

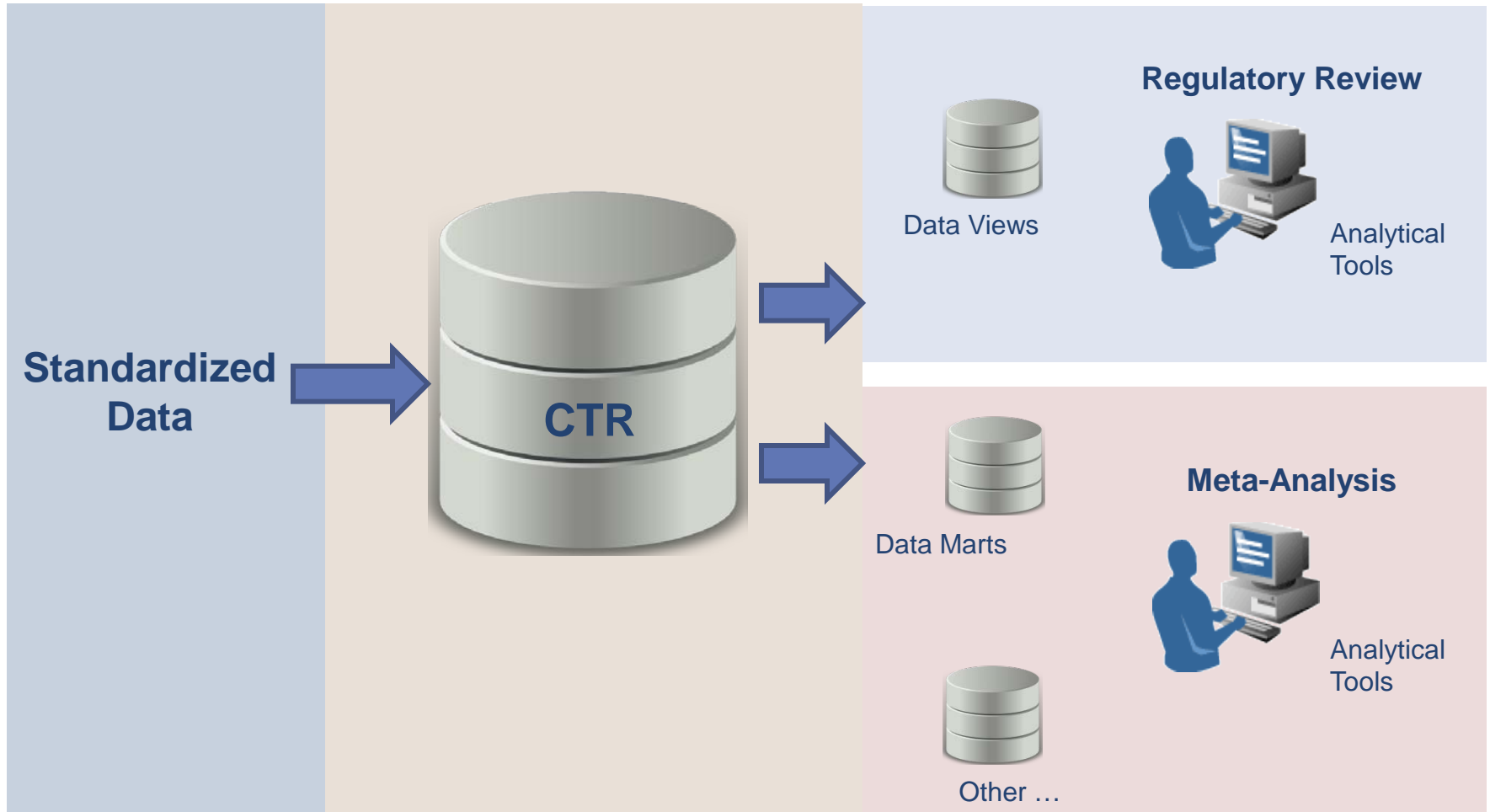


Janus Clinical Trials Repository: Modernizing the Review Process through Innovation

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Director

Office of Computational Science
Food and Drug Administration

Janus Clinical Trials Repository (CTR)



Janus Clinical Trials Repository

- Supports automated extraction, transformation, loading, management, and reviewer access to standardized clinical trials data to support the regulatory review of therapeutic biologic and drug products
- Incorporates data marts designed to address specific needs
- 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

CTR is Large Data

- CTR is designed to handle large data-sets
 - Is expected to grow into a very large data warehouse with many data marts.
 - Expected to grow by a few TB's every year

- CTR primarily handles:
 - Structured data
 - Low Velocity (~600 applications a year)
 - Analysis and reporting requirements are in real-time

CTR - Big Data Vision

- CTR will evolve into a big data system in the future
- Integrate other data-sets
 - To support the “personalized medicine” paradigm
 - Post marketing data
 - Other Data
- Explore no-SQL and Hadoop in the future



Facilitating Modernization of the Regulatory Review Process

CDER Computational Science Center

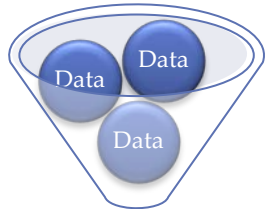
Better Data

Better Tools

Better Decisions

Intersection of data, tools and technology

Standardized Data

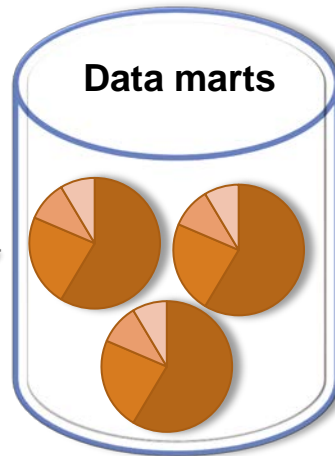


Repositories for
Electronic Data

Data
Validation



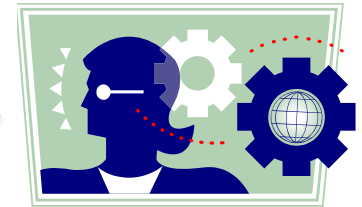
Data Warehouse



Analytic Tools



Reviewer
Decisions



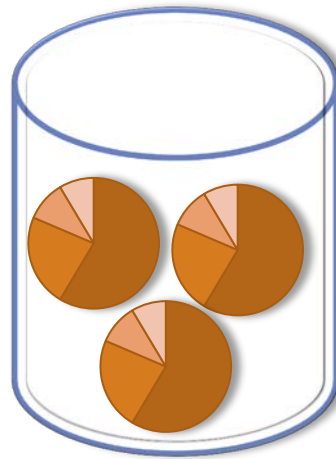
Data & Analysis
Support Services

Tools & Technology
Support Services

Training & Customer
Support Services

Computational Science Center (CSC) Reviewer Services

Data Warehouse and Data Marts



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

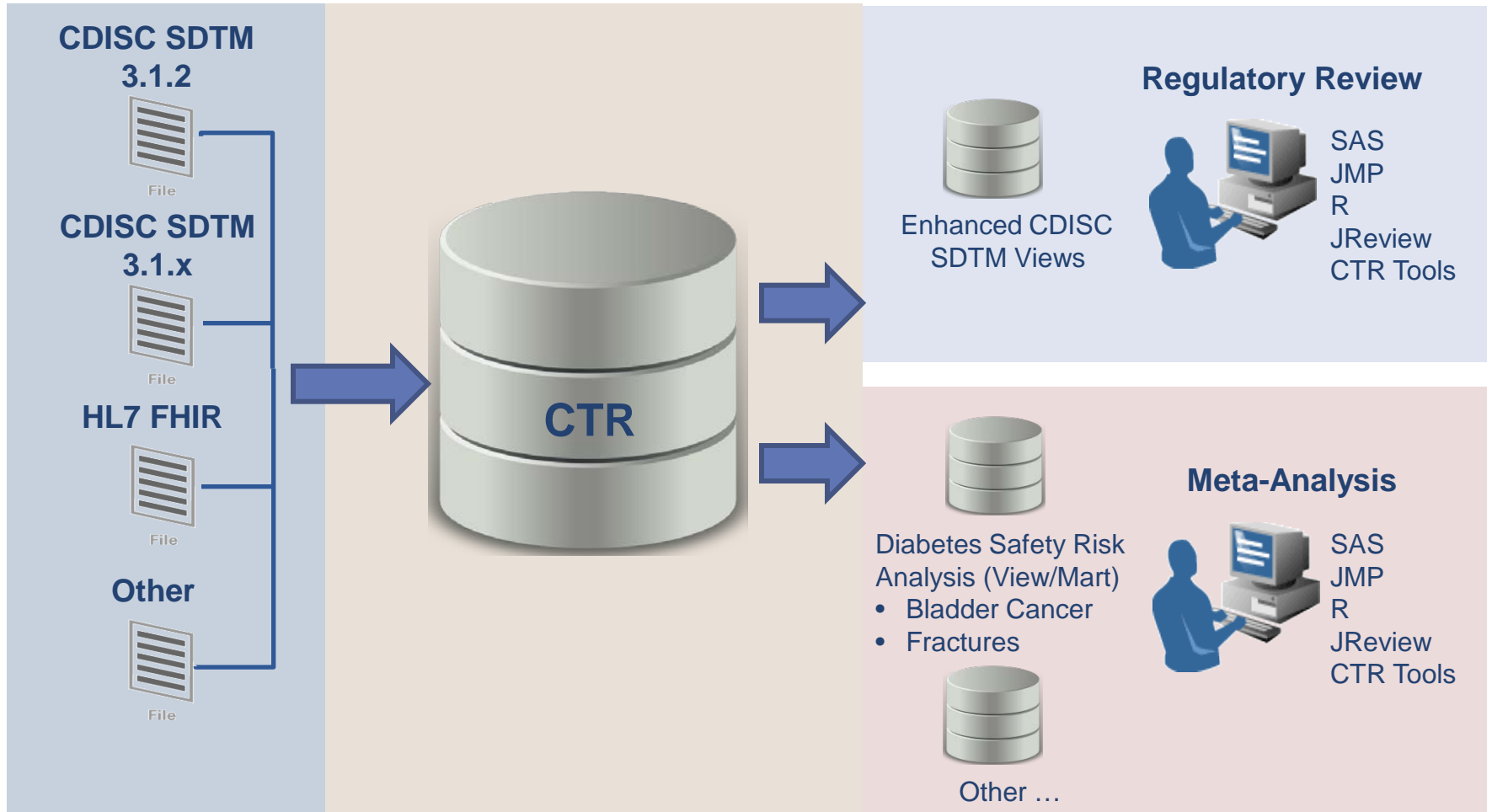
Why Do We Need a Clinical Trials Repository (CTR)?

- Clinical Trials Data will be easily **accessible**
 - One-stop shopping
 - Self-service
- Data will be more **predictable**
 - Consistent in format, content, definitions from study to study, sponsor to sponsor
- Data will be of higher **quality**
 - Data validation service will help insure minimum level of quality data
- Improved productivity
 - Less time needed for routine data management tasks
 - More time to do the analysis & interpret results
- Support Standard Analyses / Reports
- Support Cross-study Analyses

Janus CTR and the 21st Century Drug Review Process

- True potential of standardized data is unleashed with Janus CTR
 - Study data automatically transformed into “views” that are more reviewer-friendly
 - Demographic and Treatment Assignment information in every dataset
 - Numeric Dates
 - Full MedDRA Hierarchy for all adverse events
 - Data “curation” capabilities to
 - Correct misspellings; problems with coding (submitted data is not altered!)
 - Convert lab units to U.S. conventional units
 - Enables pooling of data within an application, across a drug class, or even across drug classes
 - Facilitates timely creation of custom “data marts” to support a variety of meta-analysis needs
- Janus CTR will be piloted in early 2014 in to support the JumpStart Service (in parallel with tools currently used)
 - Study Data from applications enrolled in JumpStart will be loaded into CTR

Janus Clinical Trials Repository (CTR)

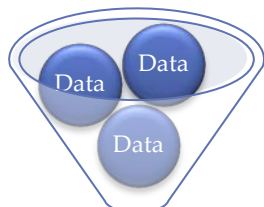


Janus Clinical Trials Repository

- 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

Intersection of data, tools and technology

Standardized Data



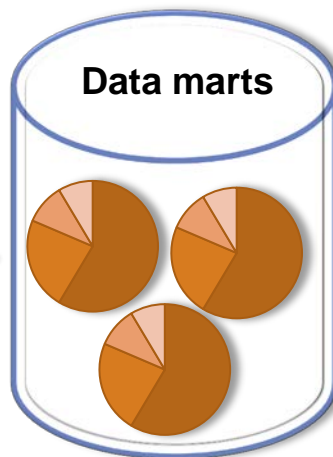
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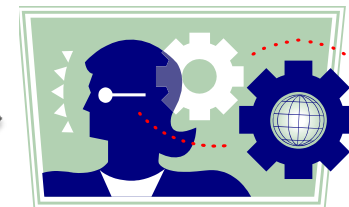
Data Warehouse



Analytic Tools



Reviewer
Decisions



Data & Analysis
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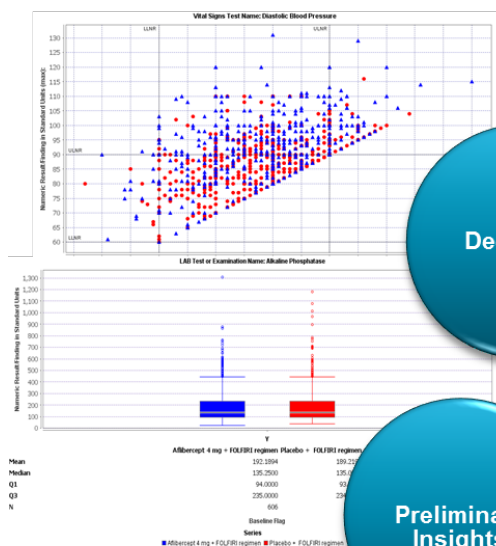
Computational Science Center (CSC) Reviewer Services

Analytic Tools

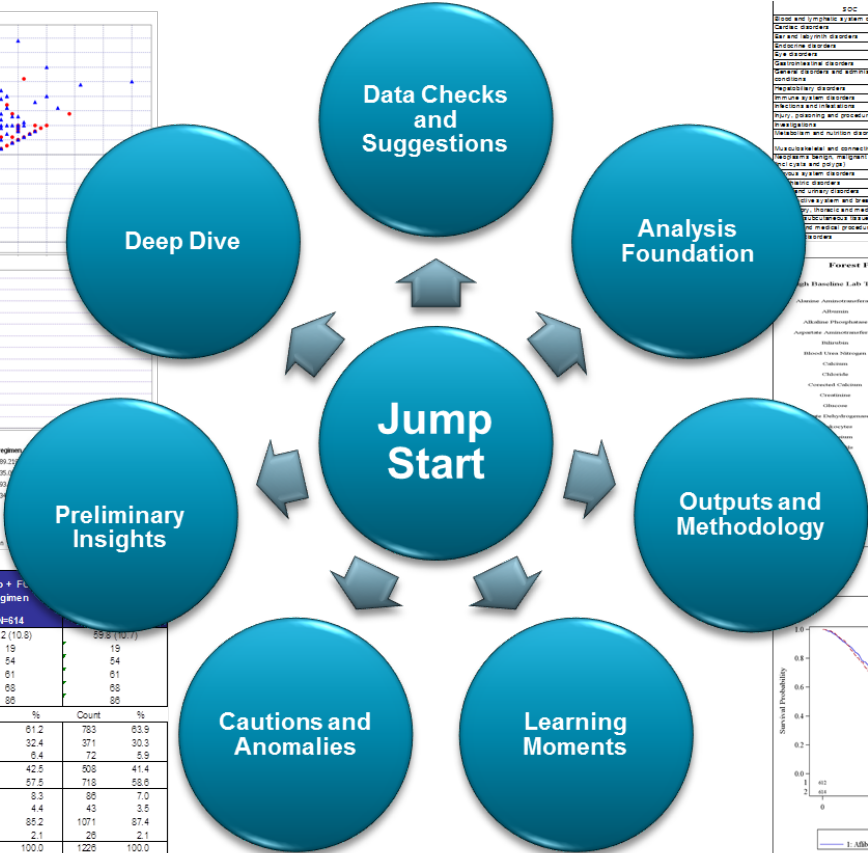
Tools	Overview
JReview	<ul style="list-style-type: none"> • Allows users to tabulate, visualize, and analyze safety and efficacy data • Provides a catalogue of standard analyses with drill down capabilities, making it easy to obtain results and graphical displays of common analyses, such as Hy's Law (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
SAS Analysis Panels	<ul style="list-style-type: none"> • Provides standard analyses (Demographics, Disposition, Exposure, Adverse Events, and Liver Labs) in Excel or Word
JMP	<ul style="list-style-type: none"> • Combines powerful statistics with dynamic graphics to enable review process
FDA Investigator's Rapid Review Service (FIRRS)	<ul style="list-style-type: none"> • Assesses the sponsors' data management and coding quality • Helps reviewers understand the contents of the data
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

CSC JumpStart Service

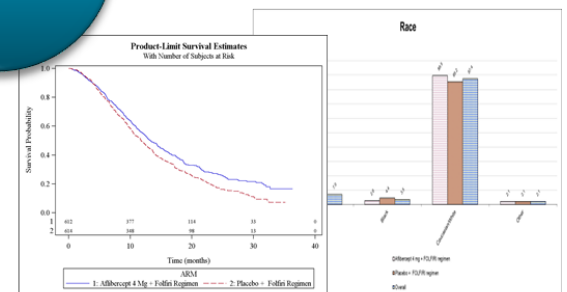
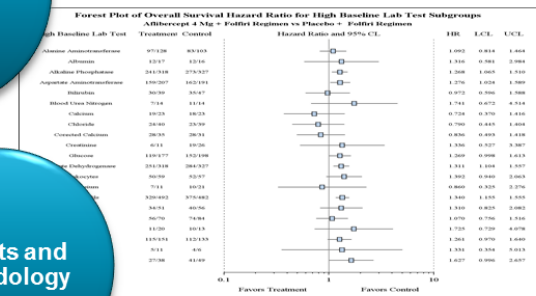
Starts a review by performing many standard analyses and identifying key information



Demographic Baseline Characteristics		Albireport 4 mg + FOLFIRI regimen (N=612)		Placebo + FOLFIRI regimen (N=614)			
Age	Mean (SE)	55.5 (10.5)	55.9 (10.7)	55.8 (10.7)	55.8 (10.7)		
	Min	21	19	19	19		
	Q1	53	54	54	54		
	Median	61	61	61	61		
	Q3	67	68	68	68		
	Max	82	88	88	88		
Age Group	Count	%	Count	%	Count	%	
	Age 65 and Under	407	66.5	376	61.2	783	63.9
	Age between 65 and 75	172	28.1	199	32.4	371	30.3
	33	5.4	39	6.4	72	5.9	
Sex	Count	%	Count	%	Count	%	
	F	247	40.4	261	42.5	508	41.4
	M	365	59.6	353	57.5	716	58.6
Race	Count	%	Count	%	Count	%	
	Asian/Oriental	35	5.7	51	8.3	88	7.0
	Black	16	2.6	27	4.4	43	3.5
	Caucasian/White	548	89.5	523	85.2	1071	87.4
	Other	13	2.1	13	2.1	26	2.1
Ethnicity	Missing	612	100.0	614	100.0	1228	100.0



SOC	n	Events	Number of subjects (%)	PROPORTION	n	Events	Number of subjects (%)	PROPORTION
Cardiac disorders	68	27	44.1	68	23	33.8	33.8	
Gastrointestinal disorders	46	24	52.2	46	21	45.7	45.7	
Genitourinary disorders	68	27	39.7	68	28	41.2	41.2	
Infections	2	2	100	2	2	100	100	
Injury, poisoning and procedural complications	38	17	44.7	38	15	39.5	39.5	
Investigations	3	3	100	3	2	66.7	66.7	
Metabolism and nutrition disorders	102	23	22.5	102	16	15.7	15.7	
Musculoskeletal and connective tissue disorders	17	2	11.8	17	2	11.8	11.8	
Neoplasms benign and malignant (incl. carcinoma)	22	9	40.9	22	6	27.3	27.3	
Psychiatric disorders	13	2	15.4	13	1	7.7	7.7	
Respiratory disorders	18	8	44.4	18	6	33.3	33.3	
Skin disorders	3	3	100	3	2	66.7	66.7	
Systemic disorders	2	2	100	2	1	50	50	
Use of concomitant medicine	19	2	10.5	19	2	10.5	10.5	
Unlabeled medicinal products	38	2	5.3	38	2	5.3	5.3	
Unknown	2	2	100	2	2	100	100	
Total	1217	222	18.2	1217	127	10.5	8.8	



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

SOC	Group 1 (n = 203)		Group 2 (n = 20)	
	Number of Subjects	Proportion (%)	Number of Events	Proportion (%)
Blind and lymphatic system disorders	30	14.8	1	5.0
Cardiac disorders	5	2.4	1	5.0
Conjugal, familial and genetic disorders	0	0	1	5.0
Ear and labyrinth disorders	7	3.4	1	5.0
Eye disorders	2	0.9	0	0.0
General disorders and administration site conditions	160	77.9	45	22.5
Immunisation disorders	179	87.9	36	18.0
Infections and infestations	4	1.9	2	10.0
Injury, poisoning and procedural complications	60	29.3	16	8.0
Investigations	16	7.8	2	10.0
Metabolism and nutrition disorders	25	12.2	9	4.5
Musculoskeletal and connective tissue disorders	65	31.8	3	1.5
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5	2.4	1	5.0
Respiratory system disorders	194	95.3	28	14.0
Skin and subcutaneous tissue disorders	32	15.6	13	6.5
Surgical and medical procedures	2	0.9	3	1.5
Teeth, oral and maxillofacial disorders	7	3.4	0	0.0
Urinary, genital and reproductive disorders	14	6.8	14	7.0
Vascular disorders	59	28.9	30	15.0

MAED: System Organ Class

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

Adverse Events MedDRA Comparison Analysis

System Organ Class | High-Level Group Term | High-Level Term | Preferred Term

System Organ Class	High-Level Group Term	High-Level Term	Preferred Term	Signal	Treatment
General disorders and administration site conditions	Body temperature conditions	Fatigue	Fatigue	4	4
General disorders and administration site conditions	Body temperature conditions	Fatigue	Fatigue	4	4
General disorders and administration site conditions	Body temperature conditions	Fatigue	Fatigue	4	4
General disorders and administration site conditions	Body temperature conditions	Fatigue	Fatigue	4	4
General disorders and administration site conditions	Body temperature conditions	Fatigue	Fatigue	4	4
General disorders and administration site conditions	Body temperature conditions	Fatigue	Fatigue	4	4
General disorders and administration site conditions	Body temperature conditions	Fatigue	Fatigue	4	4
General disorders and administration site conditions	Body temperature conditions	Fatigue	Fatigue	4	4
General disorders and administration site conditions	Body temperature conditions	Fatigue	Fatigue	4	4
General disorders and administration site conditions	Body temperature conditions	Fatigue	Fatigue	4	4

MedDRA at a Glance Report

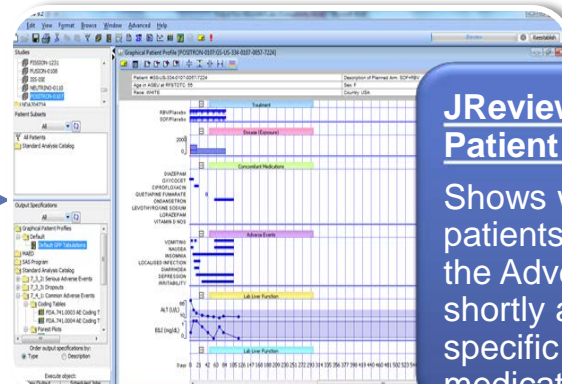
Shows same signal across multiple levels of the hierarchy for the treatment arm.

JReview: Risk Assessment

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

JReview: Risk Assessment

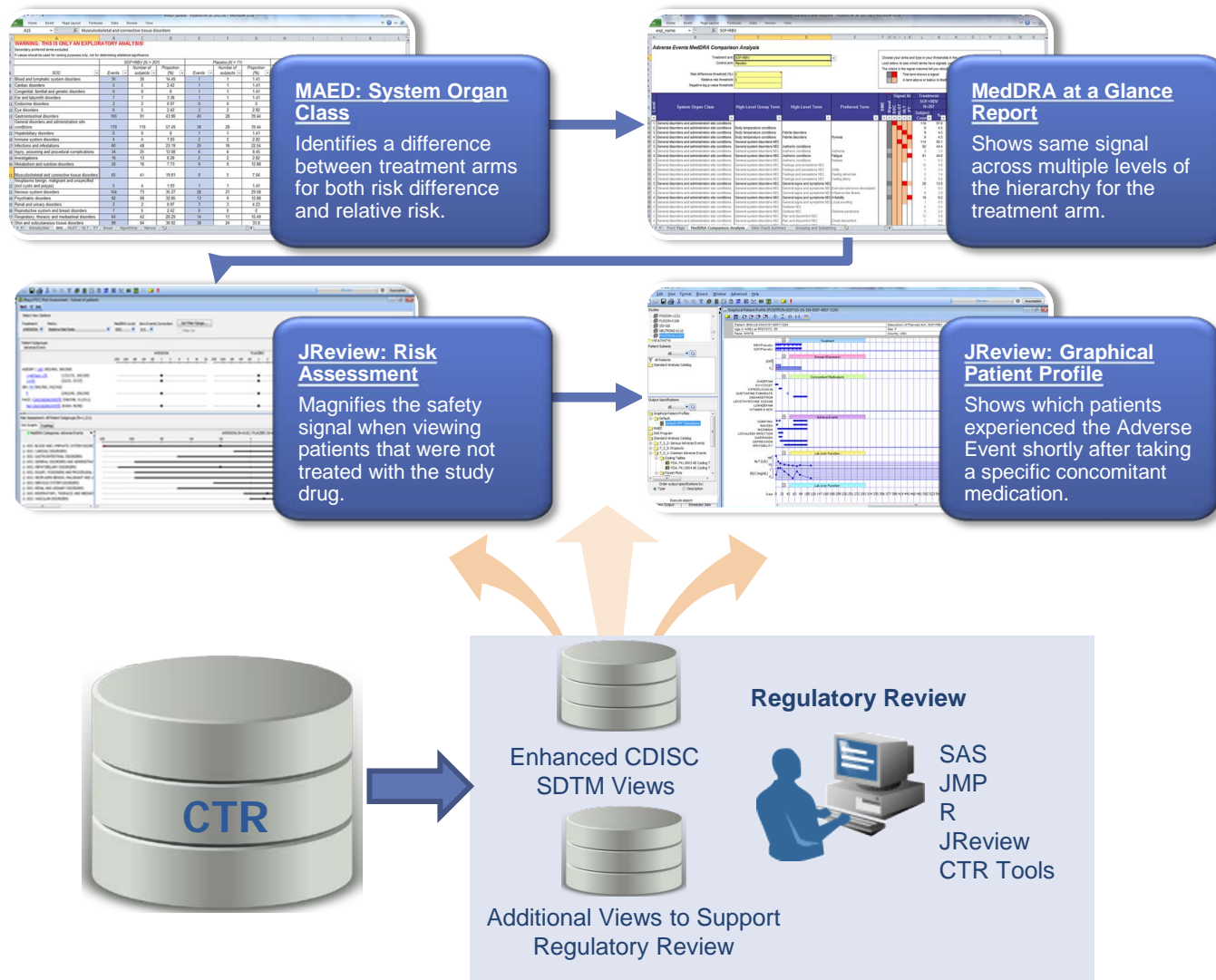
Magnifies the safety signal when viewing patients that were not treated with the study drug.



JReview: Graphical Patient Profile

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

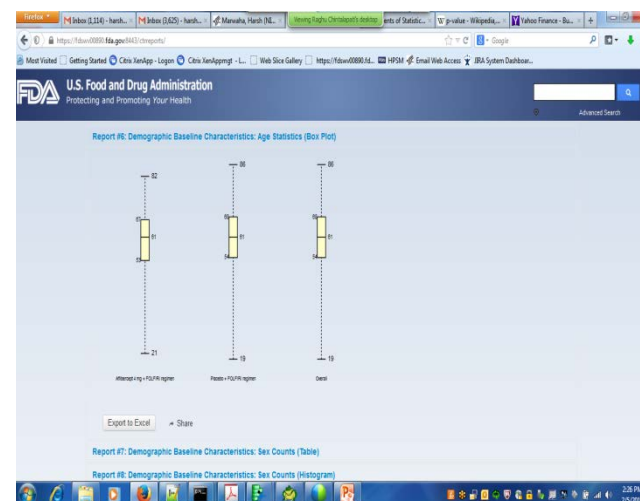
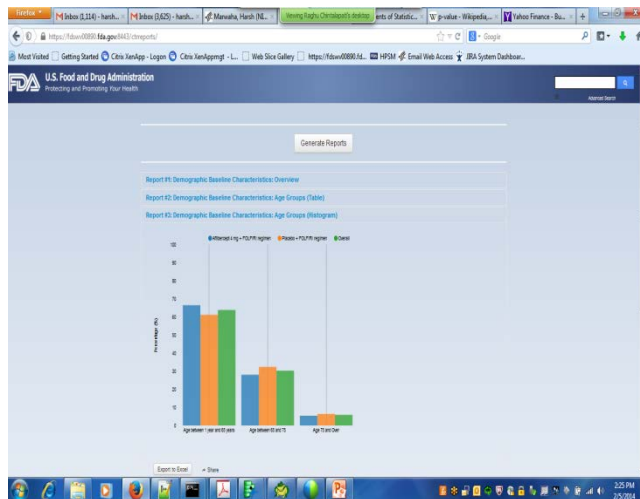
Planned CTR Support of JumpStart Service



CTR Tools to Support JumpStart

- CTR Standard Analysis Reports (web-based application)
 - Standardized reports that support safety review, including safety reports supported by JumpStart
- Study & Standards Browser (web-based application)
- Ad Hoc Query Tool (web-based application)
- Data Curation

CTR Reports



- Over 60 standardized reports
- Includes MAED, FIRRS and standard analysis reports.
- Users can filter data prior to running each report

Study & Standards Browser

- Consolidates all study meta-data
 - Access summary information about the study (Study design, trial summary, explanation of codes used, location of specific variables, etc.)
 - Study specific transforms, preferences and reports
 - User defined tags for other meta-data

- Reviewer Log
 - Ability to go back in time and recreate analyses



Study & Standards Browser



FDA U.S. Food and Drug Administration Study Browser Application Menu

Select A Study > Diabetes_Actos_01-01-TL-OPI-516

- Study Summary
- Trial Inclusion / Exclusion
- Study Protocol**
- Study Define XML
- Reviewer Preferences & Reports
- Reviewer Notes
- Reviewer Log

Study Flow

Epoch/Arm	SCREENING	TREATMENT	POST-TREATMENT
Glimepiride-Titration (1mg to 4mg) QD	1 . SCREENING Condition : RANDOMIZED TO GLIMEPIRIDE	2 . GLIMEPIRIDE Condition :	3 . POST-TREATMENT Condition :
Pioglitazone-Titration (15mg to 45mg) QD	1 . SCREENING Condition : RANDOMIZED TO PIOGLITAZONE	2 . PIOGLITAZONE Condition :	3 . POST-TREATMENT Condition :

Elements

Name	Duration	Start Condition	End Condition
GLIMEPIRIDE	0	First dose of study medication where subject is randomized to Glimepiride and Pioglitazone-matched Placebo tablets.	72 weeks after start of element
PIOGLITAZONE	0	First dose of study medication where subject is randomized to Pioglitazone and Glimepiride-matched Placebo capsules.	72 weeks after start of element
POST-TREATMENT	0	After final dose of study medication	30 Days after final dose
SCREENING	0	Informed consent obtained	Up to 2 weeks after start of element

Study Visit occurrence

Visit/Arm	DEFAULT
SCREENING	0 Start Condition : Start of Screening Epoch
RANDOM WEEK 0	1 Start Condition : Start of the Treatment Period
VISIT 2 WEEK 4	2 Start Condition : 4 Weeks after the start of the Treatment Epoch
VISIT 3 WEEK 8	3 Start Condition : 8 Weeks after the start of the Treatment Epoch
VISIT 4 WEEK 16	4 Start Condition : 16 Weeks after the start of the Treatment Epoch
VISIT 5 WEEK 24	5 Start Condition : 24 Weeks after the start of the Treatment Epoch

Ad-Hoc Query Tool

- Allows reviewers to manipulate data by
 - Pooling of data across studies
 - Filtering
 - Sub-setting
 - Complex queries with logical operators
- Reviewers can create and download customized analysis ready datasets from the CTR
 - From a single study
 - Across multiple studies
- Provides a framework for developing meta-analysis reports



Ad-Hoc Query Tool

Query Builder - Google Chrome

amistad:8080/adhocquery/index.html

First D3 experiment CTR Reports XML Editor easy query builder AMRDEC SAFE

FDA U.S. Food and Drug Administration Protecting and Promoting Your Health

Query Builder

Save Clear Load Execute

Selected Studies

- App: NDA022350, CV181014
- App: NDA022350, CV181057
- App: NDA021995, 036
- App: NDA021073, AD_4833_EC444
- App: NDA021995, 0431_051

Variables and Columns

Add New Column or Variable

- Demographics.Age
- Adverse Events.Action Taken with Study Treatment

Domains and Tables

- Adverse Events
- Clinical Assessments
- Concomitant Medications
- Death Diagnosis
- Demographics
- Disposition

Conditions

Select records where all of the following apply:

- Adverse Events.Action Taken with Study Treatment starts with "DRUG"

[Add new condition]

Result Controls

Graph type:

- Table
- Scatter Plot
- Line Chart
- Forest Plot
- Histogram
- Box Plot

X axis:

Customers

Results

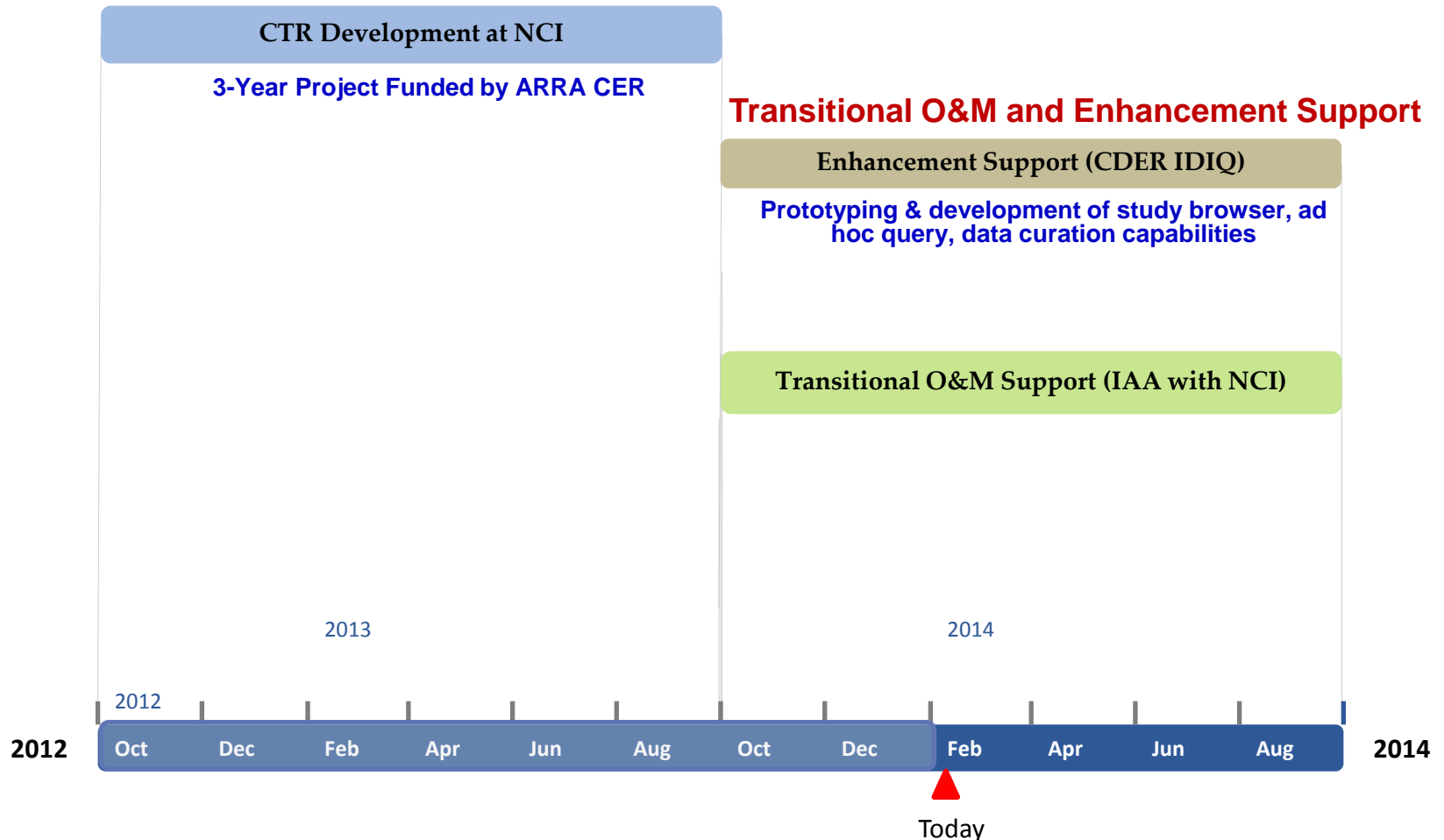
Show 10 entries

Age	Action Taken with Study Trea
27	DRUG INTERRUPTED
30	DRUG INTERRUPTED
30	DRUG INTERRUPTED
30	DRUG WITHDRAWN
31	DRUG INTERRUPTED
32	DRUG INTERRUPTED
35	DRUG INTERRUPTED
35	DRUG INTERRUPTED



Timeline for Janus Clinical Trials Repository 2012 through 2014

Contractor Support through NCI/SAIC-Frederick



Future Directions

- CTR marks the first step to integration of diverse and bigger data
 - CTR is designed to handle large data-sets
 - Is expected to grow into a very large data warehouse with many data marts.
 - Expected to grow by a few TB's every year
- **CTR will evolve into a big data system in the future**
- **Integrate other data-sets**
 - To support the “personalized medicine” paradigm
 - Pre market and Post marketing data
 - Other Data (pharmacogenomics, large simple trials, therapeutic area specific databases)
 - Support nonclinical data to clinical correlations

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