

CDER's Clinical Investigator Site Selection Tool

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FDA Disclaimer

- The views and opinions presented here represent those of the speaker and should not be considered to represent advice or guidance on behalf of the U.S. Food and Drug Administration.

Outline

- CDER's Bioresearch Monitoring (BIMO) Program
- CDER's Clinical Investigator Site Selection Tool (CISST) - Development and Functionality
- Time to Site Identification
- Inspection Outcomes
- Data Mining Potential
- Future Directions
- Clinsite Preparation Pointers



Bioresearch Monitoring (BIMO) Program

- Goals
 - Trial participants are adequately protected
 - Submitted data are reliable
 - Reliable for regulatory decision making (Approval)
 - Reliable as evidence base for instructions for clinical use of product (Labeling)

Scope of BIMO Inspections

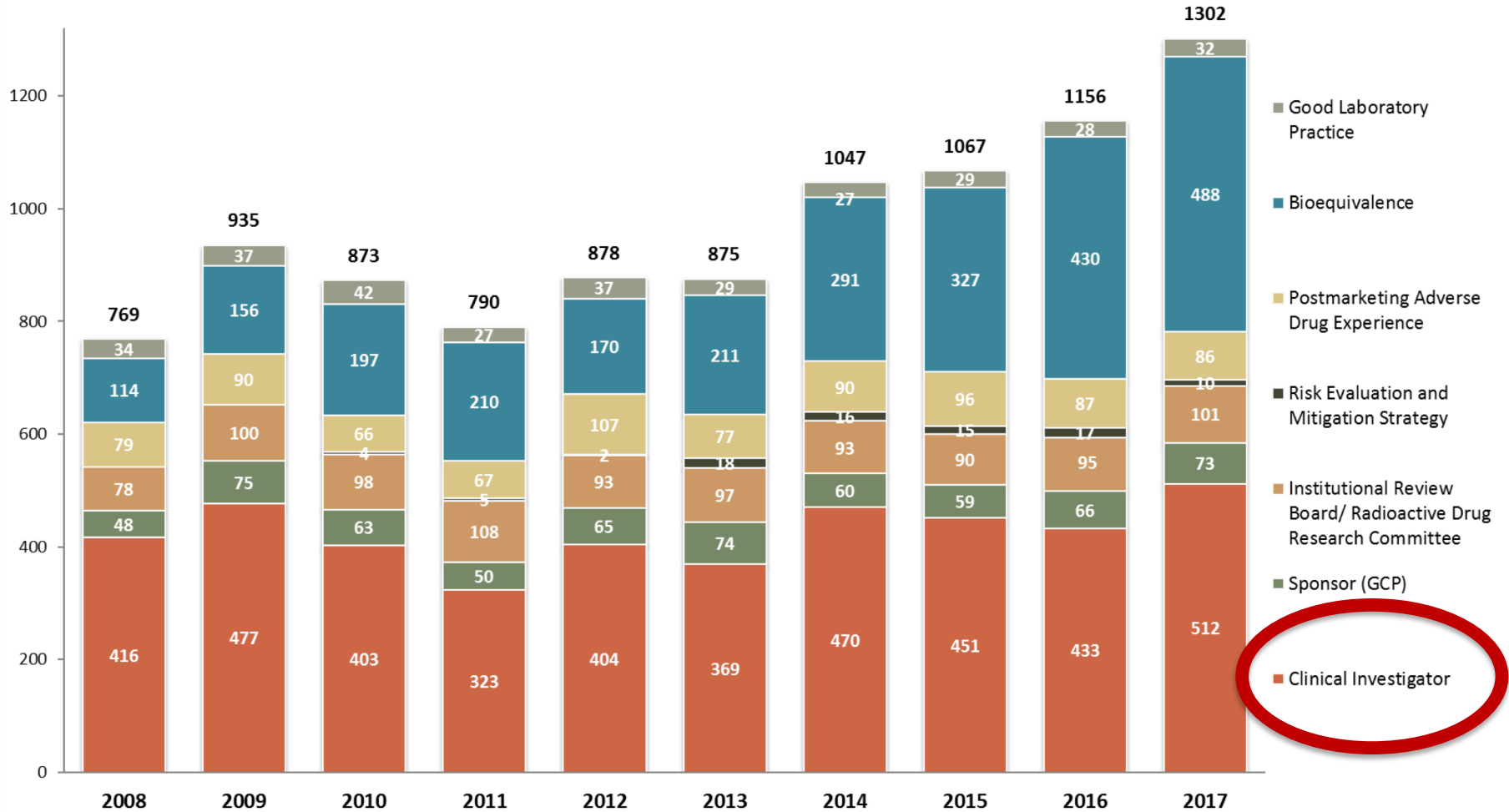
- Office of Scientific Investigations (OSI)
 - Clinical Investigator (CI)
 - Institutional Review Board (IRB)
 - Post Marketing Adverse Event Drug Experience (PADE)
 - Radioactive Drug Research Committee (RDRC)
 - Risk Evaluation and Mitigation Strategy (REMS)
 - Sponsor/CRO/Sponsor-Investigator
 - Post marketing Adverse Drug Experience
 - Risk Evaluation and Mitigation Strategy
- Office of Study Integrity and Surveillance (OSIS)
 - Bioequivalence (BE)
 - Good Laboratory Practice

Challenges

- Finite resources limit the number of inspections that can be conducted
- Identification of sites from which subject protection and/or data integrity risks are greatest to inform decisions on how to best expend limited inspectional resources

Application-Inspections Overseen by OSI/OSIS*

(CDER, FY2008 - FY2017)

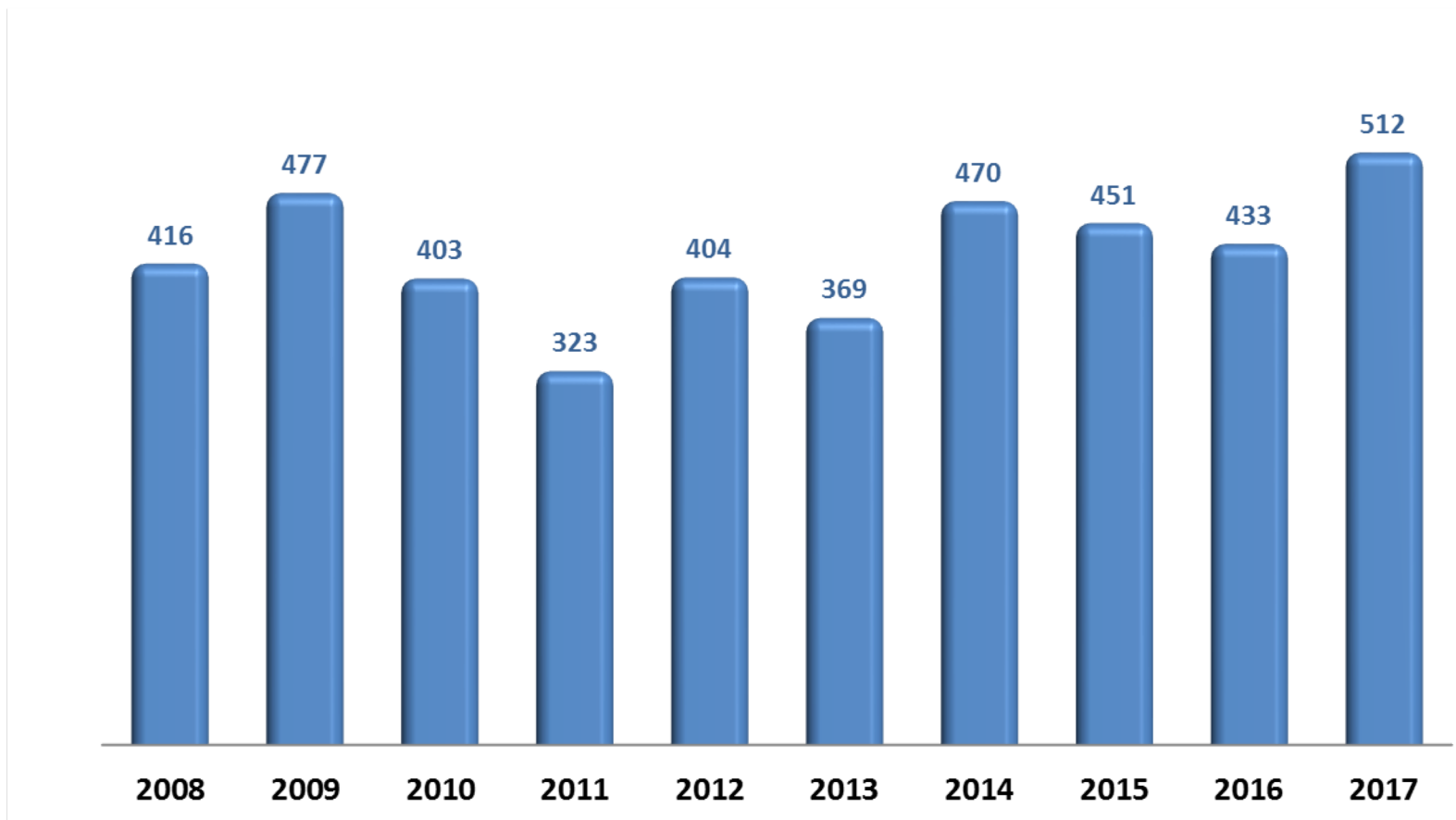


*Based on inspection start date – [Complis database as of December 29, 2017]

- Sponsor (GCP) includes Sponsor/CRO/Sponsor-Investigator
- BEQ Application-Inspections accomplished with 289 FY17 Site Visits
- Good Laboratory Practice and Bioequivalence inspection programs operated by OSIS as of January 2015

Clinical Investigator Inspections*

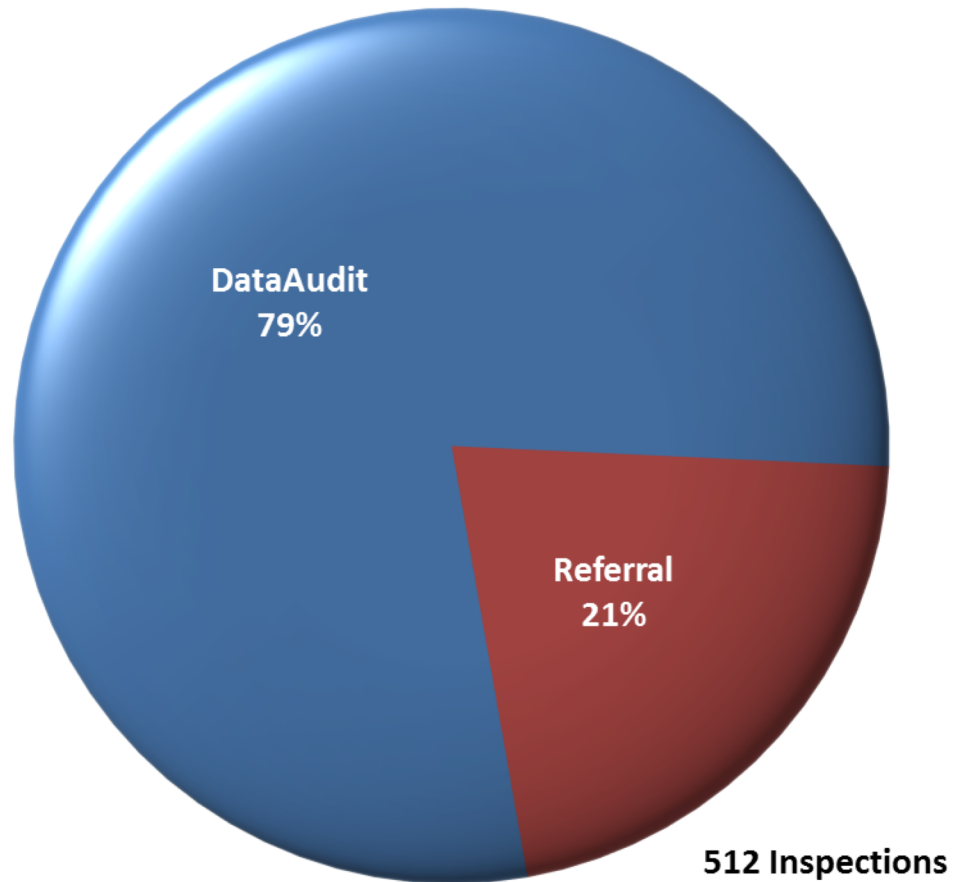
(CDER, FY2008-FY2017)



*Based on inspection start date – [Complis database as of December 29, 2017]

Clinical Investigator: Data Audit versus Referral*

(CDER, FY2017)



* Based on inspection start date – [Complis database as of December 29, 2017]

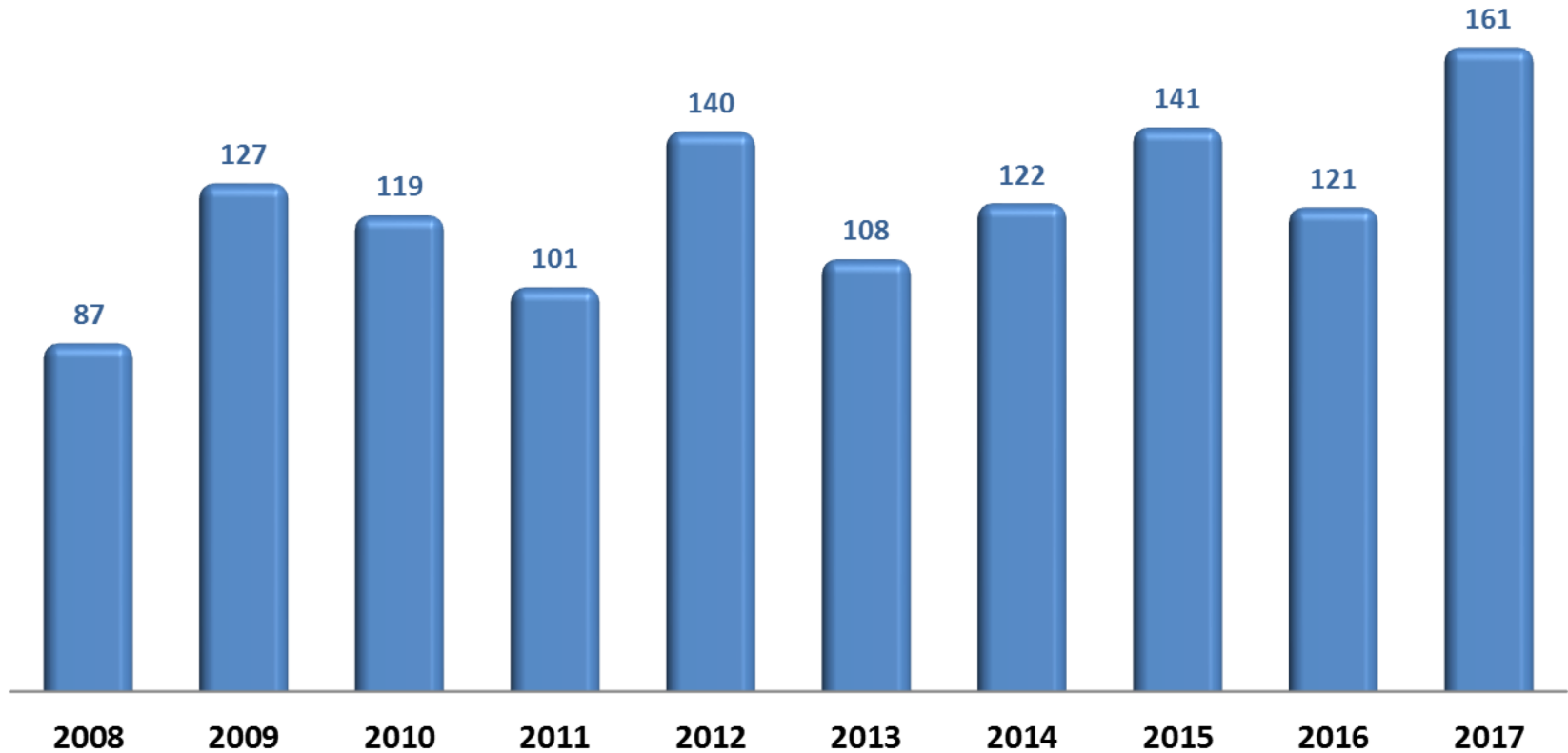
• Referrals include Complaints, Required Reports, IRB/Sponsor Notifications, and other referrals-internal and external for All OSI Branches

Additional Challenges

- Increasing numbers of
 - Sites per clinical trial
 - Foreign trial sites

International Clinical Investigator Inspections*

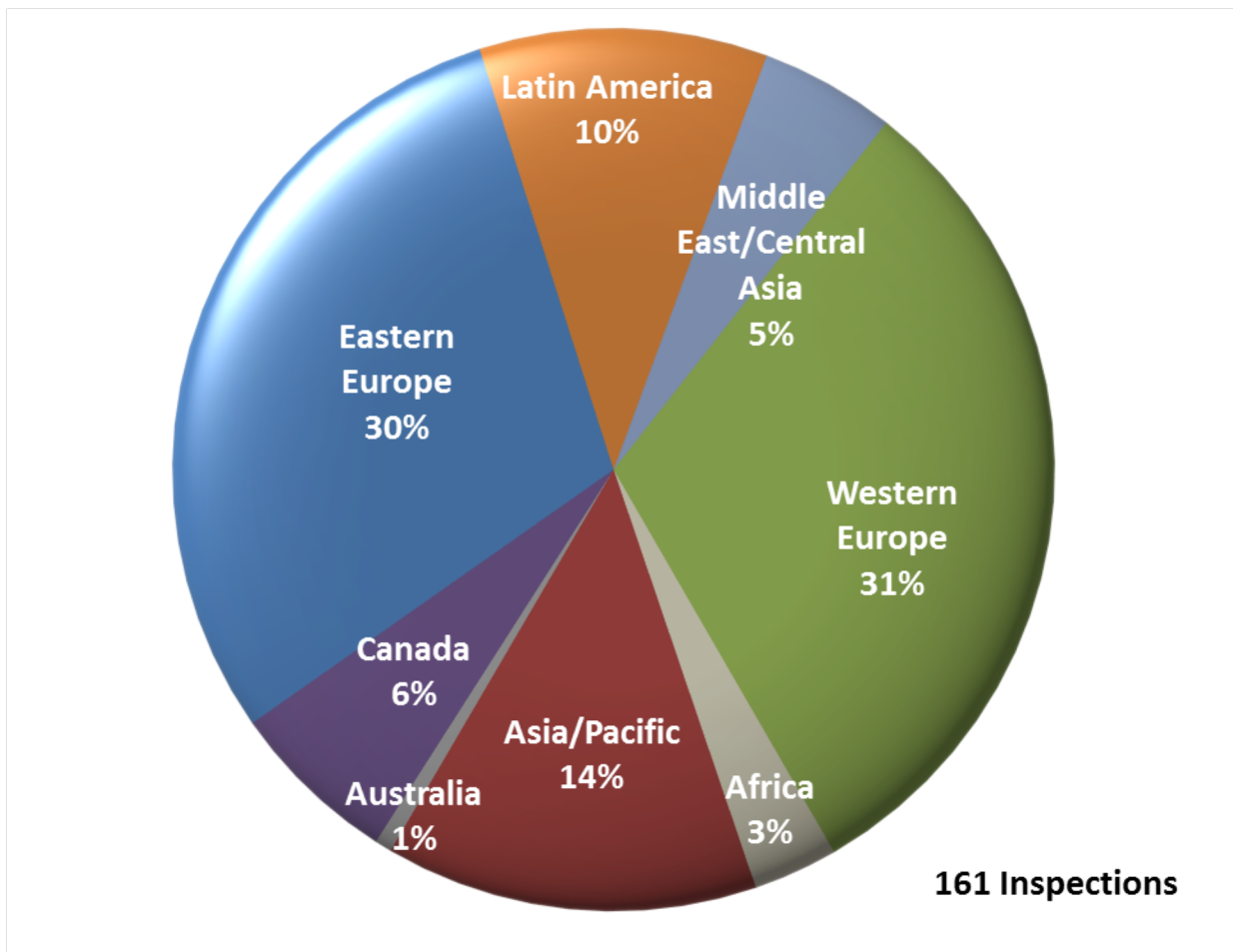
(CDER, FY2008 – FY2017)



*Based on inspection start date – [Complis database as of December 29, 2017]

International Clinical Investigator Inspections by Location*

(CDER, FY2017)

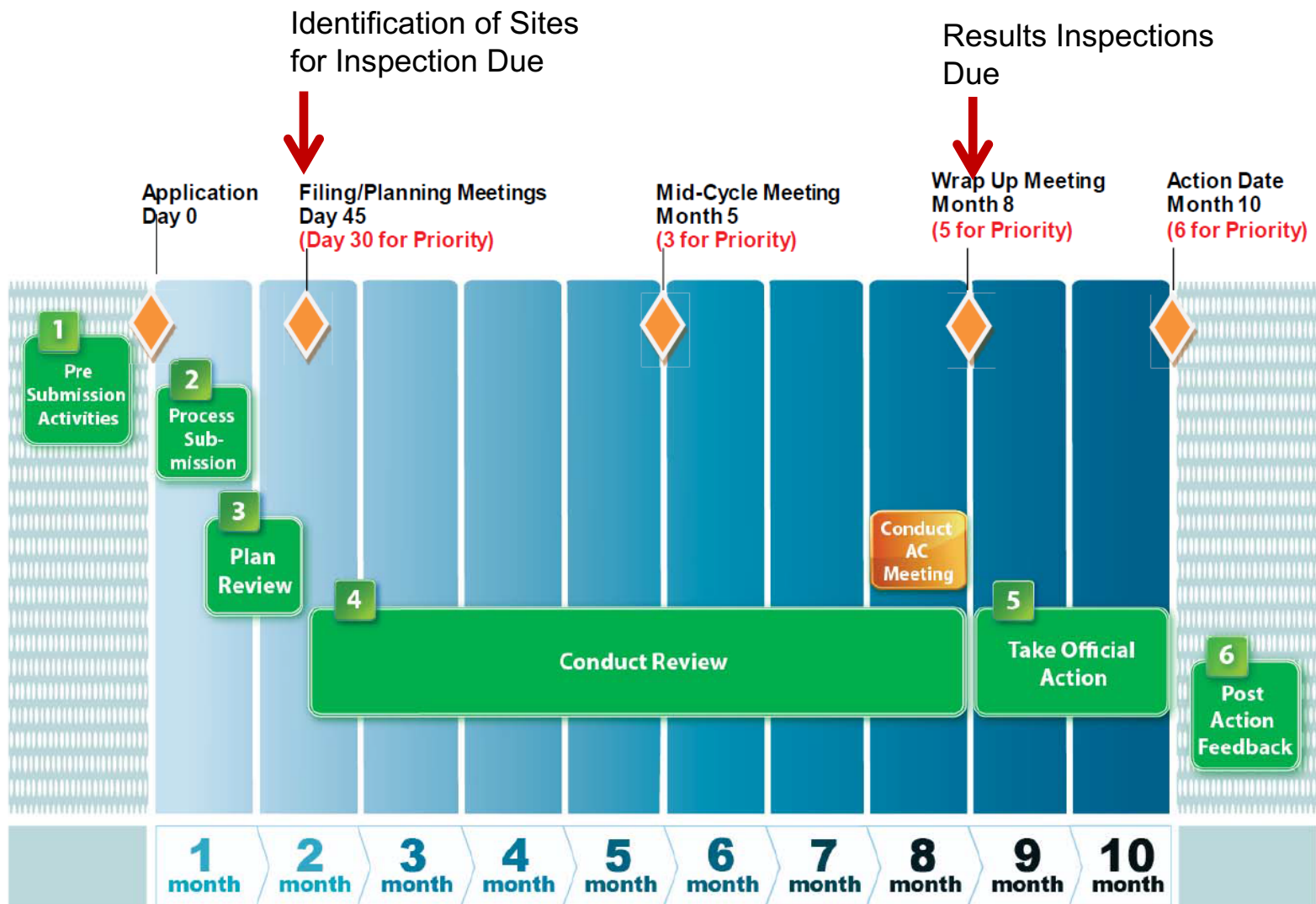


*Based on inspection start date – [Complis database as of December 29, 2017]

Additional Challenges

- Volume data and inadequate data standards increase analysis time
- PDUFA/BSUFA timelines require high level of efficiency

CDER 21st Century Review Process



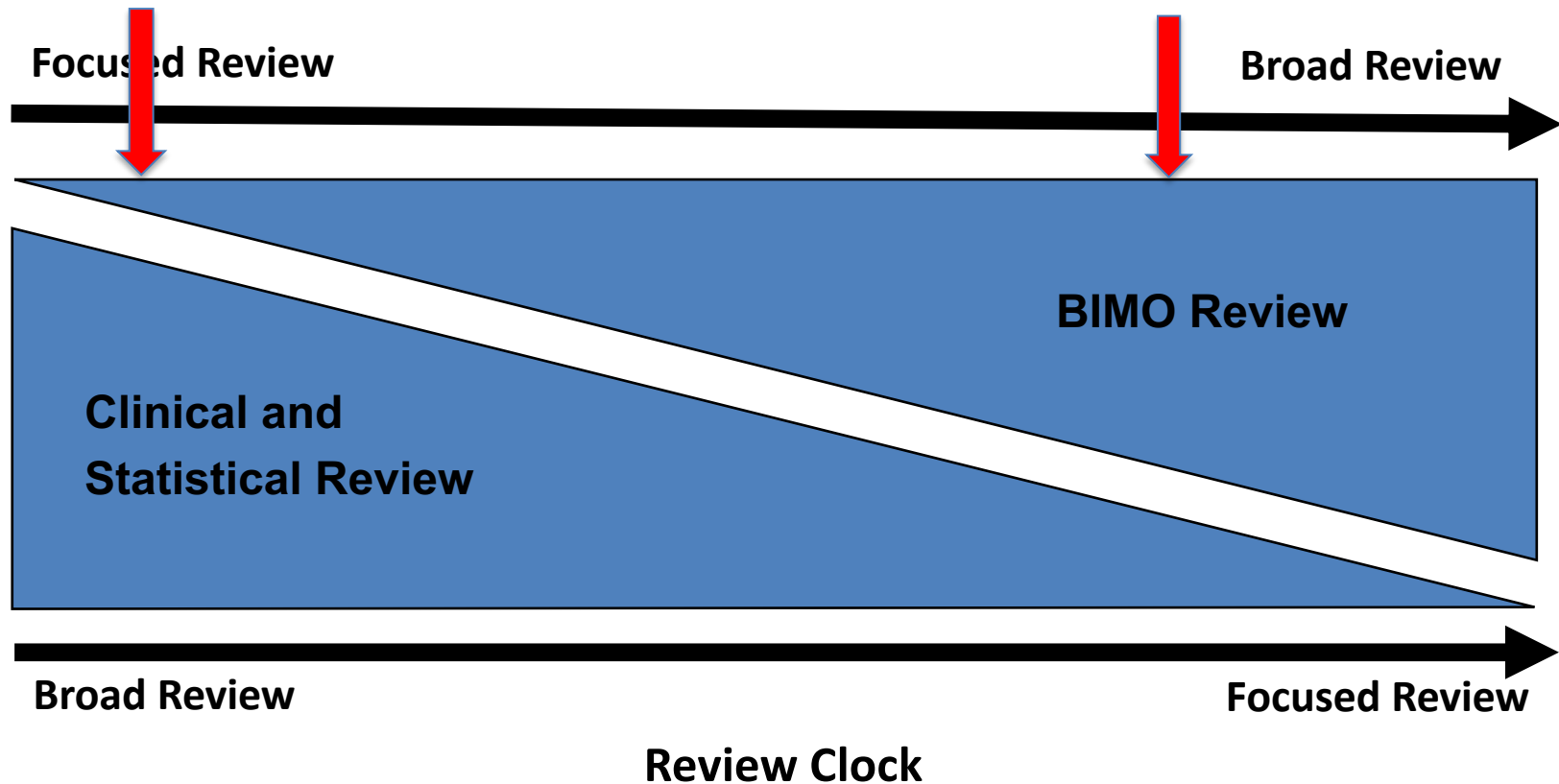
Note: The timeline for review of NMEs/BLAs under PDUFA V's "Program" Review extends the *Conduct Review* Phase by two months.

Need for Early and Well Informed Identification of Clinical Investigator Sites for Inspection



Sites selected for inspection

Inspections completed
Data reliable?
Subjects protected?



CISST Development

- Goals
 - Enable deployment of limited resources towards sites that pose the potentially greatest risk to public health
 - Facilitate early site selection/issuance of inspection assignments
 - Develop a more consistent, science-based approach to selection of clinical sites for inspection

CISST Development

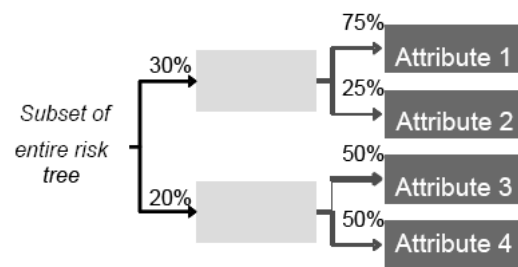
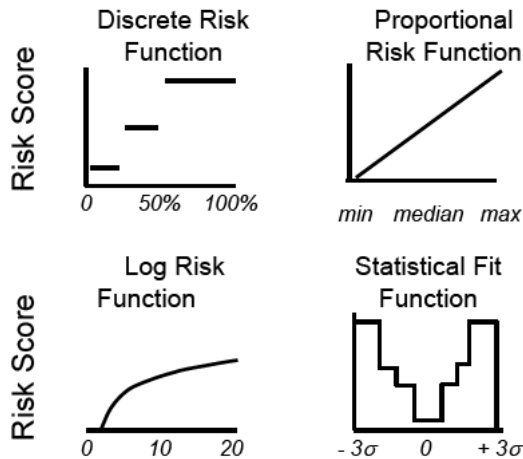
- Collaborative effort across
 - Office of Biostatistics
 - Office of Compliance
 - Office of New Drugs
 - Office of Planning and Informatics
- Attributes
 - Identified through series expert interviews across offices
 - Attributes then ranked as to importance in second round interviews
 - 21 attributes used in tool (application, study, site level)
 - Data included
 - Summary site level data provided by applicant (clinsite.xpt)
 - FDA internal sources

“Clinsite” Dataset

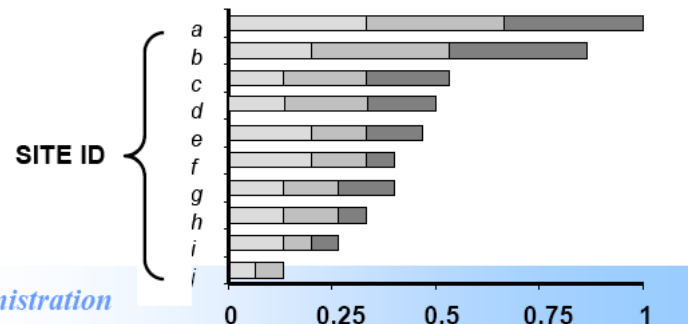
Cross Application/Study Information	IND #, NDA #, BLA #, Supplement #, Number of Sponsors, Study Number (Identifier), Study Title, Domain, Study Arms, Endpoint, Endpoint Type
CI Contact Information	Last name, First name, Middle initial, Street, City, State, Country, Postal Code, Phone, Fax, E-mail
Site Specific Data	Site ID, Under IND?, Enroll #, Screen #, Discontinued #, Non-serious adverse event #, Serious adverse event #, Death #, Protocol violation #, Max financial disclosure (single investigator), Max financial disclosure (site total), Treatment efficacy, Standard deviation treatment efficacy, Site efficacy, Standard deviation site efficacy

Inputted Data Processed via Decision Tree Algorithm

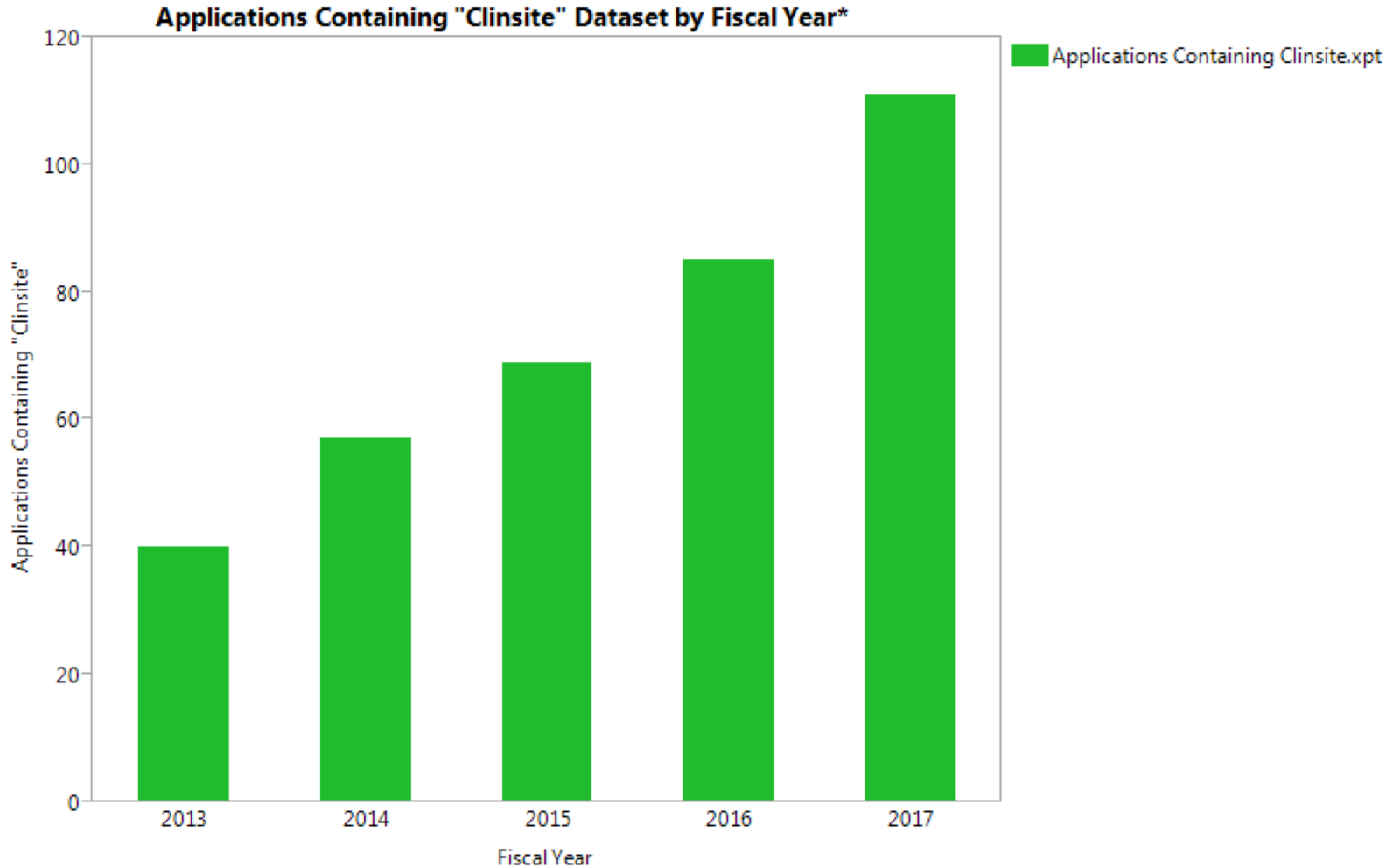
- 1 Attribute Raw Values
- 2 Risk Functions applied to Attribute Values
- 3 Hierarchical Weighting Schema applied



4 Final Risk Score for each site

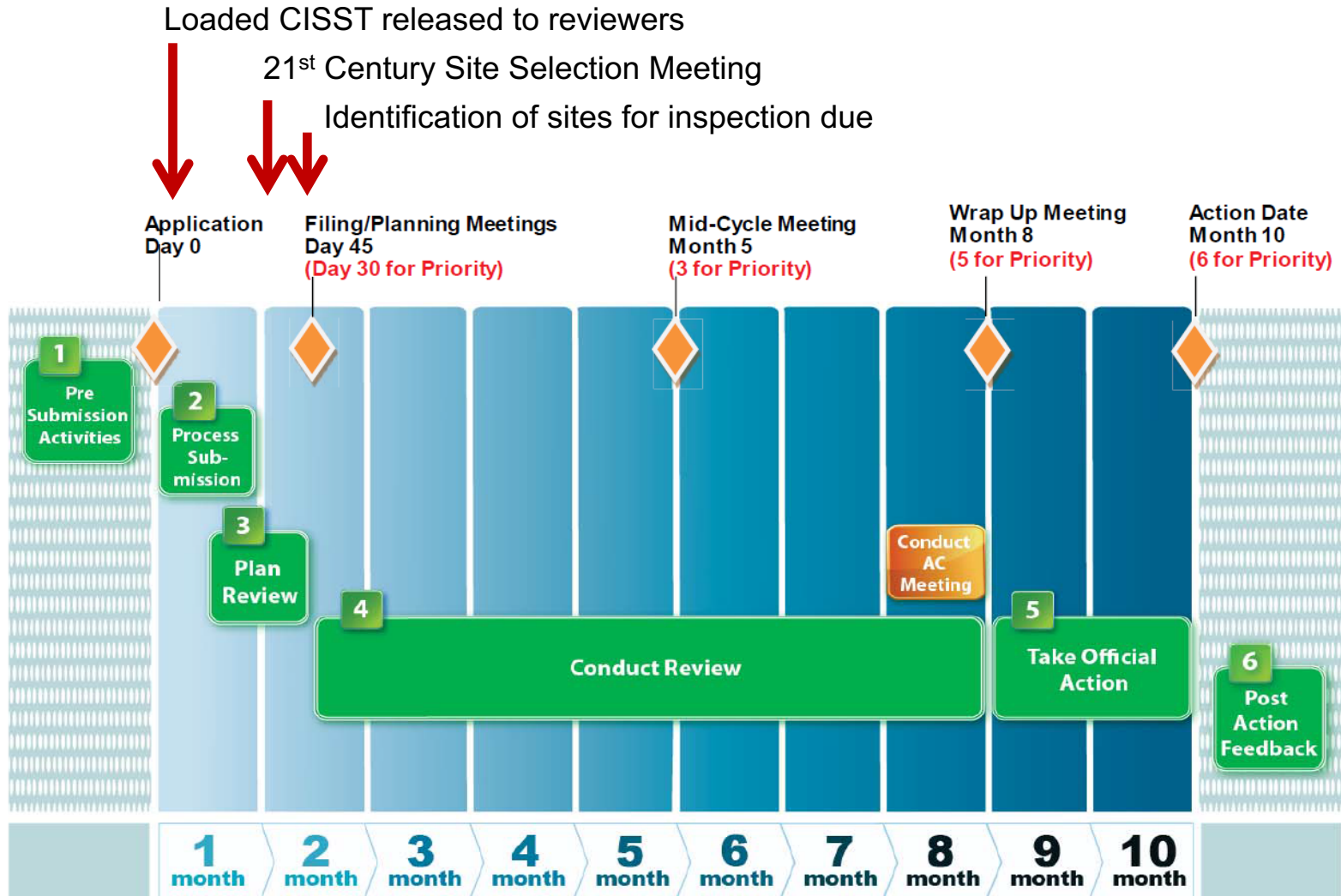


Submissions of Clinsite Dataset



*A single "clinsite" dataset may contain data supporting more than one original application or supplement, reporting in this figure counts such instances as one event.

CDER 21st Century Review Process



Note: The timeline for review of NMEs/BLAs under PDUFA V's "Program" Review extends the *Conduct Review* Phase by two months.

CISST – High Level Site Ranking View

FDA Site Selection Tool v1.2 Study: Endpoint:

Application Risk: 5.0 Study Risk: 0.0

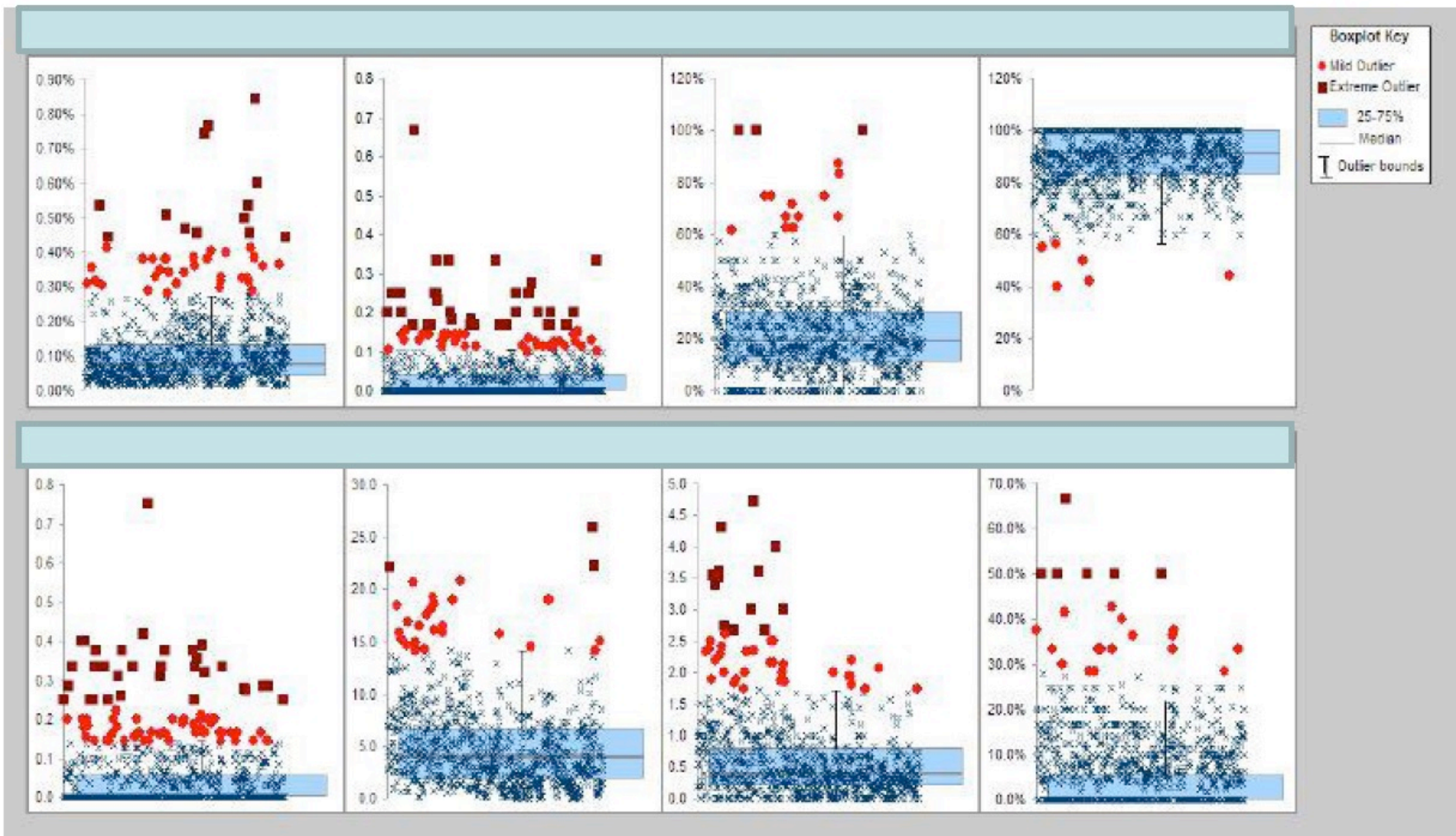
MEMO	SITEID	FRSTNAME	LASTNAME	CITY	STATE	COUNTRY	RANK	TOTAL RISK	Related Rank
No	Site ID goes here	The investigator name (First and Last Name goes here). The City, State and country for the address where the clinical trail was performed goes here				1	29.2	24.2	
No						2	27.2	22.2	
No						3	24.8	19.8	
No						4	22.0	17.0	
No						5	21.5	16.5	
No						6	19.3	14.3	
No						7	17.9	12.9	
No						8	15.8	10.8	
No						9	15.4	10.4	
No						10	15.1	10.1	
No						11	14.9	9.9	
No						12	14.4	9.4	
No						13	14.4	9.4	
No						14	14.3	9.3	
No						15	14.0	9.0	
No						16	13.8	8.8	
No						17	13.6	8.6	
No						18	13.2	8.2	
No						19	13.2	8.2	
No						20	13.0	8.0	

Key Attributes goes here

CISST – Regional and Country Views

REGION	COUNTRY	Key application, study, and site level attributes									
Canada	CA	7	14	25.0%	0.29	0.29	8.50	0.00	14.3%	7.1%	1.64
Canada Total		7	14	25.0%	0.29	0.29	8.50	0.00	14.3%	7.1%	1.64
United States	US	4	17	35.4%	0.49	0.49	10.53	0.65	23.5%	0.0%	1.06
United States Total		4	17	35.4%	0.49	0.49	10.53	0.65	23.5%	0.0%	1.06
Western Europe	BE	6	17	33.3%	0.13	0.13	11.35	0.41	5.9%	0.0%	2.06
	FR	8	34	32.7%	0.54	0.54	7.88	0.24	14.7%	0.0%	0.41
	GM	9	60	31.7%	1.23	1.23	6.22	0.35	23.3%	16.7%	0.93
	IT	4	9	22.0%	0.00	0.00	4.67	0.33	0.0%	0.0%	0.00
	SW	5	17	32.7%	0.56	0.56	5.59	0.35	23.5%	0.0%	3.29
	UK	9	32	34.0%	0.58	0.58	7.25	0.22	15.6%	0.0%	1.06
	AU	2	8	80.0%	0.67	0.67	4.38	0.13	12.5%	0.0%	2.75
	NO	1	6	37.5%	0.50	0.50	5.33	0.17	16.7%	0.0%	2.00
	SZ	1	8	29.6%	1.88	1.88	2.88	0.38	37.5%	0.0%	2.25
	GI	3	8	22.2%	0.33	0.33	6.63	0.00	12.5%	0.0%	0.25
Western Europe Total		48	199	32.1%	0.60	0.60	6.76	0.29	17.6%	5.0%	1.25

CISST – Outlier Displays



CISST – Site Specific Displays

FDA Site Selection Tool v1.2 Study: **Study Name** Endpoint: **End Point** Arm 1: **Arm Name** Arm 2: **Placebo**

SITEID: **600** View: Converted Raw

Site Summary

MEMO	RANK	FRSTNAME	LASTNAME	COUNTRY
No	1	Name	UK	
SITE RISK 24.2				
Highlighted Attributes				

Site Risk Overview

ATTRIBUTE	ARM 1	ARM 2	ALL ARMS	VALUES
14 Key Application, Trail, and Site Level Attributes				49
				344.00
				204.00
				15.9
				1.1
				53%
				84%
				0.7
				98%
				0
				0
				3
				0
				-

Study Summary

# SITES	# ENROLLED
147	1192

TOTAL

0	0
1	0
2	4
3	2
	141

Arm 1 Summary

	Max	Study Rate	Min	Site	Attribute 1	Attribute 2	Attribute 3	Attribute 4	Attribute 5	Attribute 6	Attribute 7	Attribute 8	Attribute 9	Attribute 10
Max	34	472.00	358.00	36.7	3.0	100%	100%	19.0	14722.00	6528.00				
Study Rate	6	350.06	72.69	12.3	0.7	42%	71%	3.9	2082.09	432.33				
Min	1	28.00	-355.00	0.0	0.0	0%	0%	0.0	28.00	-4056.00				
Site	32	446.00	204.00	16.0	0.7	50%	81%	0.8	14272.00	6528.00				

Arm 2 Summary

	Max	Study Rate	Min	Site	Attribute 1	Attribute 2	Attribute 3	Attribute 4	Attribute 5	Attribute 6	Attribute 7	Attribute 8	Attribute 9	Attribute 10
Max	17	407.00	0.00	15.7	1.8	100%	100%	23.0	4114.00	4114.00				
Study Rate	3	277.30	0.00	11.0	0.8	55%	85%	3.4	883.34	883.34				
Min	1	25.00	0.00	0.0	0.0	0%	0%	0.0	25.00	25.00				
Site	17	242.00	0.00	15.7	1.8	59%	88%	0.5	4114.00	4114.00				

Overall Summary

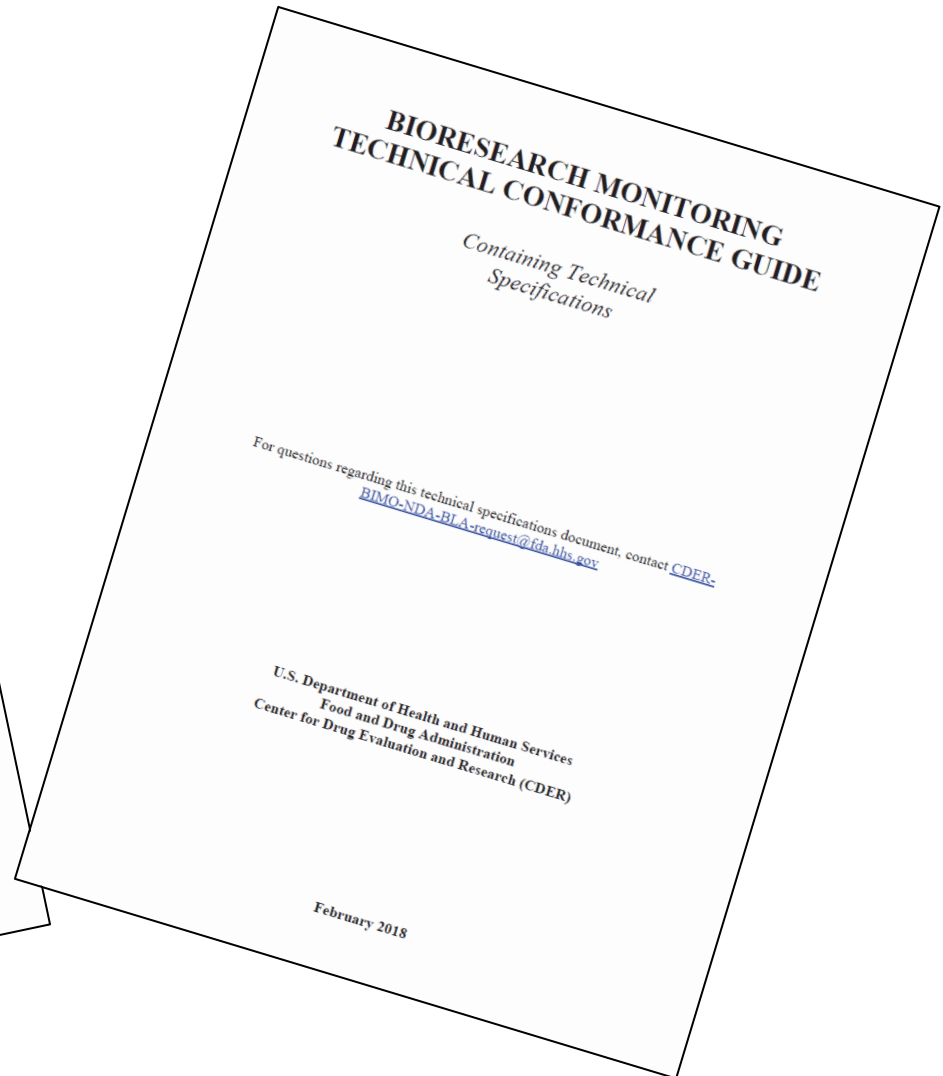
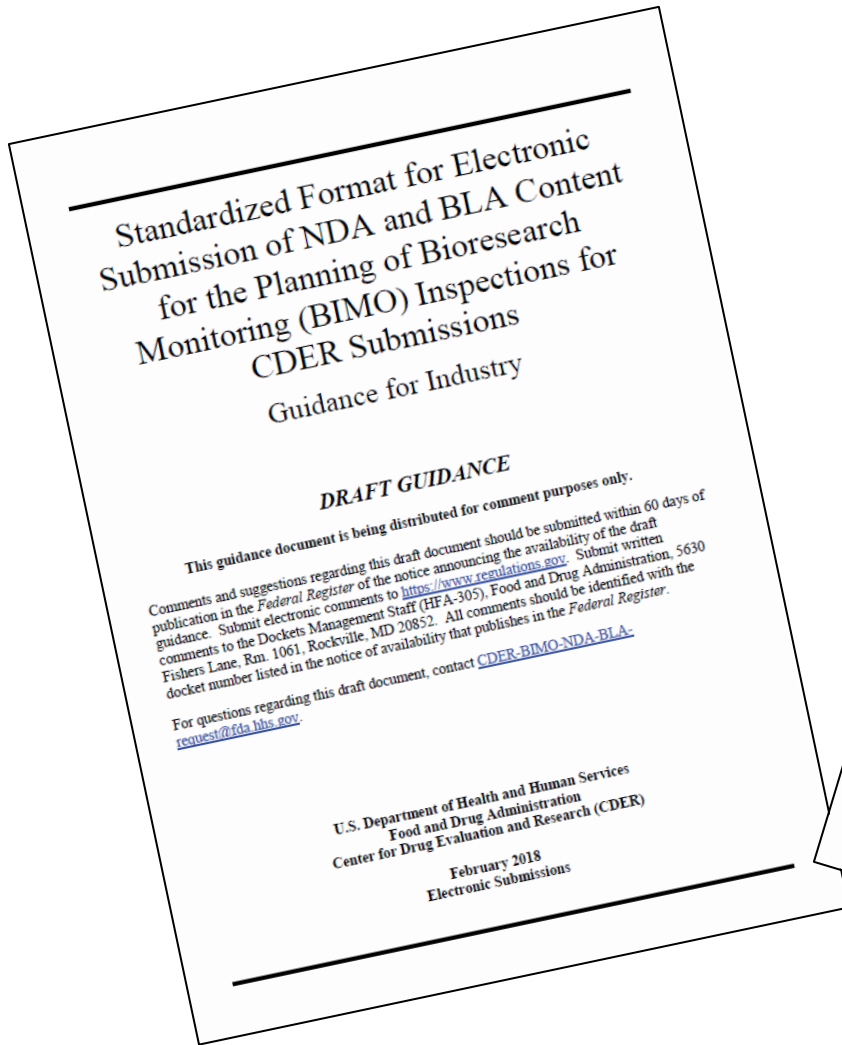
	Max	Study Rate	Min	Site	Attribute 1	Attribute 2	Attribute 3	Attribute 4	Attribute 5	Attribute 6	Attribute 7	Attribute 8	Attribute 9	Attribute 10
Max	6.7	28	120%	49	470.00	358.00	36.5	4.5	100%	100%	23.0	18594.69	10642.00	
Study Rate	1.0	2	100%	8	313.63	69.03	11.7	0.7	48%	79%	3.6	2643.09	1139.23	
Min	0.2	0	40%	1	59.00	-355.00	0.0	0.0	0%	0%	0.0	59.00	-1621.00	
Site		0	98%	49	344.00	204.00	15.9	1.1	53%	84%	0.7	18386.00	10642.00	

CISST Provides

- Risk ranking of sites provides a framework for site selection
- Provides standard data exploration methodology
- Assembles many site characteristics in one tool and gives the user the ability to choose sites based on site views of:
 - Data Irregularities
 - Outliers analysis with filters
 - Inspection history and Investigator experience
 - Clinical investigator cross-study participation
 - Regional and country-specific summaries
 - Comparison of variables across treatment arms
 - Raw data versus converted data views
- Easy navigation and functionalities
- Improves data analysis time
- Automated documentation and form generation



Guidance on Providing clinsite.xpt

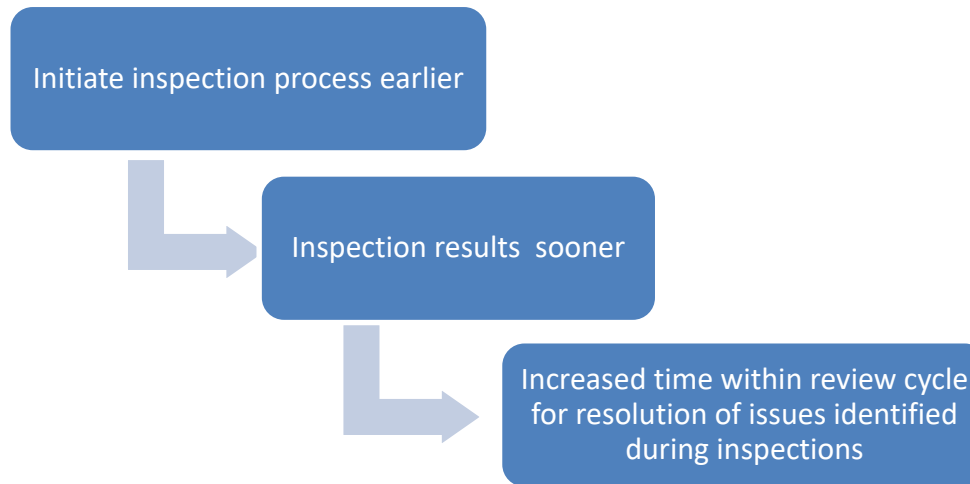


<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf>

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>

Benefits Realized with CDER CISST

- Clinical sites identified earlier in review clock



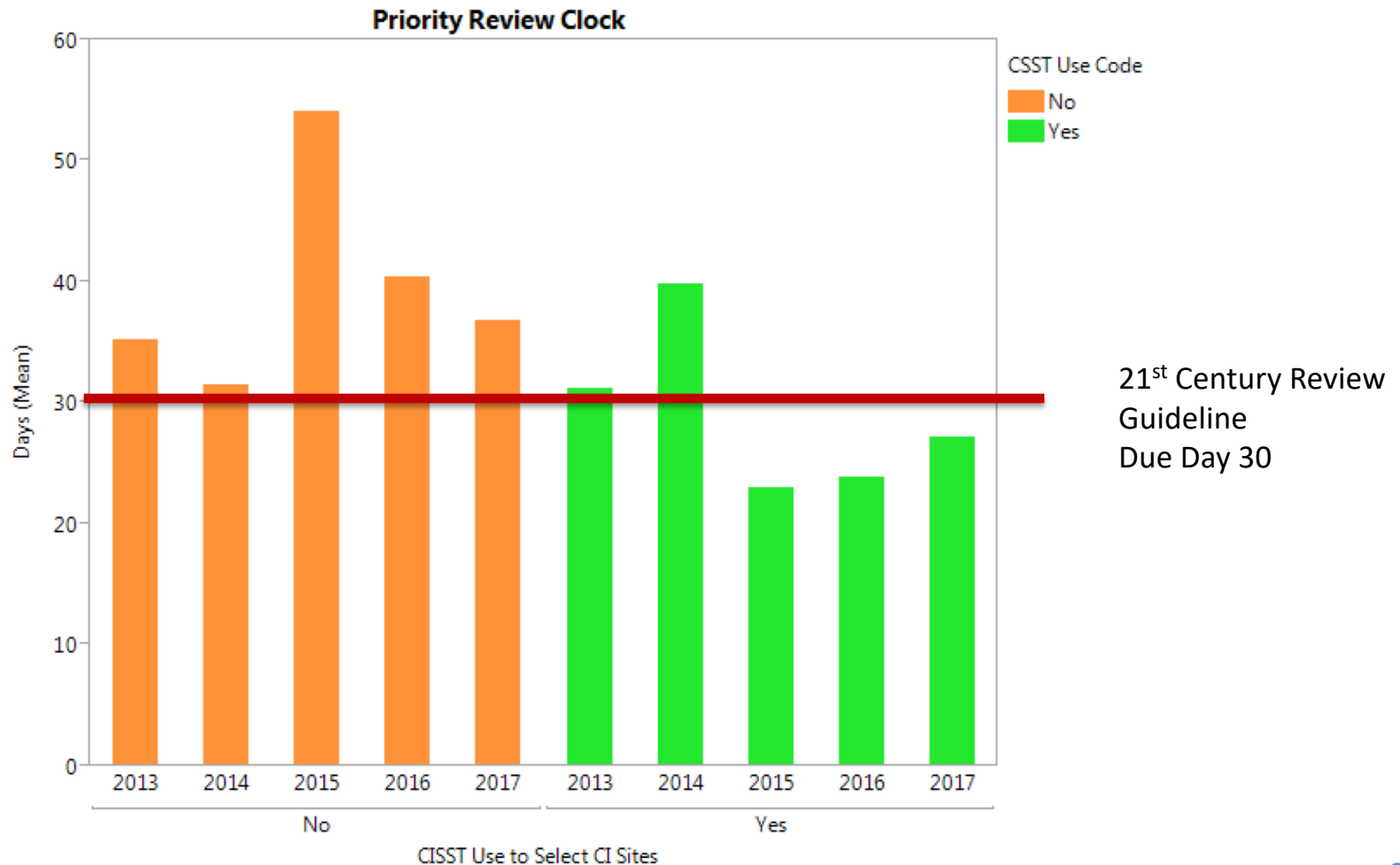
- Enhanced identification of clinical sites with GCP non-compliance
- Archived clinsite data available for data mining



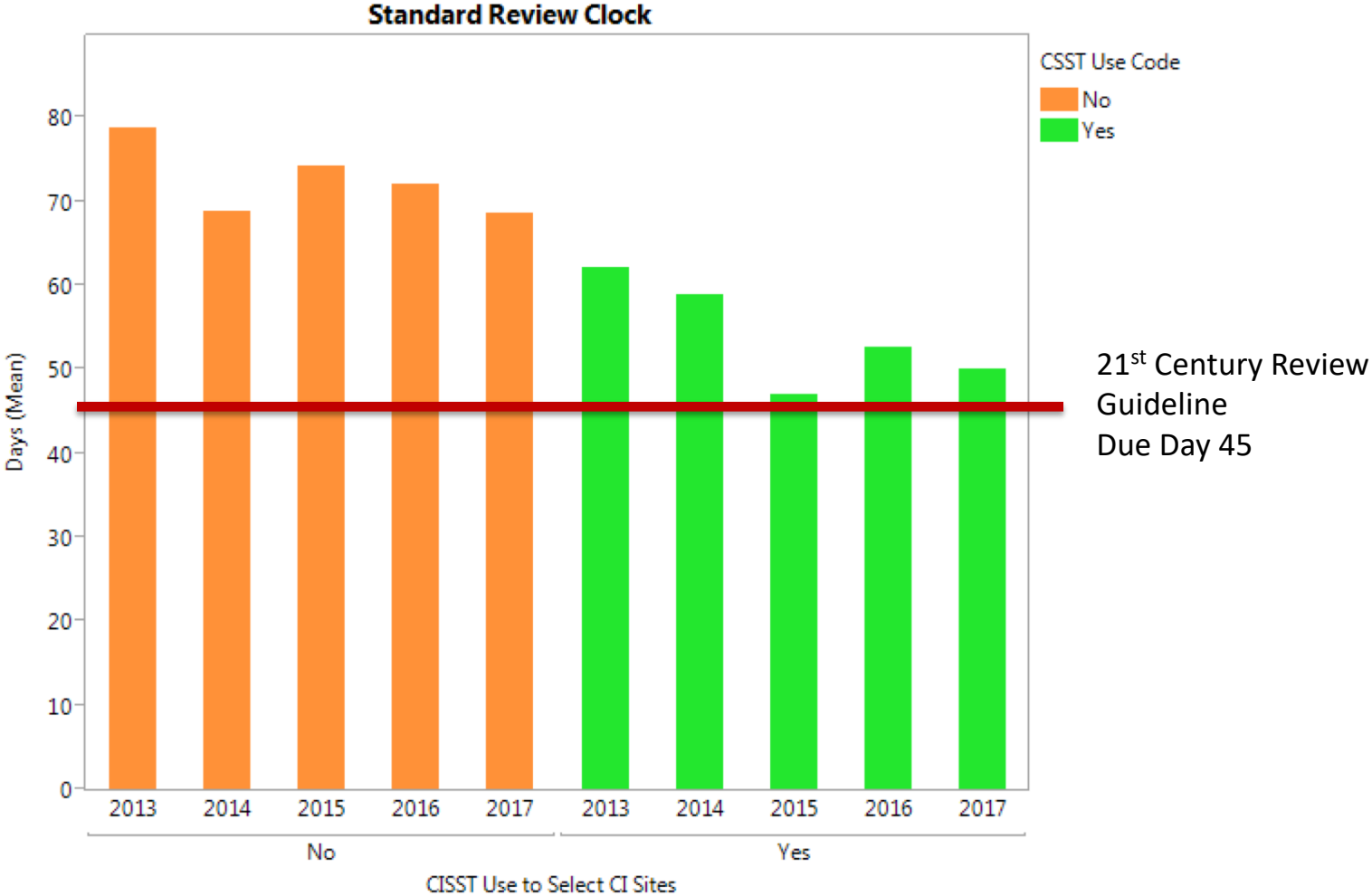
Time to Determine Inspection Sites (FY2013 – FY2017)

- Grouped by fiscal year application submitted
- Original submission date to receipt DARRTS notification
- Excluded
 - Review of CISST resulted in determination no inspections needed
 - Late submission of clinsite.xpt by applicant

Mean Days to Complete Selection of Clinical Sites for Inspection



Mean Days to Complete Selection of Clinical Sites for Inspection

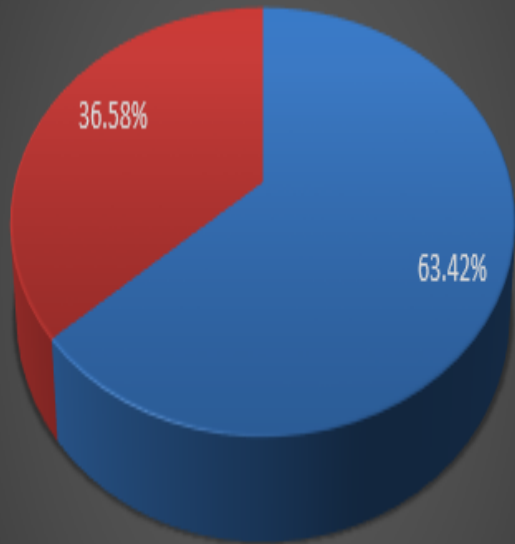


Final Classification Inspections (FY2013 – FY2016)

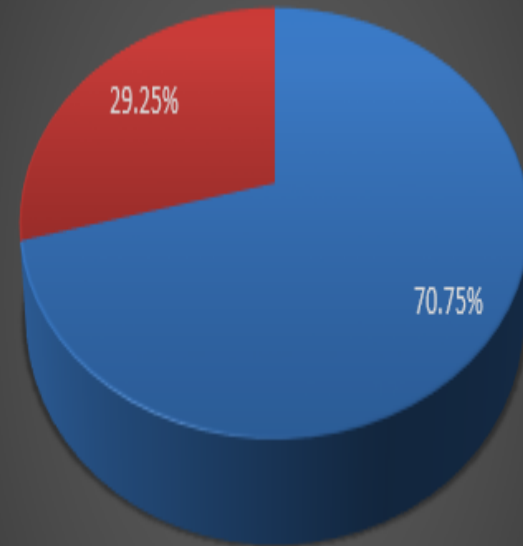
- Based on date application submitted
- Final Classifications
 - No Action Indicated (NAI)
 - Voluntary Action Indicated (VAI)
 - Official Action Indicated (OAI)
- Analysis looked at absence (NAI) versus presence (VAI + OAI) of regulatory violations

Inspection Outcomes By Method of Site Selection (CISST Use Versus Non-Use)

FY2013-FY2016 PERCENTAGE TOTAL OF OAI OR VAI INSPECTIONAL OUTCOME



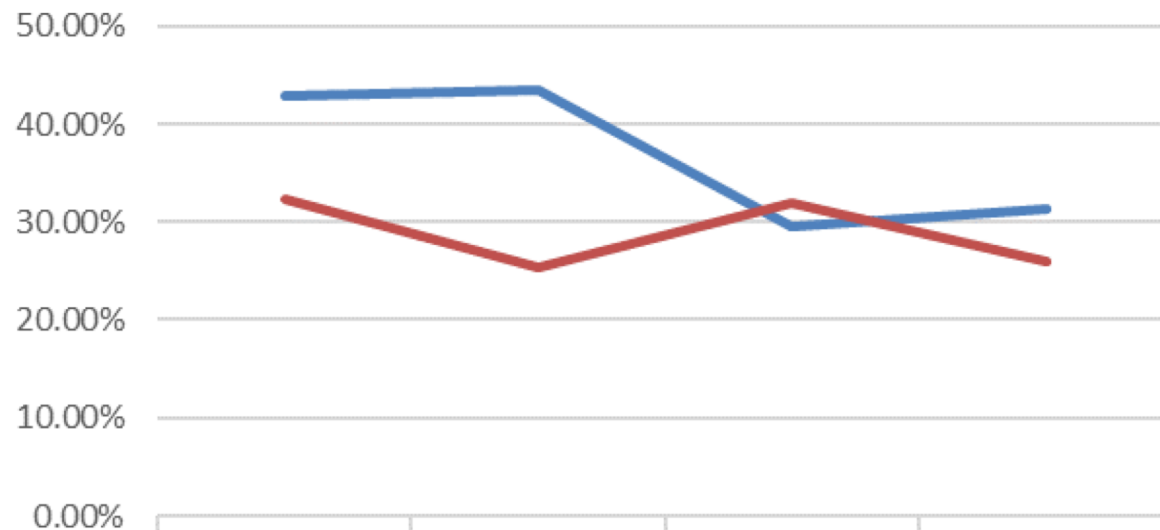
▼ CISST: NAI ▼ CISST: VAI or OAI



▼ No CISST: NAI ▼ No CISST: VAI or OAI

Inspection Outcomes By Method of Site Selection (CISST Use Versus Non-Use)

Percentage Total of OAI or VAI
Inspectional Outcome



	FY2013	FY2014	FY2015	FY2016
CISST: VAI or OAI	42.86%	43.42%	29.52%	31.34%
No CISST: VAI or OAI	32.34%	25.38%	31.97%	25.95%

Data Mining Capabilities (FY2009 – FY2016)

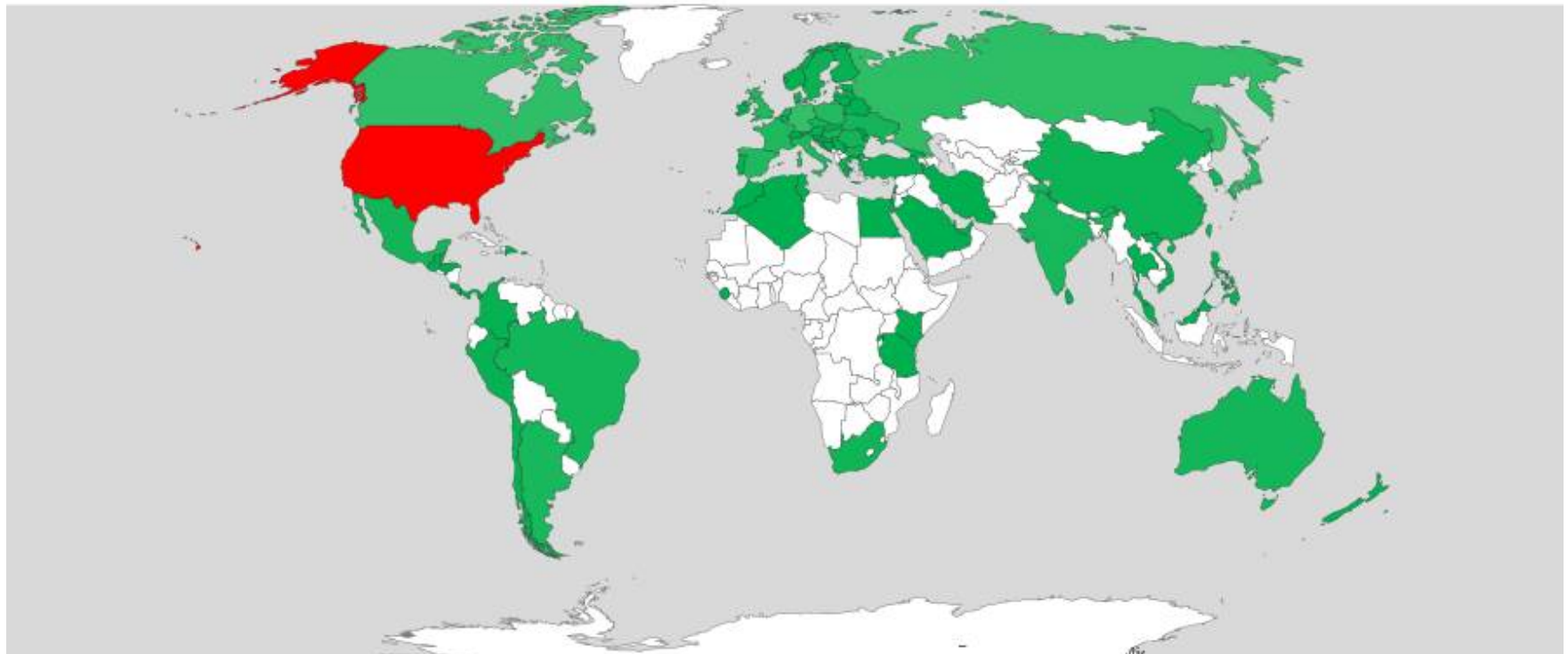
- CISST Database
 - 729 Clinical Studies
 - 69,370 Clinical Investigator Sites
 - 902,203 Enrolled Trial Participants

Geographic Distribution Clinical Investigators (FY2009 – FY2016)



Clinical Trial Sites

Total number of Clinical Trial Sites

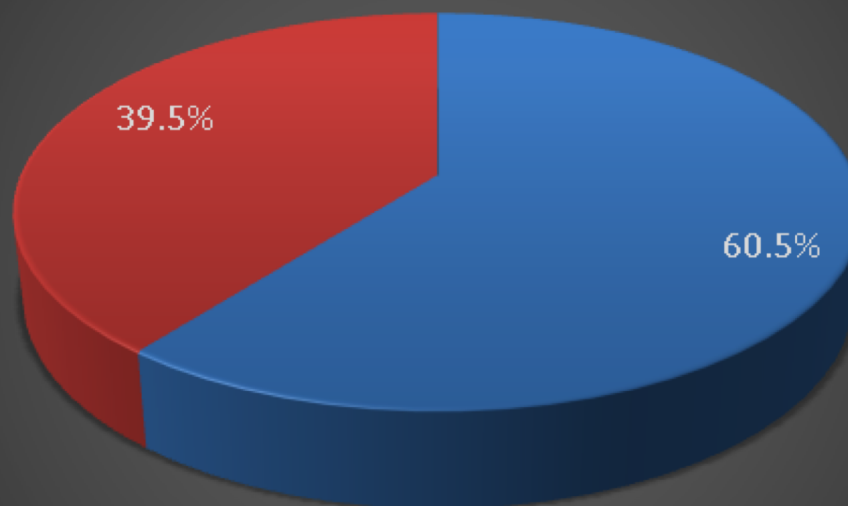


(Source: CISST Database)

Geographic Distribution Clinical Investigators (FY2009 – FY2016)



Foreign Versus Domestic Clinical Trial Sites



Foreign Domestic


(Source: CISST Database)

Geographic Distribution Clinical Investigators (FY2009 – FY2016)

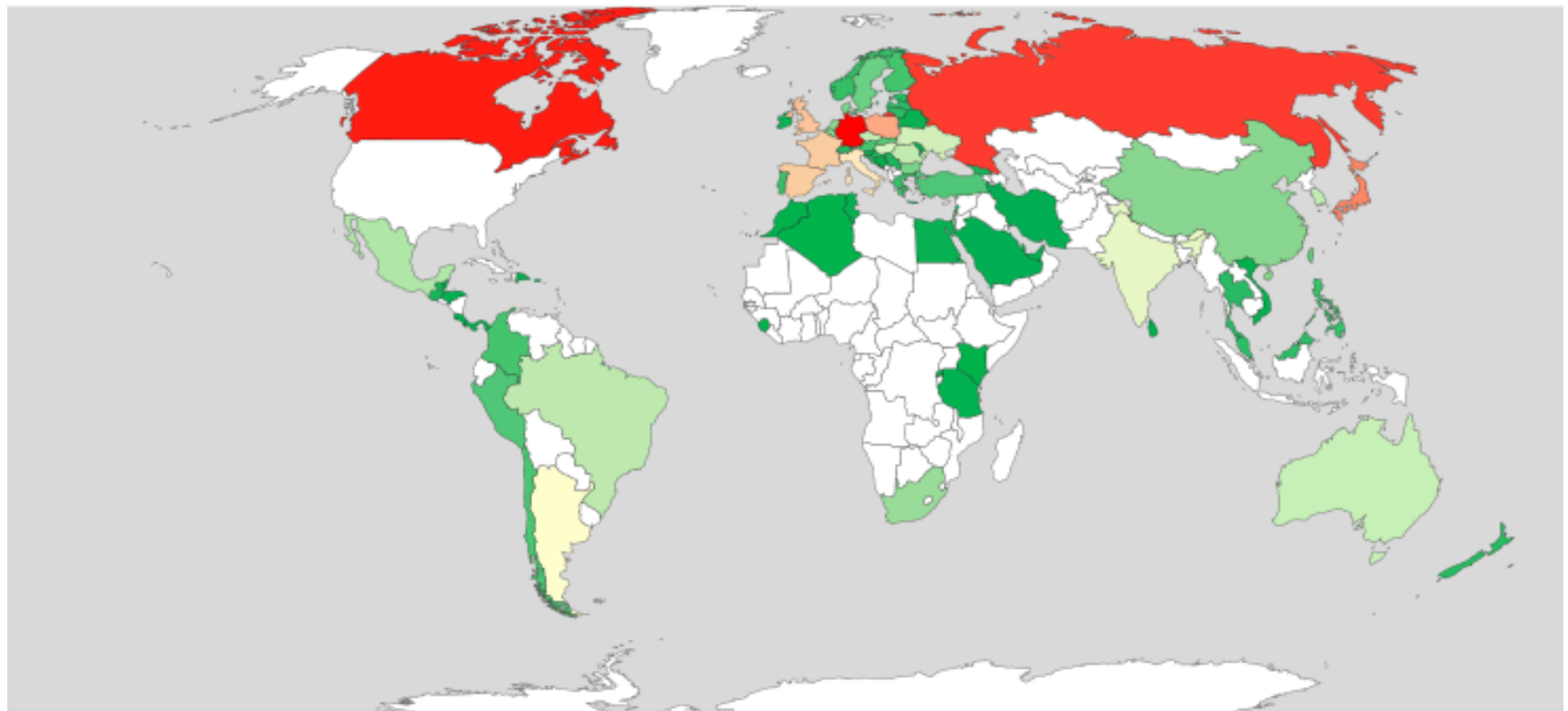


Foreign Clinical Trial Sites

Total number of Clinical Trial Sites

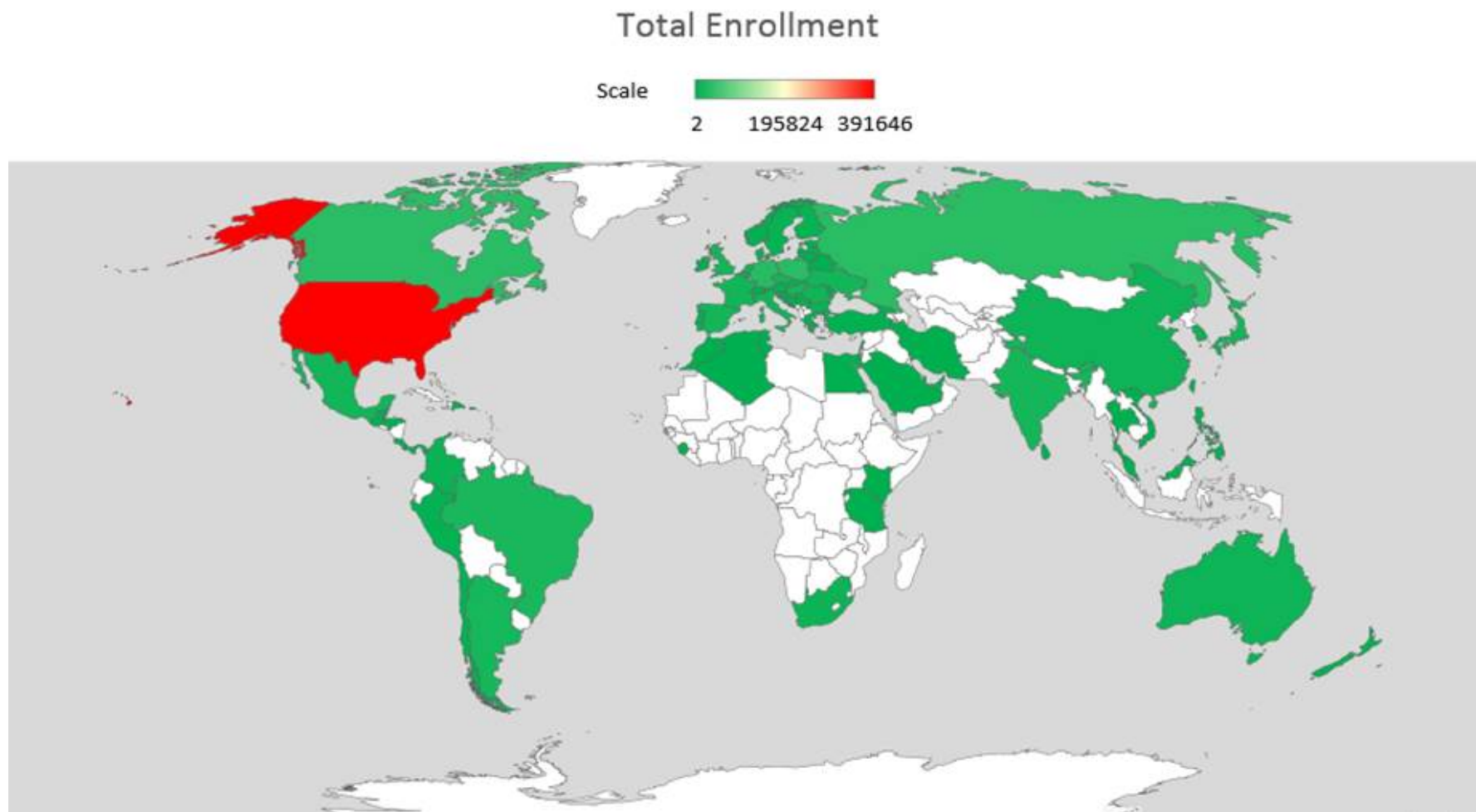


1 1374 2747



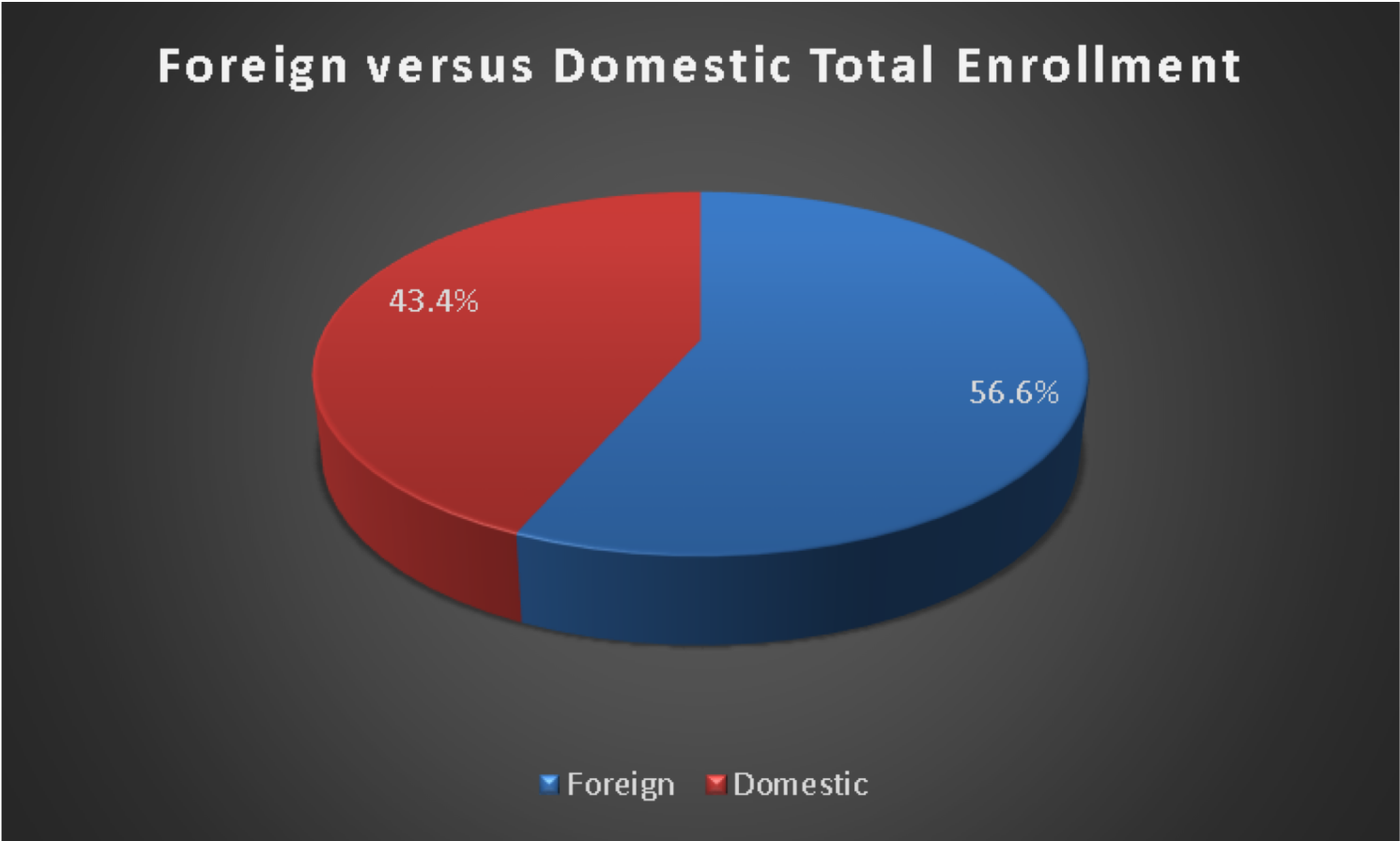
(Source: CISST Database)

Geographic Distribution Subject Enrollment (FY2009 – FY2016)



(Source: CISST Database)

Geographic Distribution Subject Enrollment (FY2009 – FY2016)

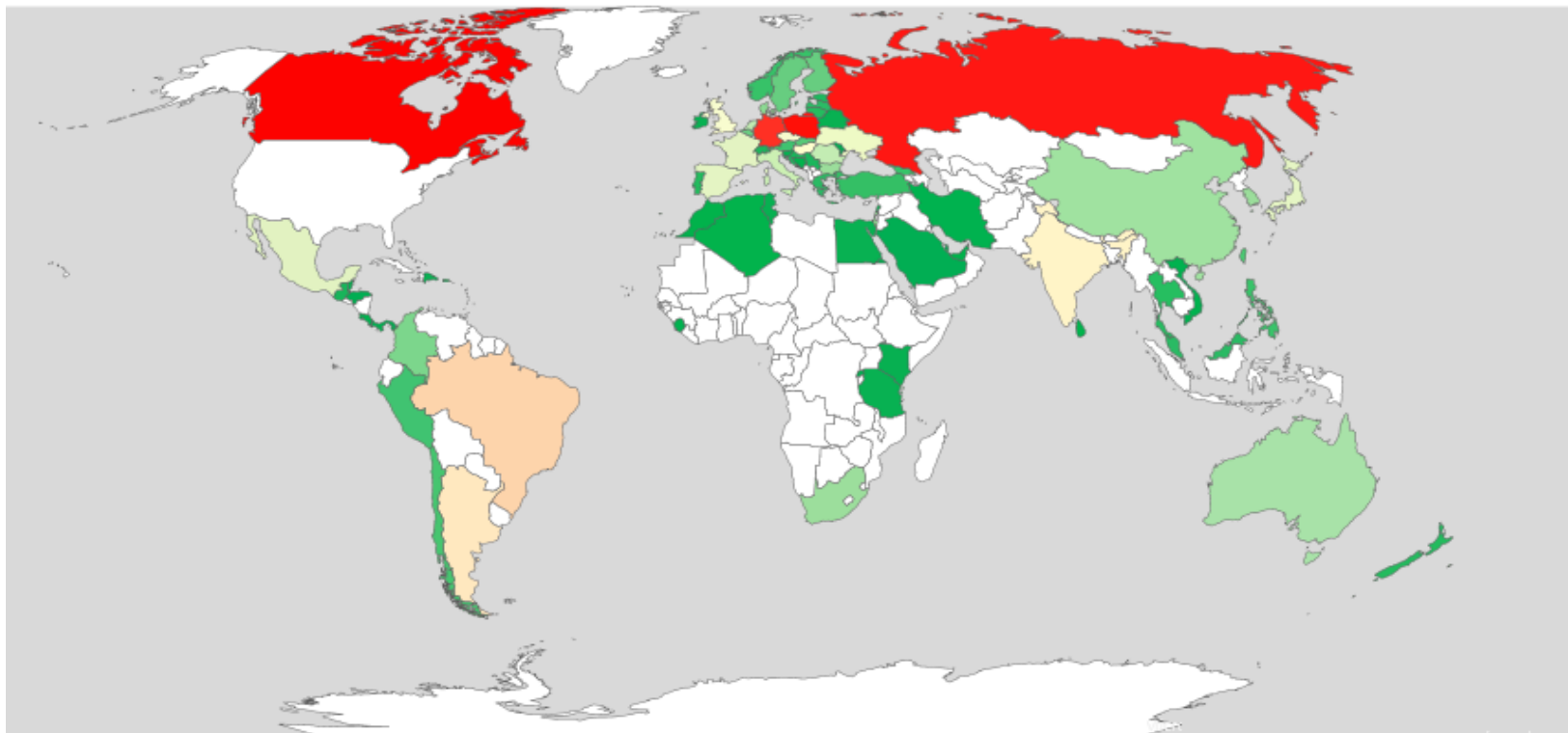
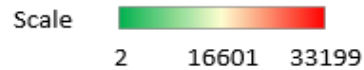


(Source: CISST Database)

Geographic Distribution Subject Enrollment (FY2009 – FY2016)



Foreign Enrollment



(Source: CISST Database)

CDER CISST Moving Forward

- Finalization of Guidance
- Continue work initiated with PhUSE Working Group (White Paper on clinsite variables vs CDISC variables available) to develop CDISC standards to address summary site level variables
- Evaluation of current site attributes and risk algorithm versus inspection outcomes to determine whether modification to algorithm indicated
- Exploring additional methods for identification of site level anomalous data patterns for incorporation into CISST

Clinsite Preparation Pointers

Reporting Multiple Efficacy Endpoints

Incorrect Formatting

SITEID	ARM	SAFEPOP	SCREEN	ENDPOINT	ENDPTYPE	TRTEFFR	TRTEFFR1
10038	PBO	4	20	Endpoint	Binary	0.25	0
10038	TEST Product	11	20	Endpoint	Binary	0.45	0.73
10038	COMPARATOR Product	4	20	Endpoint	Binary	0.25	0

Correct Formatting

SITEID	ARM	SAFEPOP	SCREEN	ENDPOINT	ENDPTYPE	TRTEFFR
10038	PBO	4	20	Endpoint A	Binary	0.25
10038	TEST Product	11	20	Endpoint A	Binary	0.45
10038	COMPARATOR Product	4	20	Endpoint A	Binary	0.25
10038	PBO	4	20	Endpoint B	Binary	0
10038	TEST Product	11	20	Endpoint B	Binary	0.73
10038	COMPARATOR Product	4	20	Endpoint B	Binary	0

Clinsite Preparation Pointers Reporting Screened Subjects

Incorrect Formatting

SITEID	ARM	SAFEPOP	SCREEN
018	Arm A	3	3
018	Arm B	3	3
018	Placebo	4	4
018	Screen Failure	0	1

Correct Formatting

SITEID	ARM	SAFEPOP	SCREEN
018	Arm A	3	11
018	Arm B	3	11
018	Placebo	4	11
018	Screen Failure	0	11

SITEID	ARM	SAFEPOP	SCREEN
018	Arm A	3	11
018	Arm B	3	11
018	Placebo	4	11

Other Clinsite Preparation Pointers

- Data for all studies may be placed in single clinsite.xpt file
- Please name file “clinsite” and place in “BIMO” folder in Module 5.3.5.4

(See draft guidance Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions)

- Define file
 - If HTML format not readily readable, please also include PDF
 - Consider including in “Comment” field specifics about your data derivation
- Quality Control Inadequate - Examples
 - TRTEFFR is the same for all sites
 - DEATH count is greater than SAFEPOP count
 - DISCONT count is greater than SAFEPOP count

