates, an actual arm variable, a death flag, and a date of death variable?
- ▶ Are domains missing the EPOCH variable?
- ▶ Did the sponsor include the trial summary domains?
- ▶ Does the AE domain include a treatment emergent flag?

FY2015 Findings:

- EPOCH variable was missing from key domains (AE, LB, CM, EX, VS, DS) in 90% of applications
- TS domain missing in 30% of applications



Note: *Please refer to the Technical Conformance Guide -

<http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>

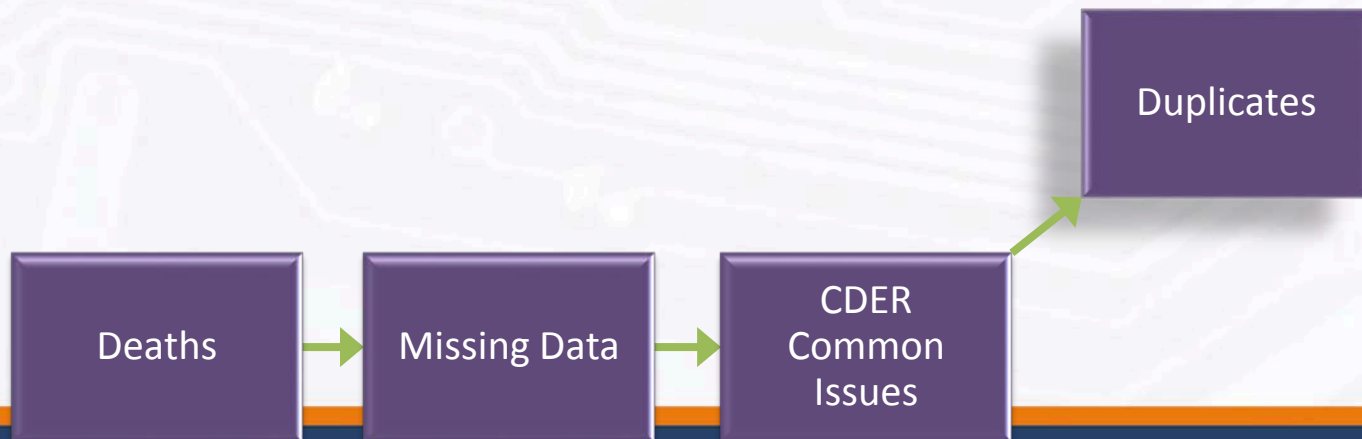
Duplicates

Review Questions:

- ▶ Do any of the datasets contain potential duplicate records?
- ▶ How will these duplicates impact analyses?

FY2015 Findings:

Potential duplicate issues found in 40% of applications



Duplicates Findings and Impact

Findings

- ▶ There are contradictory duplicate records present in the LB domain

Impact

- ▶ Manipulations may have to be made to ensure results are not double counted for particular subjects. In some cases, it will be difficult to tell which record is correct

Illustrative Examples:

USUBJID	LBTEST	LBORRES	LBORRESU	LBORNRL0	LBORNRLHI	LBFAST	LBDTC
001-123-5551	GLUCOSE	3.9	mmol/L	4.6	6.4	Y	2011-04-13T10:45
001-123-5551	GLUCOSE	3.9	mmol/L	3.6	7.7	N	2011-04-13T10:45

Term Matching

Review Questions:

- ▶ How can you efficiently review coding quality?
- ▶ Was an adverse event mapped to the appropriate dictionary term?
- ▶ Was the disposition term reported using the appropriate dictionary term?
- ▶ Did the sponsor use the term “Other” appropriately?

FY2015 Findings:

Potential coding issues found in 40% of applications



Term Matching Findings and Impact

Findings

- ▶ AEDECOD is missing for AETERMS
- ▶ DSDECOD of “Other” could have been coded more appropriately

Impact

- ▶ These events will not be included in analyses unless they are manually coded
- ▶ Clinically relevant disposition events could be lost from analysis

Illustrative Example:

USUBJID	DSDECOD	DSTERM
001-123-5551	OTHER	SUBJECT WITHDREW DUE TO WORSENING PAIN
001-123-5555	OTHER	LESION CONTINUED TO GROW
001-123-5560	OTHER	SUBJECT DECEASED

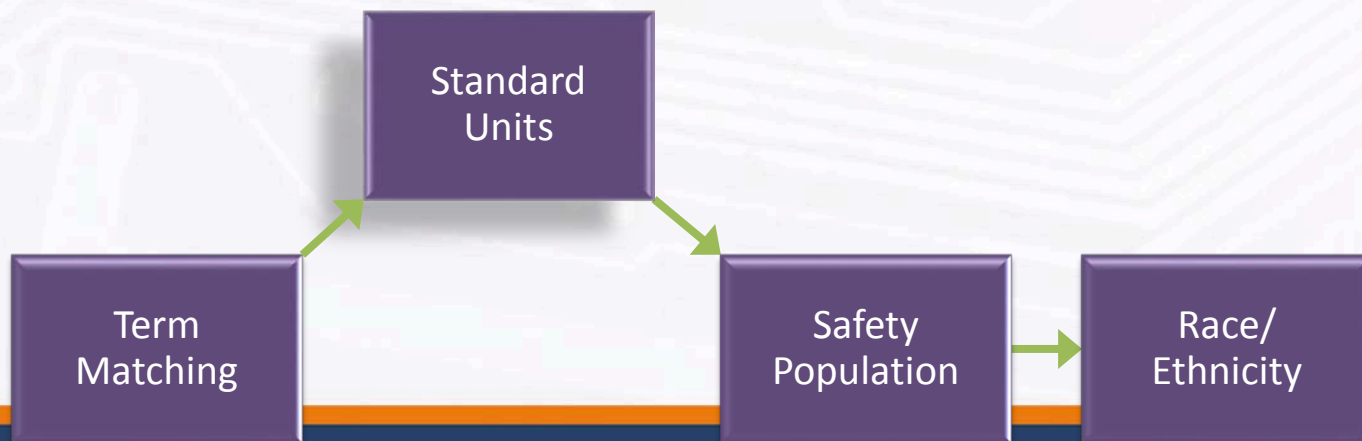
Standard Units

Review Questions:

- ▶ Did the sponsor use standard units?
- ▶ Did the sponsor use the same units for each type of test?
- ▶ Did the list of standard units submitted by the sponsor match the data?

FY2015 Findings:

30% of applications have inconsistent units or missing standard units when original units are given



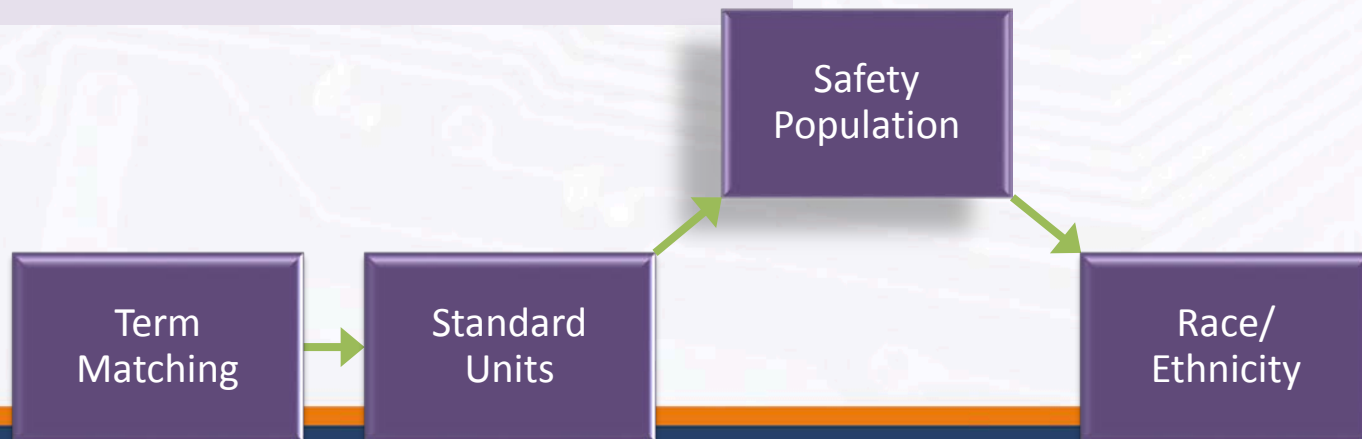
Safety Population

Review Questions:

- ▶ Are there population inconsistencies between the SDTM data and the study report?
- ▶ Are there any subjects who were randomized but not treated?
- ▶ Are there any subjects who received a treatment that was different from their planned treatment?

FY2015 Findings:

For every application that goes through JumpStart, the team searches for inconsistencies between DM, EX, and the clinical study report to determine the appropriate Safety Population to use in analyses.



Race and Ethnicity

Review Questions:

- ▶ How does the sponsor indicate race/ethnicity?
- ▶ Where is detailed information about race/ethnicity located?
- ▶ Are there any subjects who are missing race or ethnicity data?

FY2015 Findings:

80% of applications have had race/ethnicity issues



JumpStart analyses and outputs are provided to support specific sections within review

Clinical Review Sections

- **6.1.2 Demographics**
- **6.1.3 Subject Disposition**
- ▶ 7. Review of Safety
 - 7.3 Major Safety Results
 - **7.3.1 Deaths**
 - **7.3.2 Nonfatal Serious Adverse Events**
 - **7.3.3 Dropouts and/or Discontinuations**
 - **7.3.4 Significant Adverse Events**
 - 7.3.5 Submission Specific Primary Safety Concerns
 - 7.4 Supportive Safety Results
 - **7.4.1 Common Adverse Events**
 - **7.4.2 Laboratory Findings**
 - **7.4.3 Vital Signs**
 - 7.4.4 Electrocardiograms (ECGs)
 - 7.4.5 Special Safety Studies/Clinical Trials
 - 7.4.6 Immunogenicity

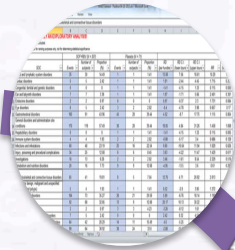
Clinical Review Template:

<http://inside.fda.gov:9003/downloads/ProgramsInitiatives/Drugs/21stCenturyReview/UCM247419.doc>

***Bold, red font** indicates sections covered during JumpStart presentations

The following diagram is a quick review of the complementary capabilities of each AE analysis

Adverse Event Flow



Identify possible safety signals by looking at risk differences and relative risks at the PT and SOC levels



Drill down from the SOC level to see what PTs are driving each SOC and check to see if baseline characteristics have an effect on risk estimators



Easily follow a potential signal across multiple levels of the hierarchy in this combined view. Identify any DMEs that occurred in the study



Drill down to the specific patients for which a signal exists and determine if an AE coincides with any other events/exposures



Determine if similar AEs have been split across SOC levels to identify specific medical conditions or areas of interest

MAED



JReview AE Risk Assessment



MedDRA At a Glance



JReview Graphical Patient Profile



SMQs

Laboratory and Vital Sign Findings Output Flow

1

- LFT ULN Tables
- LFT Baseline vs Max Shift tables

Upper Limit
Normal Tables

2

Hy's Law

- Possible Hy's Law
Tables and Plots

3

- Box & Whisker Plots
by Visit for LB and
VS tests
- Mean Line Summ.
by Visit for LB and
VS tests

Lab Findings
Over Time

