

CDER's Computational Science Center

Modernizing the Review Process through Innovation

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Director

Office of Computational Science

Office of Translational Sciences

Food and Drug Administration

AGENDA

- CSC – Past , Present & Future
- Goals & Priorities
- Key Activities

CSC – PAST

- Goals
 - Provide robust scientific computing capabilities to CDER reviewers
 - Dedicated resources & technologies
 - Aimed at incorporating innovation at every level
- Challenges – Infrastructure, Tools & Resources
- Overall Focus – Laying the foundation

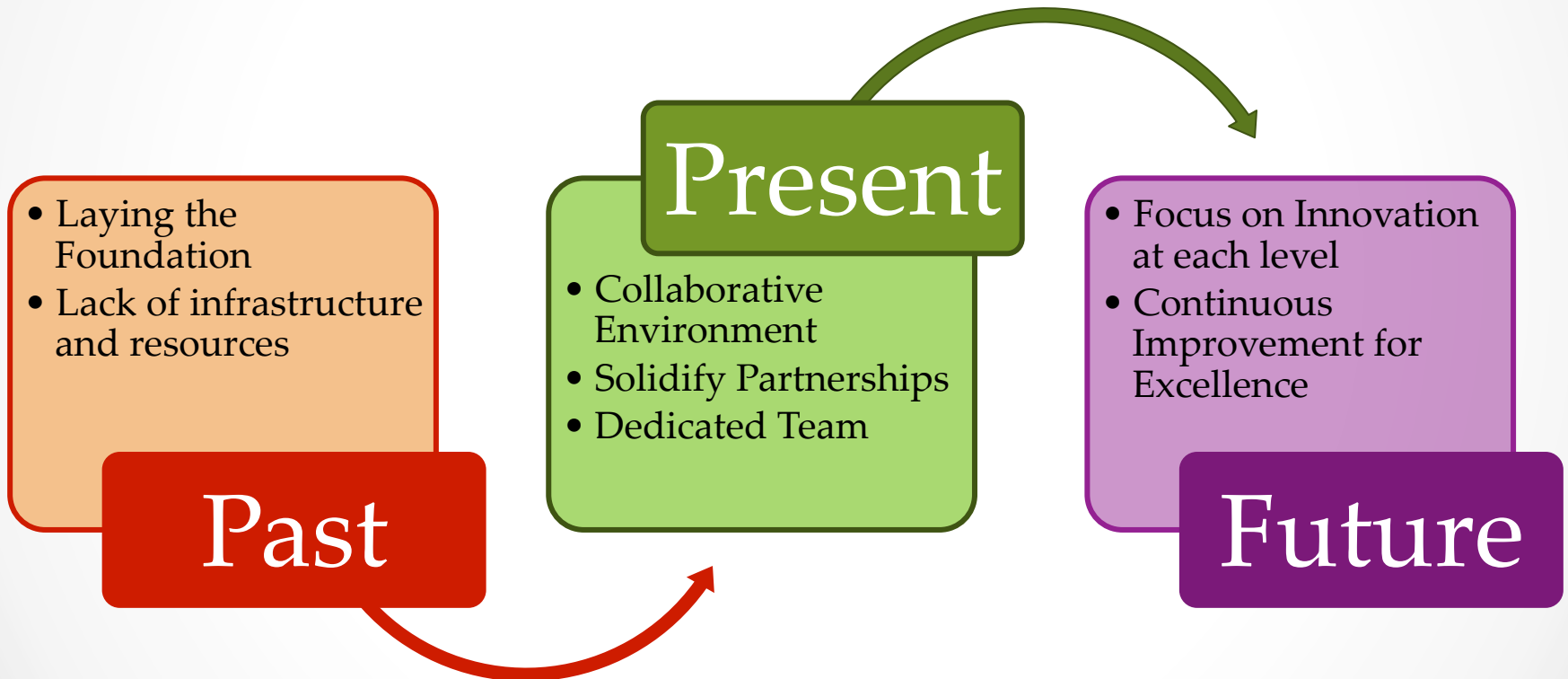
CSC - PRESENT

- Goals
 - Collaborative environment - Strategize & Execute
 - Strategic roadmap in place in alignment with FDA CDER's mission
 - An officially dedicated team
 - Solidify Partnerships
- Overall Focus – Establishment

CSC - FUTURE

- Goals
 - Be a recognized 'Service Organization' for providing innovative technological solutions and services addressing CDER's review challenges
 - Be a catalytic agent by leveraging targeted tools directly improving the CDER review process
- Overall Focus – Excellence through Innovation

Recap



Office of Computational Sciences



Why the OCS?

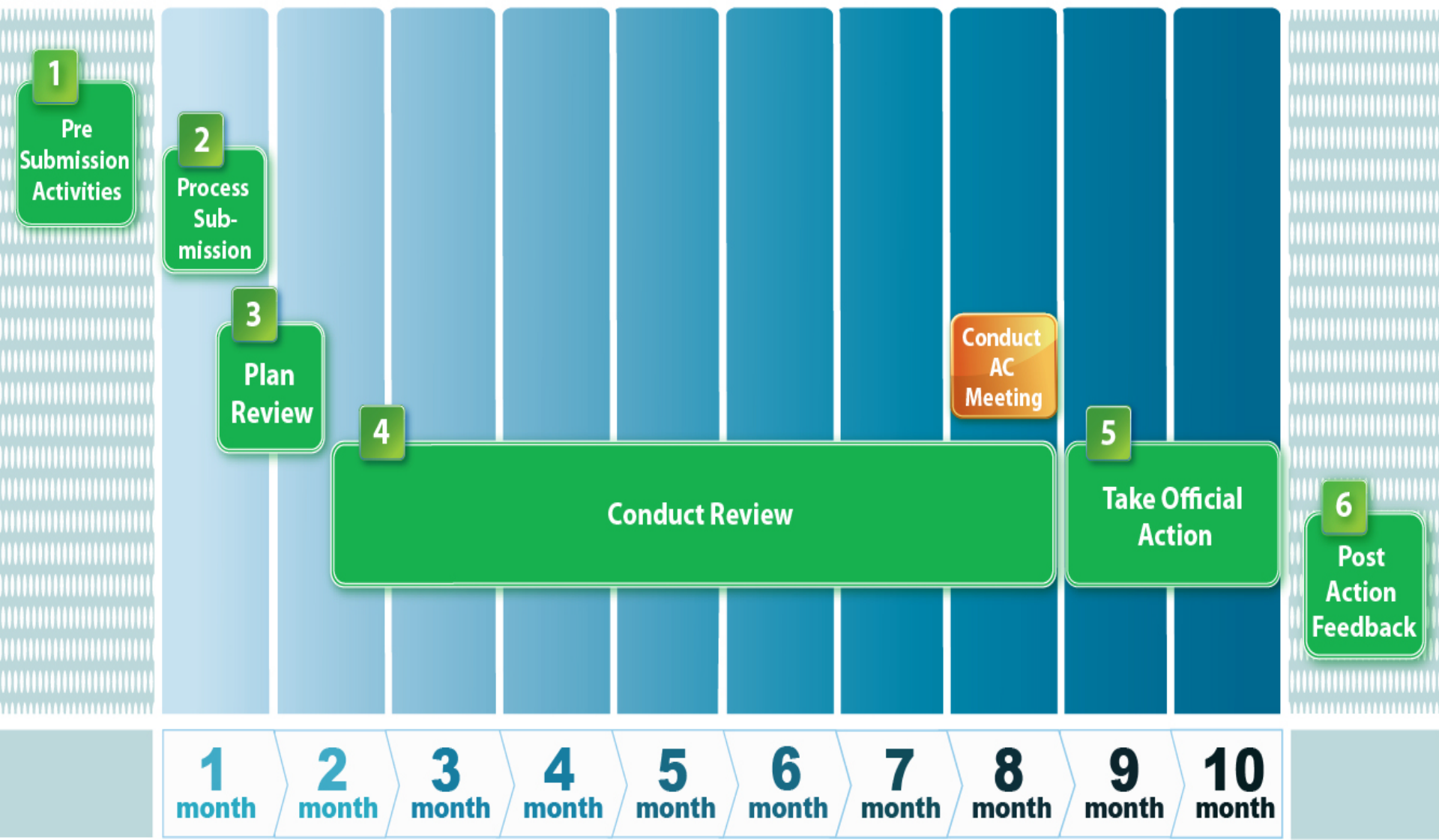
- FDA mission
- Modernization of CDER's scientific computing abilities and operations
 - Enhance the accessibility of data, strive to reduce data integrity issues, and support robust data governance.
 - Improve coordination and prioritization of CDER's scientific computing plans and activities.
 - Couple data, tools, and technology with reviewer-focused training.
 - Recognize the need to be at the forefront of innovation and to adapt to ever-evolving computational demands.
 - Facilitate the exploration of tools and technology to meet the demands of the modern review process.

Office of Computational Science Houses CDER's

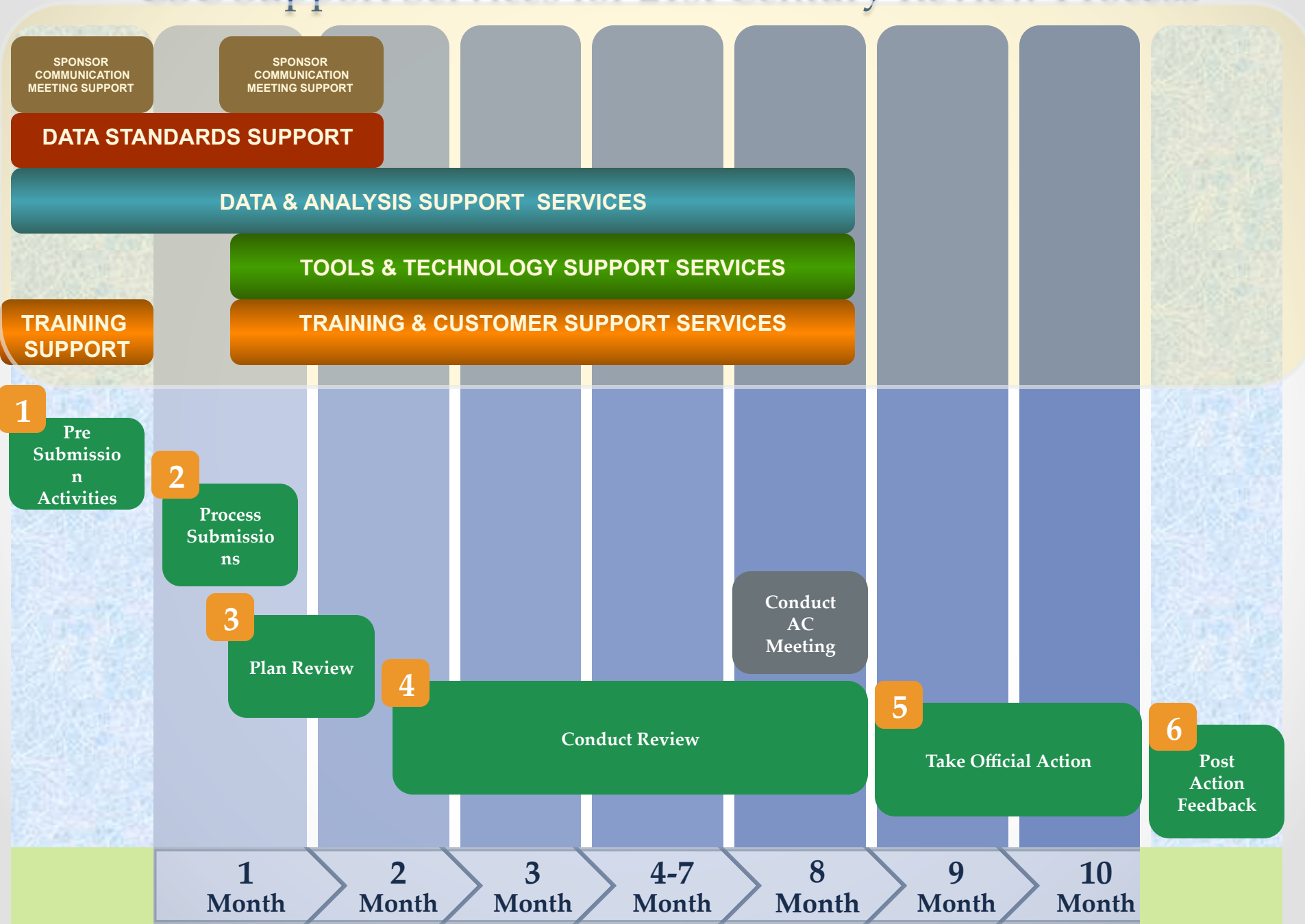
Computational Science Center

- CDER's Computational Science Center (CSC) is one of the key initiatives of OCS.
- CSC to help reviewers leverage technology at the intersection of analytical tools and science
- CSC provides services supporting the submission and use of high quality data, and access to analytical tools, technology, and training
- CSC helps empower reviewers to conduct their regulatory reviews with greater efficiency by providing targeted services supporting the evaluation and analysis of study data.

21st Century Review Process



CSC Support Services for 21st Century Review Process



CDER

CSC SERVICES

**DATA & ANALYSIS
SUPPORT SERVICES**

Data Validation /Quality
Assessments

Support Data
Standardization

Facilitate Data
Transformation

Script Development &
Sharing to support analysis

**TOOLS & TECHNOLOGY
SUPPORT SERVICES**

Analytical tools support

Regulatory Review Service

Scientific Environment /
Infrastructure

**TRAINING & CUSTOMER
SUPPORT SERVICES**

Analytical Tool training

Data Standards training

Process training

Access to CSC SMEs and
mentors

INNOVATION

DATA & ANALYSIS SUPPORT SERVICES

Data Validation /Quality
Assessments

Support Data
Standardization

Facilitate Data
Transformation

Script Development &
Sharing to support analysis

- CDER Data Validation Service (DataFit)
- Data Standards Initiatives
 - Supporting CDISC SDTM/SEND implementation
 - Supporting HL7 study data standards testing
- SAS Clinical Data Integration (CDI)
- Scripts/analytics development

DataFit

- Objectives
 - Create validation profiles that are designed to assess if data is fit for use
 - Share validation specifications with industry
- Value
 - Improve ability of submitted data to support actual review activities
 - Reduce uncertainty for sponsor on how to submit data
 - Reduce need for post-submission Request for Information/Data resubmission
 - Serve as basis for IND-stage discussions about data implementation

TOOLS & TECHNOLOGY SUPPORT SERVICES

Analytical tools support

Regulatory Review Service

Scientific Environment /
Infrastructure

- Tools
Clinical: MAED, JREVIEW, FIRRS
Non-Clinical: NIMS
Data Warehousing – Janus CTR
- Jumpstart
- Environments (Scientific Workstations, Regulatory Research Environment)

Clinical Tools

- MAED (MedDRA Adverse Events Diagnostics)
 - Compares rates of AEs between treatment arms
 - All levels of MedDRA Hierarchy and all SMQs (narrow, broad, algorithmic)
 - Currently in limited production roll-out (about 110 reviewers)
- JReview & Standard Analysis
 - Standard Analysis Catalog (possible with standardized data)
 - Produces a variety of standard, automated analyses accompanied by robust documentation
 - In use now in CDER by clinical reviewers and new analyses added quarterly
- FIRRS (FDA Investigators Rapid Review System)
 - Designed to help reviewers perform a rapid assessment of the submitted data's ability to support analysis.
 - In development to perform an assessment of the quality of sponsor's standardized clinical data management activities (coding, use of standard dictionaries, completion of critical labs, etc.)

MedDRA Adverse Events Diagnostics

MAED is a web-based application

- Provides an initial assessment of adverse
- Powerful safety signal detection tool
- Reviewers can prioritize and explore potential signals that might be important to determine if those signals are meaningful
- Risk estimators are not meant to be statistically definitive
- They are used to highlight differences between arms
- Currently in Pre-Production in CDER
- Currently ~110 of active users in system
- Check out details at poster

MAED

Example of findings:

- Severe neuropsychiatric events (Hostility/Aggression) appear higher in study drug compared to placebo.
- Confirmed after a more detailed analysis and review by medical officer

A6												
A												
WARNING: THIS IS ONLY AN EXPLORATORY ANALYSIS!												
* after SMQ name indicates SMQ with narrow terms only. Broad search will yield the same results.												
Number in parenthesis before SMQ name represents SMQ level.												
P-values should be used for ranking purposes only, not for determining statistical significance.												
	Group 1 (N=103)			Placebo (N=103)			Group 1 vs. Placebo					
SMQ (Narrow Search)	Events	Number of subjects	Proportion (%)	Events	Number of subjects	Proportion (%)	RD (per hundred)	RD C.I. (lower bound)	RD C.I. (upper bound)	RR	RR C.I. (lower bound)	RR C.I. (upper bound)
(1) Hostility/aggression	47	31	2.99	4	3	0.68	2.31	1.02	3.6	4.4	1.352	14.317
(2) Vestibular disorders	64	40	3.85	4	4	0.9	2.95	1.48	4.42	4.258	1.533	11.83
(1) Hearing and vestibular disorders	74	48	4.62	5	5	1.13	3.49	1.88	5.11	4.088	1.638	10.199
Groups SOC HLGT HLT PT Broad Algorithmic Narrow												

Showing as Narrow SMQ

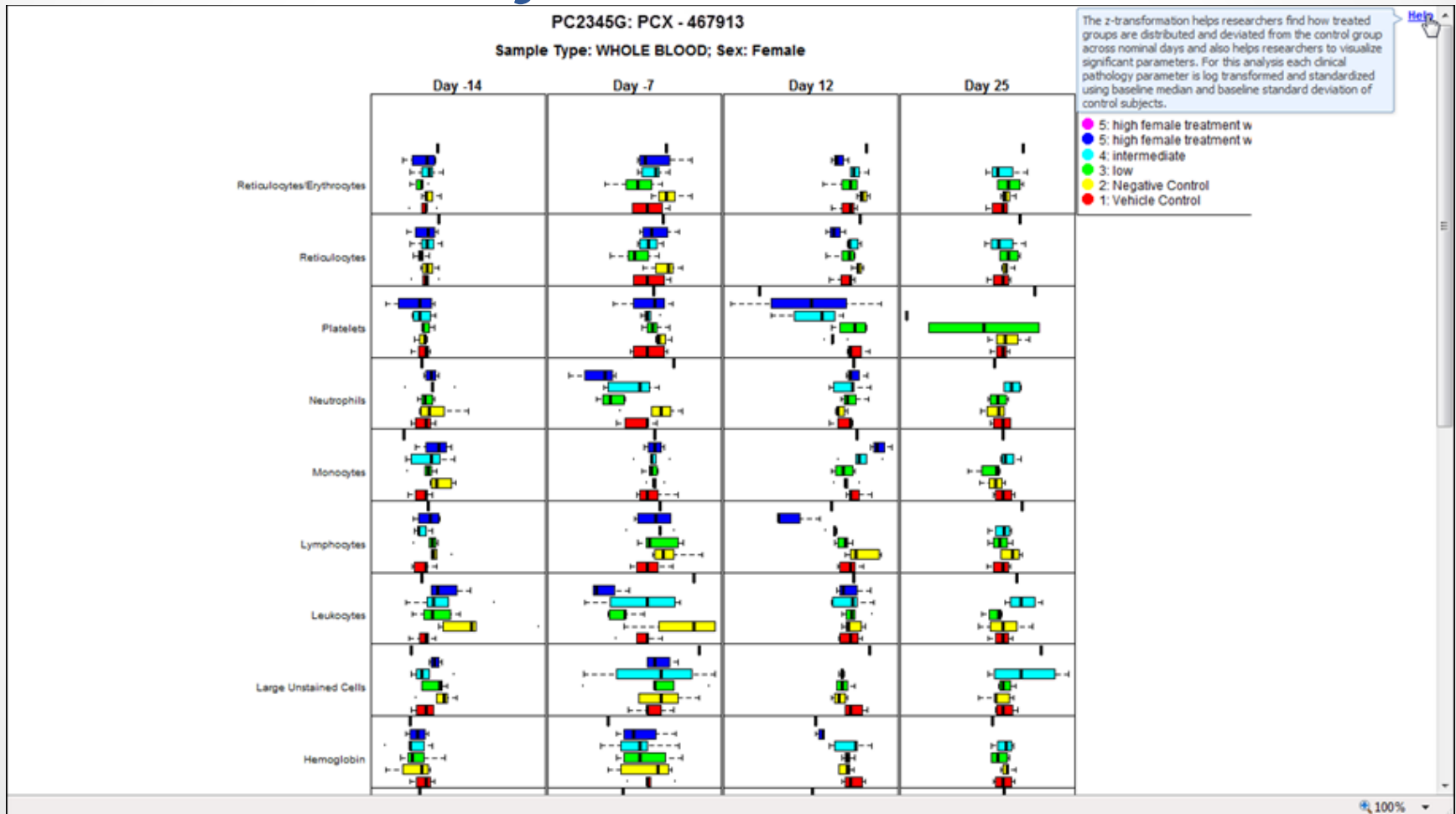
Non Clinical Tools

Nonclinical Information Management System (NIMS)

NIMS is a repository, visualization & analyses, search and orienteering tool that puts information dynamically at a reviewer's fingertips

- Allows reviewers to look across studies, class, findings, and finding types
- See all findings for an individual animal in one place
- Drill down and roll up from summary information to individual

Data normalization for analysis in NIMS



Data Warehousing Tools

Janus Clinical Trials Repository (CTR)

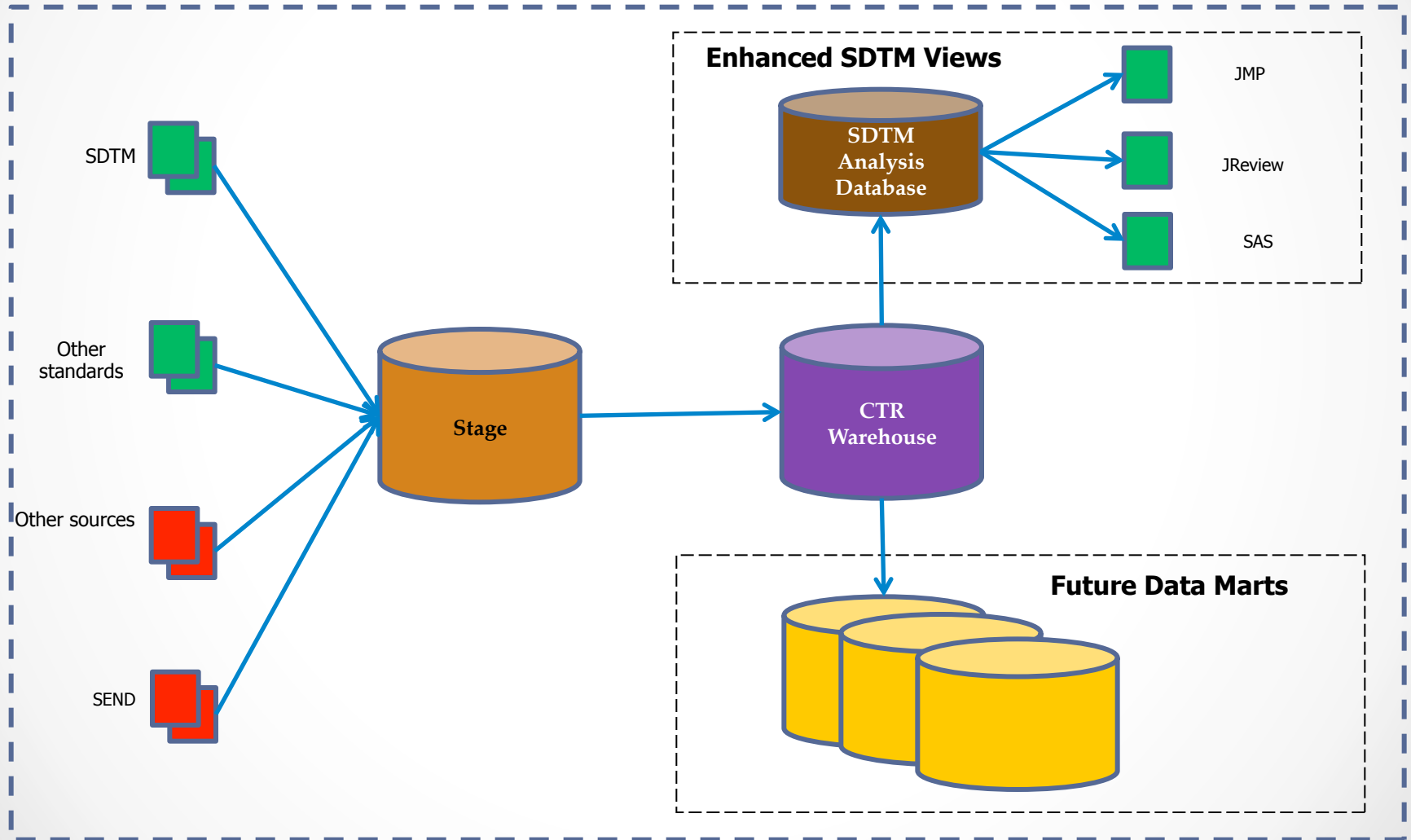
Overall Scope

- Develop and implement a Clinical Trials Repository and associated services to support the automated validation, transformation, and loading of standardized datasets
- Develop an extract database of enhanced Study Data Tabulation Model (SDTM) views that can be accessed by reviewers using analytical tools (e.g. JReview, JMP, and SAS)
- Deploy the CTR into a production environment at FDA

Status

- “Value” testing of enhanced SDTM views was completed in December 2012
- User acceptance testing planned for July-August 2013
- Deployment at FDA scheduled for September 2013

Janus CTR



Janus CTR

JANUS CTR Data and Cross Study Analysis at FDA: Five Minutes versus Five Years and Millions of Dollars

(Slides from a presentation given to Janet Woodcock, Dec. 2012)

Iffat Chowdhury, Bobbie Witczak, Helena Sviglin

The findings and conclusions in this poster have not been formally disseminated by the Food and Drug Administration and should not be construed to represent any agency determination or policy.

Introduction: The FDA has limited options when faced with detecting emerging safety signals. A powerful new tool, the Janus Clinical Trials Repository (CTR) enables analysis of emerging signals in clinical trials and supports a more informed regulatory decision-making process. Specifically, the CTR is a modern data warehouse application that automatically processes and maintains a database of structured, standardized study data, and makes it available for reviewer access through a variety of analytical tools. Conceptually, the CTR will allow us to create databases easily to support meta-analyses of clinical trial data so that reviewers can focus on analysis of the data instead of spending time in preparing the datasets for analysis. The CTR is currently in development and only houses legacy diabetes data that CDER has converted under an ARRA PCOR-funded contract.

JumpStart Process

JumpStart takes various tools and technologies CSC has developed and applies them to NDA submissions in a consolidated process that can support reviewers in multiple ways.

1. Assess and report on whether data is fit for purpose
 - Quality
 - Tool loading ability
 - Analysis ability
2. Automate analyses that are universal or common
 1. e.g. demographics, simple AE, etc
3. Provide analyses to highlight areas that may need focus for review
4. Load data into tools for reviewer use.

TRAINING & CUSTOMER SUPPORT SERVICES

Analytical Tool training

Data Standards training

Process training

Access to CSC SMEs and
mentors

- Analytical Tools Training (Reviewer's tool guide, JReview, MAED, NIMS)
- Data Standards Training (Online & In-Class training)
- Process Training (IT Approval Process Guide, Contractor Onboarding, Data Standards Process Development)



The CSC is committed to enabling reviewers to utilize tools for regulatory review by providing **Reviewer-Centric training.**

PhUSE Collaborations

Workgroup	Activity
1	<ul style="list-style-type: none">• Development of charter for a validation Change Control Board• Development of a white paper on syntax for validation rules, including best practices and example• Addressing issues in list of validation rules
2	<ul style="list-style-type: none">• Gap analysis to support site selection tool
4	<ul style="list-style-type: none">• Development of Study Data Guide Template (SDRG) with instructions and examples
6	<ul style="list-style-type: none">• White paper on collection and prioritization of nonclinical informatics needs• SEND implementation wiki as a resources and forum• Poster - Collection and prioritization of data types to be addressed in the Standardization roadmap group.• Poster – Modeling and testing out stakeholder interactions around nonclinical datasets• Development of use cases and associated algorithms to be run on endpoint for nonclinical to clinical prediction

Office of Computational Science

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Questions?

Please contact us at cdercsc@fda.hhs.gov