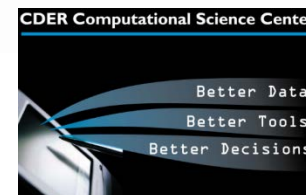




JumpStart the Regulatory Review: Applying the Right Tools at the Right Time to the Right Audience

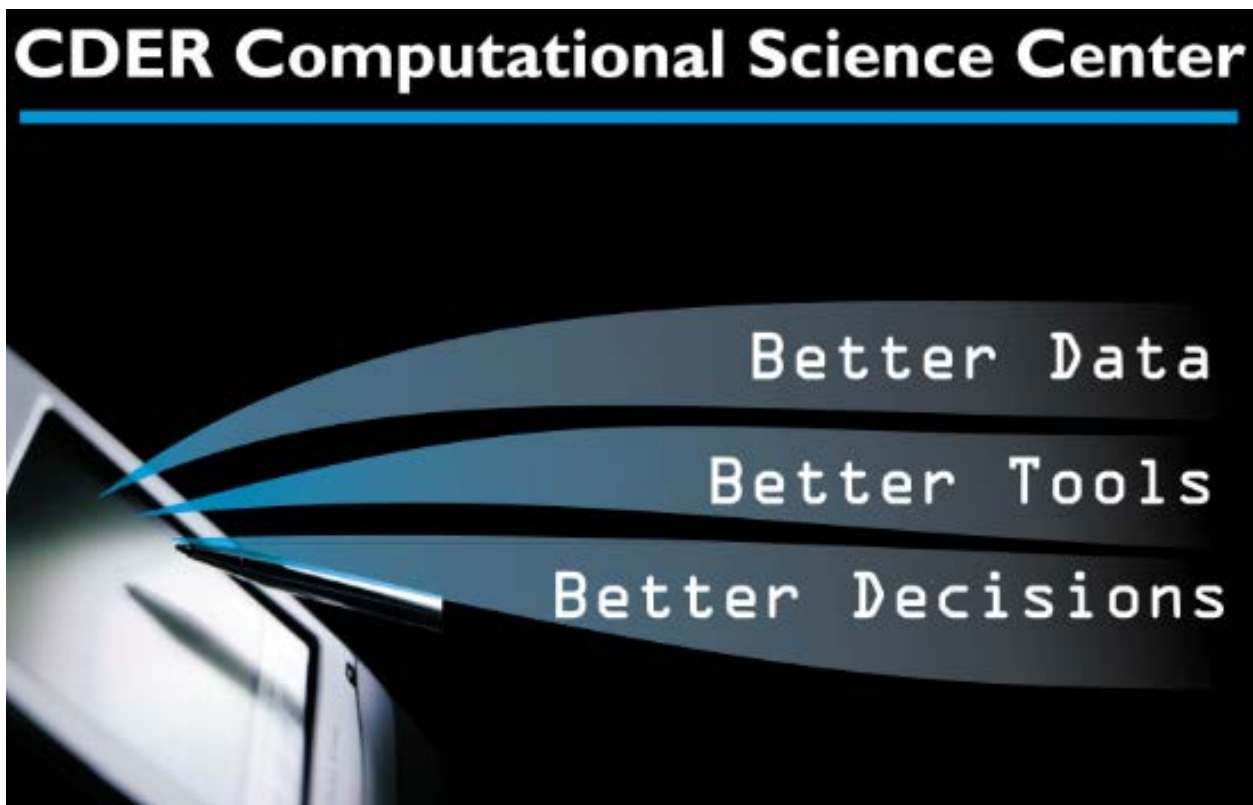
**Lilliam Rosario, Ph.D.
Director
Office of Computational Science**

Agenda



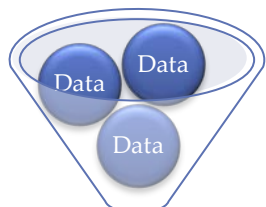
- Office of Computational Science
 - o Who we are
 - o What we do
- CSC Reviewer Services
 - o Data and Analysis
 - o Tools and Technologies
 - o Training and Communications
- JumpStart the Regulatory Review
 - o What we do
 - o How we do it

Facilitating Modernization of the Regulatory Review Process



Intersection of data, tools and technology

Standardized Data



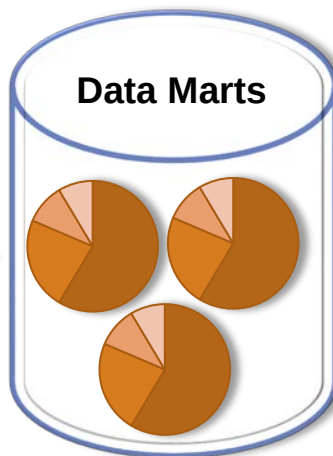
Repositories for
Electronic Data



Data
Validation



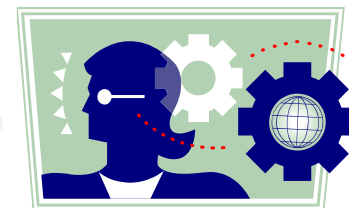
Data Warehouse



Analytic Tools



Reviewer
Decisions



Data & Analysis
Support Services

Tools & Technology
Support Services

Training & Customer
Support Services

Computational Science Center (CSC) Reviewer Services

CSC Reviewer Services

DATA & ANALYSIS SUPPORT SERVICES

Data Validation &
Quality
Assessments

Support Data
Standardization

Script
Development &
Sharing to Support
Analysis

TOOLS & TECHNOLOGY SUPPORT SERVICES

Analytic Tool
Support

Regulatory Review
Service

Scientific
Environment &
Infrastructure

TRAINING & CUSTOMER SUPPORT SERVICES

Analytic Tool
Training

Data Standards
Training

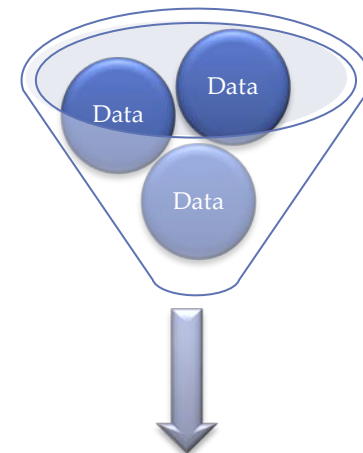
INNOVATION



High quality data is
the key to enabling
regulatory reviewers
to fully utilize
the Computational
Science Center's tools
and services
**to support decision
making**

Standardized Data

- Data standards are the foundational prerequisite to success
 - o Develop re-useable tools and analytic capabilities that automate common assessments and support data exploration
 - o Allow us to integrate data automatically with the Clinical Trial Repository (Janus)
 - o Facilitate data integration



Objective – Improve Standardized Data

- Inform reviewers of data quality or fitness issues that will impact their review
- Improve the quality of submitted study data
- Reduce the number of information requests to industry

DataFit

- Assesses the ability of submission data to support actual review activities
- Identifies data issues that could impact review
 - o Can I use standard review tools (e.g., JReview, MAED)?
 - o Can I run common analyses (e.g., liver function, Hy's Law plot)?
 - o What other data quality issues could impact my review?
- Checks are based on review needs and will evolve as new issues are discovered
- Measures by evaluating whether:
 - o Appropriate variables are available
 - o Values are populated for data points as expected
 - o Standard terminology was appropriately use
 - o Data are well described by metadata





DataFit

Validates sponsor study data upon arrival

Study Quality Report: 1220-0019

Evaluation date: 24-May-2013 7:19 PM [Download](#)

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Profile	Score	Pass/Fail	Domains	Issues	Failures	Errors	Warnings	Notices
MAED	0	Fail	3	13	1,536	1,534	0	2
Oncology Adverse Events Analysis Panel	0	Fail	4	16	1,575	1,572	0	3
Demographics Analysis (1 Profiles)								
Demographics Analysis Panel	0	Fail	3	2	27	24	0	3
Dropouts Analysis (1 Profiles)								
JReview Dropouts Disposition Event Standard Terms	0	Fail	3	2	24	24	0	0
Exposure Analysis (1 Profiles)								
Exposure Analysis Panel	0	Fail	3	4	43	43	0	0
General Data Quality (2 Profiles)								
CDER Common Data Standards Issues	62	Pass	30	12	129	0	129	0
SDTM v3.1.3 General Data Quality	0	Fail	30	63	6,239	4,370	1,861	8
Laboratory Findings Analysis (6 Profiles)								
JReview Hy's Law Patient Listing	100	Pass	3	1	39	0	36	3
JReview Hy's Law Plots	100	Pass	3	1	39	0	36	3
JReview Labs Baseline vs Max/Min Scatter Plots	100	Pass	3	1	39	0	36	3
JReview Liver Function Baseline Box Whiskers	100	Pass	3	1	39	0	36	3
Liver Function Analysis Panel	0	Fail	3	4	92	75	15	2
eDISH	0	Fail	6	10	2,122	1,877	241	4
Metadata (1 Profiles)								
Study Metadata	0	Fail	30	43	4,378	4,375	3	0
Overall Survival Analysis (1 Profiles)								

Objective – Improve Review Effectiveness

- Provide various analytic tools and views to improve the effectiveness and efficiency of regulatory review:
 - o Support ability to answer regulatory related questions involving large amounts of data
 - o Improve reviewer efficiency by providing automated analysis
 - o Identify coding problems that may impact the interpretation of results

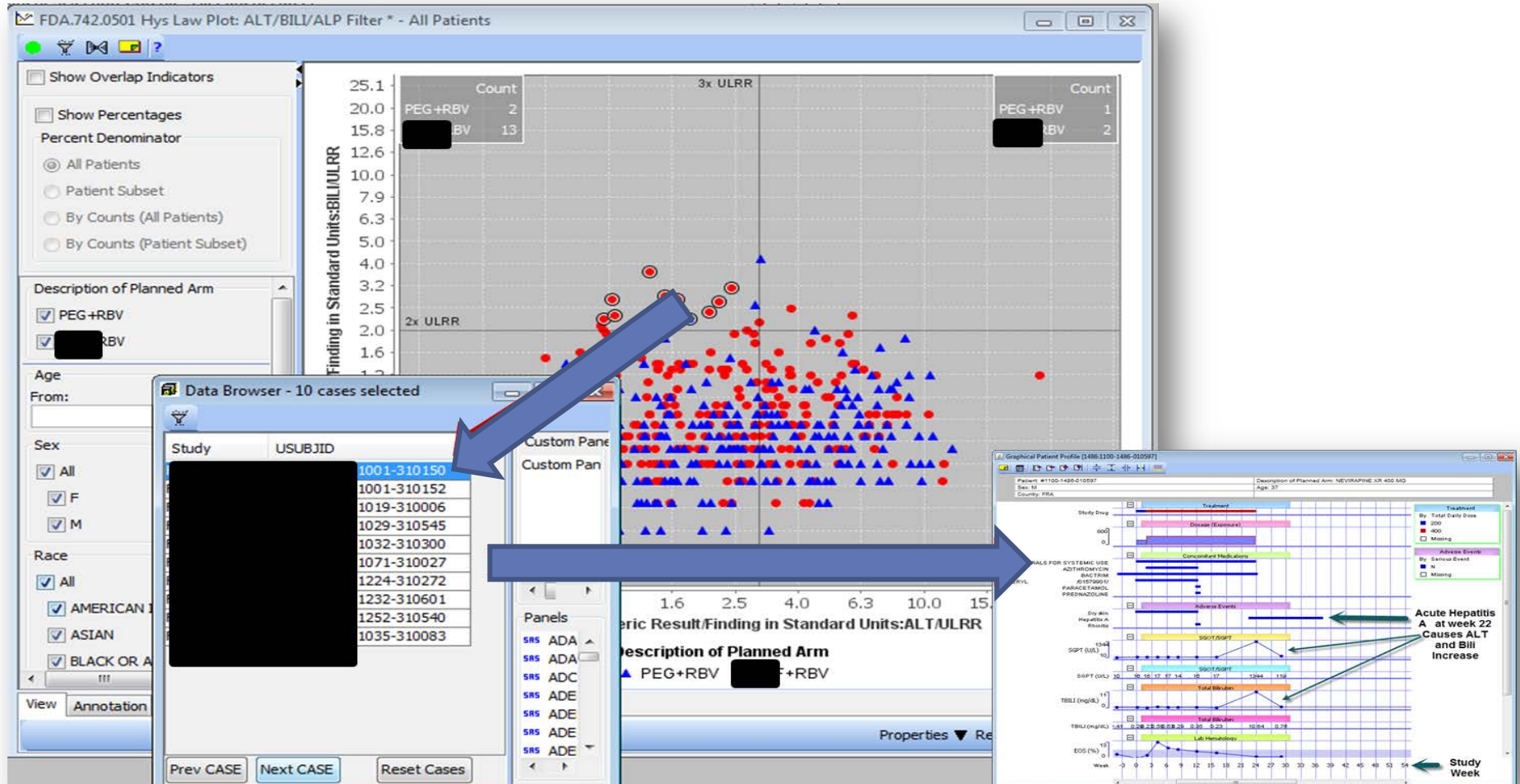


Analytic Tools

- Data available in an array of different analytic tools

Tools	Overview
JReview	<ul style="list-style-type: none"> Allows users to tabulate, visualize, and analyze safety and efficacy data Provides a catalogue of standard analyses with drill down capabilities, making it easy to obtain results and graphical displays of common analyses, such as Hy's Law (relies on availability of SDTM study data)
MAED (MedDRA Adverse Events Diagnostics)	<ul style="list-style-type: none"> Allows dynamic and efficient review of adverse event data Performs over 200 Standardized MedDRA Queries and Adverse Events analyses on all levels of the MedDRA hierarchy in minutes
JMP	<ul style="list-style-type: none"> Combines powerful statistics with dynamic graphics to enable review process
NIMS (Non-clinical Information Management System)	<ul style="list-style-type: none"> Enables dynamic study visualization, search, orientation, and analytics capabilities in the review of non-clinical data Enables cross-study metadata and study data searching across the data repository (across studies, class, findings, and finding types) Allows reviewers to see all findings for an individual animal in one place

JReview Standard Analysis – Hy's Law Plot



JReview Standard Analysis Catalog

JREVIEW Standard Analysis Catalog

CDER Computational Science Center



Better Data, Better Tools, Better Decisions

February 18, 2013

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MAED (MedDRA Adverse Event Diagnostics)

* after SMQ name indicates SMQ with broad terms only. Narrow search will yield no results.

Number in parenthesis before SMQ name represents SMQ level.

P-values should be used for ranking purposes only, not for determining statistical significance.

SMQ (Broad Search)							SCREEN		
	Events	Number of subjects	Proportion (%)	Events	Number of subjects	Proportion (%)	RD (per hundred)	RD C.I. (lower bound)	RD C.I. (upper bound)
(1) Hearing and vestibular disorders	36	35	10.12	133	109	31.32	-21.21	-27.02	-15.39
(1) Anticholinergic syndrome	70	50	14.45	173	127	36.49	-22.04	-28.31	-15.77
(2) Vestibular disorders	35	34	9.83	126	104	29.89	-20.06	-25.8	-14.32
(1) Noninfectious encephalopathy/delirium	37	24	6.94	68	51	14.66	-7.72	-12.3	-3.14
(1) Anaphylactic reaction	76	53	15.32	135	84	24.14	-8.82	-14.7	-2.94
(1) Noninfectious encephalitis	34	21	6.07	60	43	12.36	-6.29	-10.56	-2.01
(1) Noninfectious meningitis	26	19	5.49	53	40	11.49	-6	-10.13	-1.88
(1) Lipodystrophy	17	14	4.05	36	32	9.2	-5.15	-8.83	-1.47
(1) Dementia *	26	18	5.2	42	35	10.06	-4.86	-8.79	-0.92
(1) Acute central respiratory depression	1	1	0.29	10	8	2.3	-2.01	-3.68	-0.34
(1) Dyslipidaemia	20	12	3.47	29	24	6.9	-3.43	-6.72	-0.14
(1) Pseudomembranous colitis	47	39	11.27	72	57	16.38	-5.11	-10.23	0.01
(1) Pulmonary hypertension	1	1	0.29	9	7	2.01	-1.72	-3.3	-0.14
(1) Guillain-Barre syndrome	21	17	4.91	37	30	8.62	-3.71	-7.43	0.02
(2) Hearing impairment	1	1	0.29	7	7	2.01	-1.72	-3.3	-0.14

SAS Analysis Panels

Panel	Description of Analysis
Demographics	Produces tables and graphs that show the number and percent of cases that correspond to the demographic variables such as age, race and sex as well as descriptive statistics of the variable age.
Disposition	Details the number and percent of cases that correspond to each disposition category.
Liver	Evaluates specific laboratory measurements that signal the potential for drug induced liver injury (DILI). The analyses include counts/percents of possible Hy's Law candidates; an evaluation of measurements that are major indicators for severe DILI, and graphical analysis of subject's baseline measurement to his/her maximum change in serum measures.
Adverse Events	Provides various analyses to find the most frequent AEs, largest differences in AEs between treatment arms and produce graphs of relative risk/odds ratio.
Enrollment	Produces tables and graphs that details the enrolled study subjects by country and site. In addition demographics, protocol deviations and disposition can be viewed by site.
Exposure	Analyzes exposure on drug such as total number of days on drug, cumulative dose and average daily dose.

SAS Analysis Panels

Maximum Post-Baseline Lab Tests vs Baseline Lab Tests

NDA/BLA: 12345
Study: 123
Analysis run date: 2011-04-07 1:13:08 PM

ALT Baseline	E7389 N= 509					
	ALT < 2x ULN		2x ≤ ALT < 5x ULN		5x ≤ ALT < 10x ULN	
	Subject Count	%	Subject Count	%	Subject Count	%
ALT Maximum						
ALT < 2x ULN	0	0.00	0	0.00	0	0.00
2x ≤ ALT < 5x ULN	0	0.00	0	0.00	0	0.00
5x ≤ ALT < 10x ULN	0	0.00	0	0.00	0	0.00
10x ≤ ALT < 20x ULN	0	0.00	0	0.00	0	0.00
ALT ≥ 20x ULN	0	0.00	0	0.00	0	0.00

AST Baseline	E7389 N= 509					
	AST < 2x ULN		2x ≤ AST < 5x ULN		5x ≤ AST < 10x ULN	
	Subject Count	%	Subject Count	%	Subject Count	%
AST Maximum						
AST < 2x ULN	0	0.00	0	0.00	0	0.00
2x ≤ AST < 5x ULN	0	0.00	0	0.00	0	0.00
5x ≤ AST < 10x ULN	0	0.00	0	0.00	0	0.00
10x ≤ AST < 20x ULN	0	0.00	0	0.00	0	0.00
AST ≥ 20x ULN	0	0.00	0	0.00	0	0.00

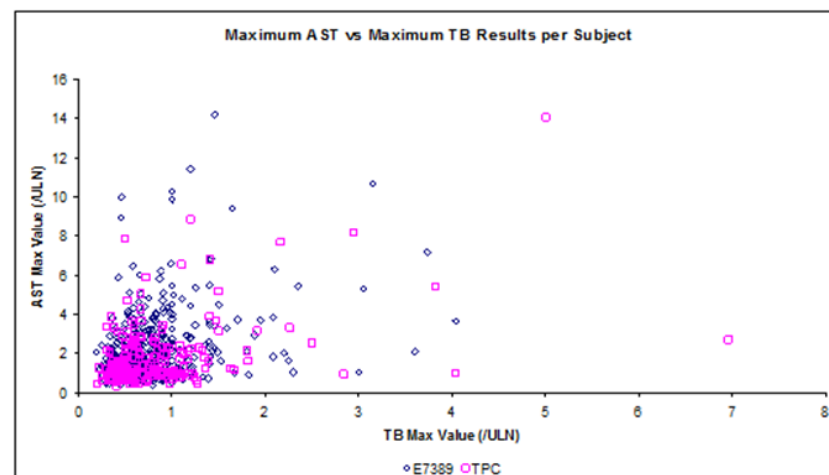
ALP Baseline	E7389 N= 509					
	ALP < 2x ULN		2x ≤ ALP < 5x ULN		5x ≤ ALP < 10x ULN	
	Subject Count	%	Subject Count	%	Subject Count	%
ALP Maximum						
ALP < 2x ULN	0	0.00	0	0.00	0	0.00
2x ≤ ALP < 5x ULN	0	0.00	0	0.00	0	0.00
5x ≤ ALP < 10x ULN	0	0.00	0	0.00	0	0.00
10x ≤ ALP < 20x ULN	0	0.00	0	0.00	0	0.00
ALP ≥ 20x ULN	0	0.00	0	0.00	0	0.00

E7389

Analysis 4

Maximum AST and ALT vs Maximum TB Lab Test Results per Subject Charts

NDA/BLA: 12345
Study: 123
Analysis run date: 2011-04-27 11:29:30 PM

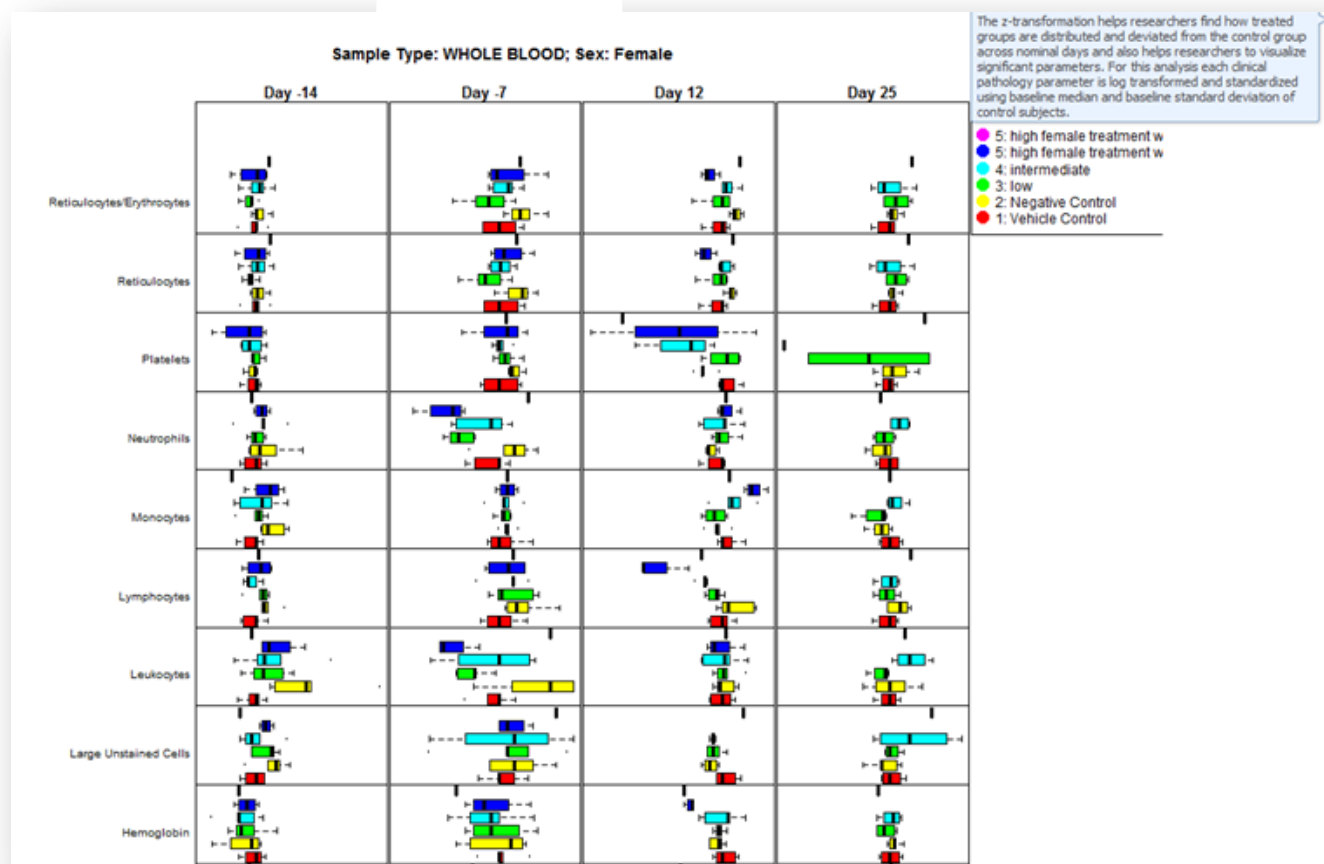


NIMS: Histopathology Data with Ability to View Temporal Information and Drill Down

[illegible]

NIMS (Non-clinical Information Management System)

Normalization of laboratory data by Z-transform for cross study analysis





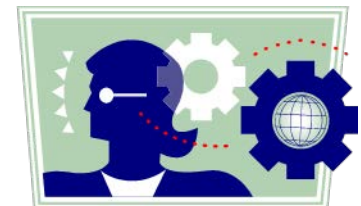
JumpStart the Regulatory Review:

...

Applying the Right Tools at the Right Time to the Right Audience

Objective: Implement CSC Services

- Developed JumpStart to:
 - o Allow reviewers more time to “think” about the data rather than “clean” the data
 - o Allow for more efficient exploration of safety issues



CSC JumpStart Service

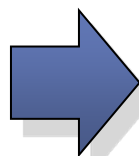
Purpose

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 standard analyses to allow the reviewer to uncover safety signals that may need a focus for review



Benefits for Reviewers

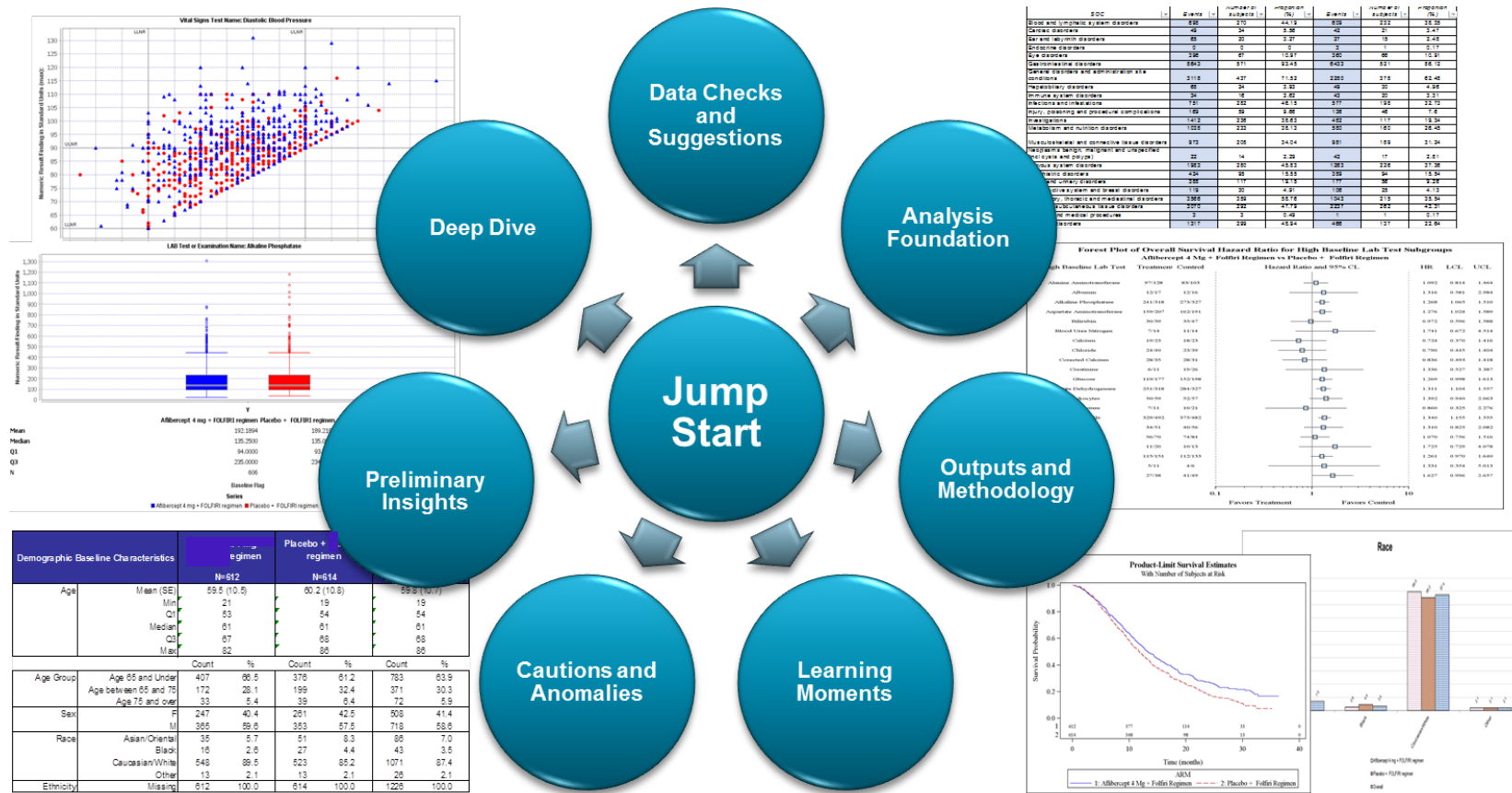
1 Understand what tools and analyses can be run and whether they might be compromised by data quality or structure issues

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

3 Points reviewer to a possible direction for deeper analysis

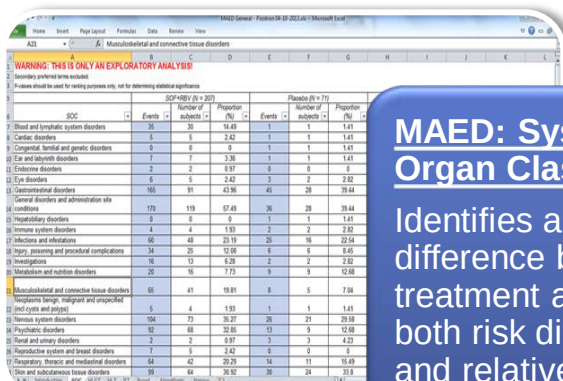
CSC JumpStart Service

Starts a review by performing many standard analyses and identifying key information



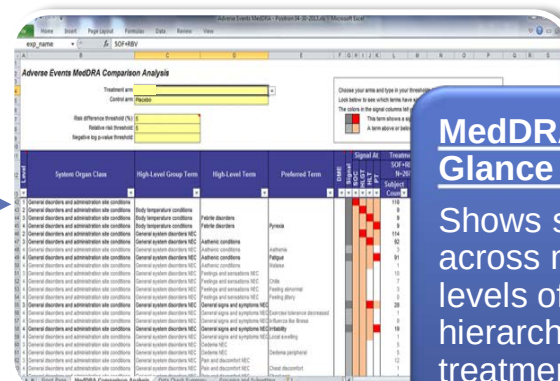
CSC JumpStart Service

- Provides a recommended sequence for using the outputs
- Allows reviewer to follow a safety signal from a high-level to the specific patient details with complementary tools



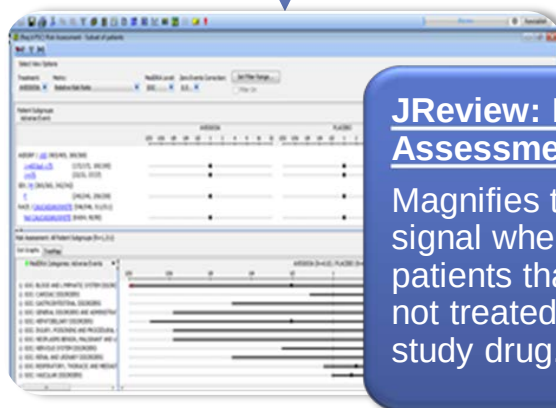
MAED: System Organ Class

Identifies a difference between treatment arms for both risk difference and relative risk.



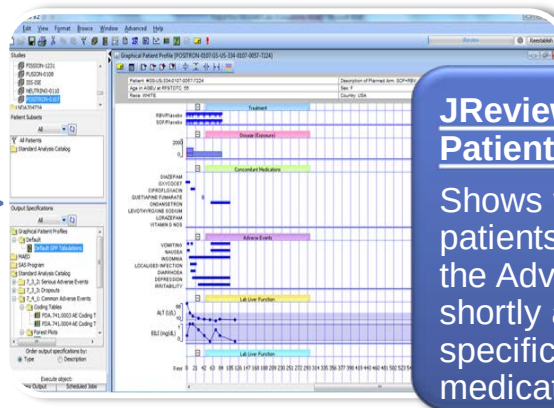
MedDRA at a Glance Report

Shows same signal across multiple levels of the hierarchy for the treatment arm.



JReview: Risk Assessment

Magnifies the safety signal when viewing patients that were not treated with the study drug.



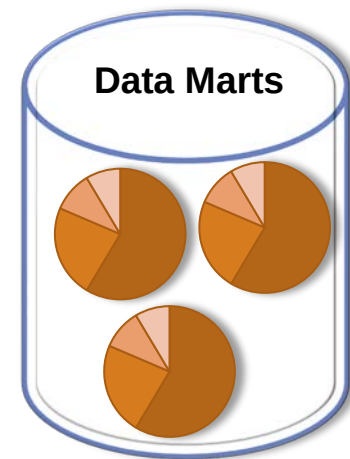
JReview: Graphical Patient Profile

Shows which patients experienced the Adverse Event shortly after taking a specific concomitant medication.

Objective – Improve Data Storage/Access

- Develop and implement a clinical trials data warehouse that supports the validation, transformation, loading, and integration of study data
- Support reviewer access to the data via a variety of analytic views (or data marts) and analytic tools

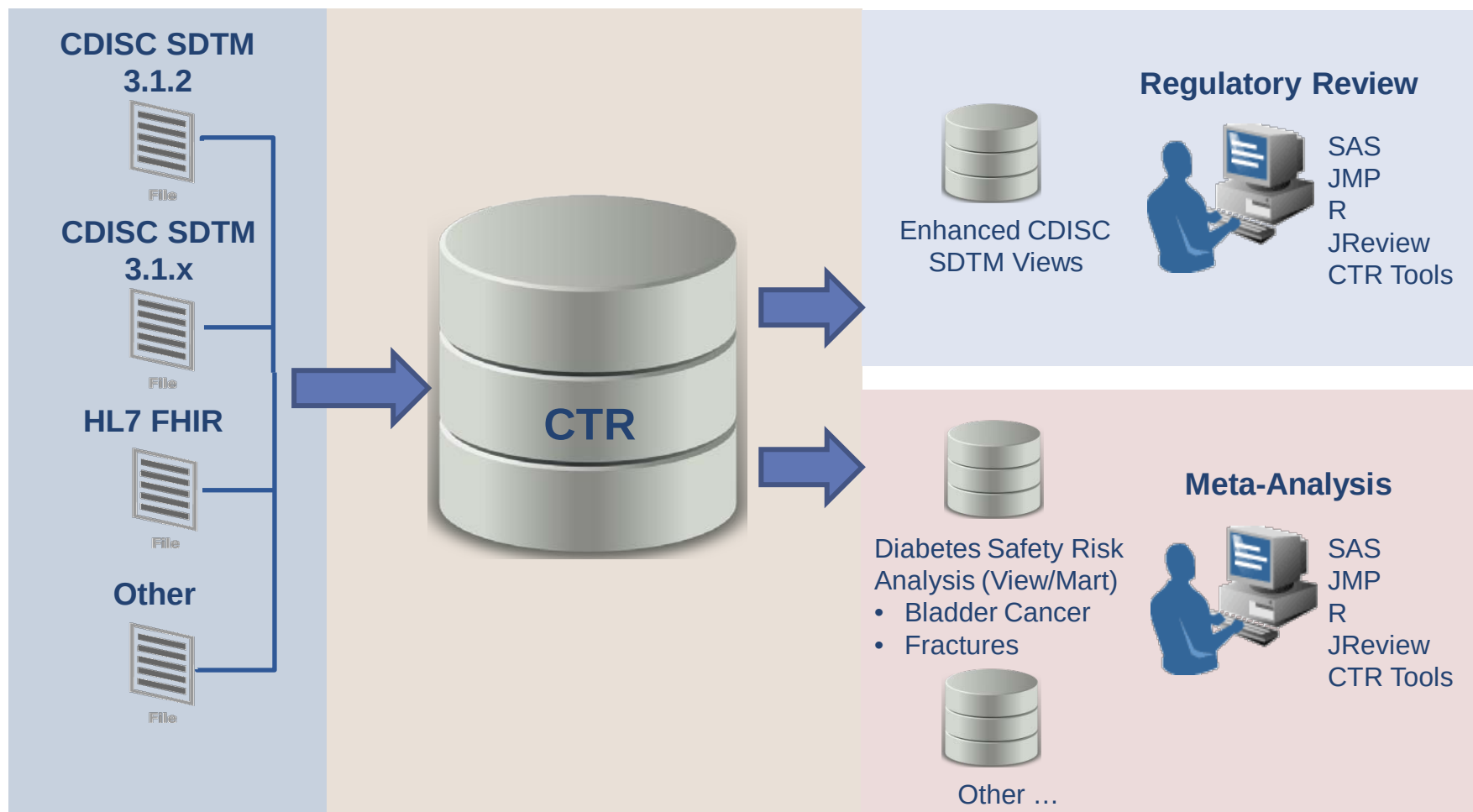
Data Warehouse



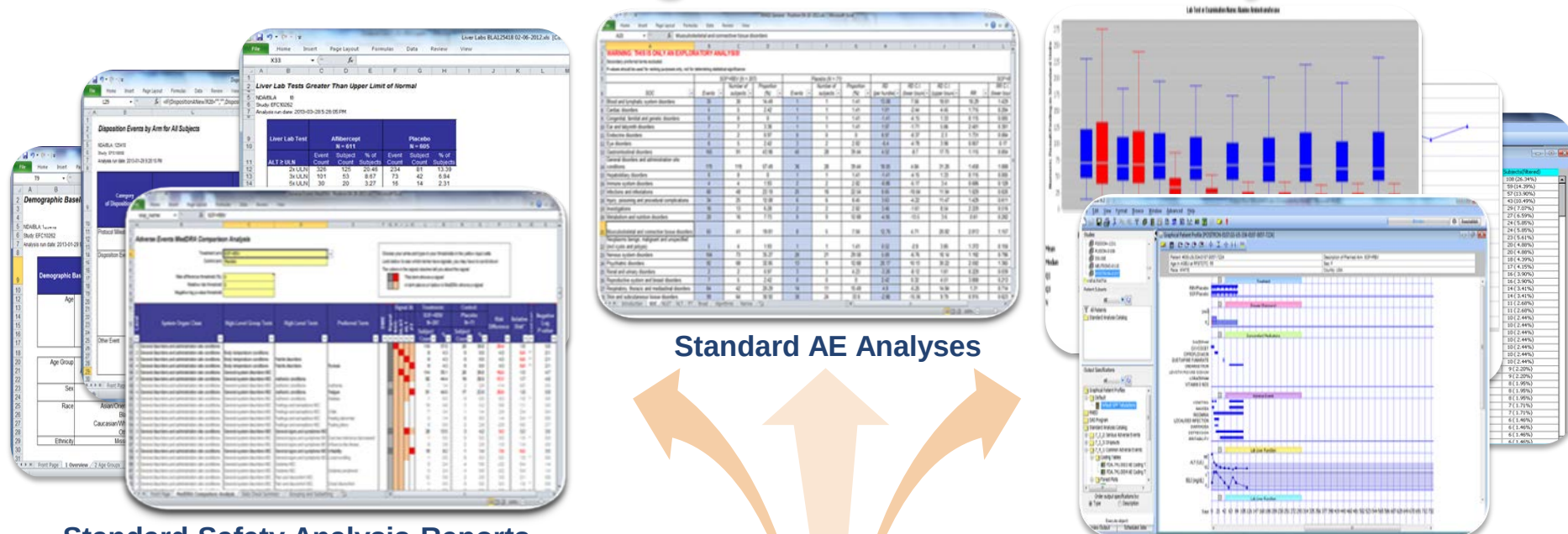
Solution – Janus Clinical Trials Repository

- Supports automated extraction, transformation, loading, management, and reviewer access to standard clinical trials data to support the regulatory review of therapeutic biologic and drug products
- Incorporates data marts designed to address specific needs, such as therapeutic areas, SDTM views for tools, etc.
- Enables queries to be run using various analytic tools from these data marts to meet individual reviewer needs
- Leverages pre-specified analysis scripts and analytic tools

Janus Clinical Trials Repository (CTR)



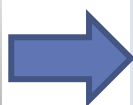
Planned CTR Integration with Analytic Tools



Standard AE Analyses

Standard Safety Analysis Reports

JReview Standard Reports



Enhanced CDISC
SDTM Views



Additional Views to Support
Regulatory Review

Regulatory Review



SAS
JMP
R
JReview
CTR Tools

Conclusion

- Rapidly moving towards a modernized, integrated bioinformatics-based review environment
- High quality, standardized data
- Easy data analysis using leading practices
- Access to powerful, standard data-based review tools