Creating Centralized Risk-Based Monitoring Reports for the Study Team

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SCT

SOCIETY FOR CLINICAL TRIALS

Disclosures

- This work was supported by NINDS
- No Other Relevant Disclosures

NIH StrokeNet

National Data Management Center NDMC

- The NIH StrokeNet Network infrastructure consists of one National Coordinating Center (NCC), one National Data Management Center (NDMC), and 27 Regional Coordinating Centers (RCCs) able to coordinate and conduct stroke clinical trials in a large number of centers across the United States
- The NCC provides scientific and organizational leadership
- The NDMC provides scientific and organizational leadership to the NIH StrokeNet in all aspects of data management, data quality, statistical design, and statistical analysis.
  - Centralized Risked Based Monitoring

https://www.ninds.nih.gov/current-research/trans-agency-activities/ninds-role-heal-initiative/early-phase-pain-investigation-clinical-network-eppic-net

Objective

- This presentation will demonstrate the process used to assess site performance to identify “high-risk” sites in need of on-site monitoring or re-training. Aggregated analyses are used to identify sites that are outliers relative to other sites or based on pre-defined expected performance metrics for enrollment, retention, protocol violations, etc. If there is fabrication of data, then there is often too little variability within subjects, too low of correlation between variables collected on the same subject, a digit-preference, or data are too perfect. Fraud detection methods such as mahalanobis distance, inlier score plots, funnel plots and trailing digit analysis will be discussed.

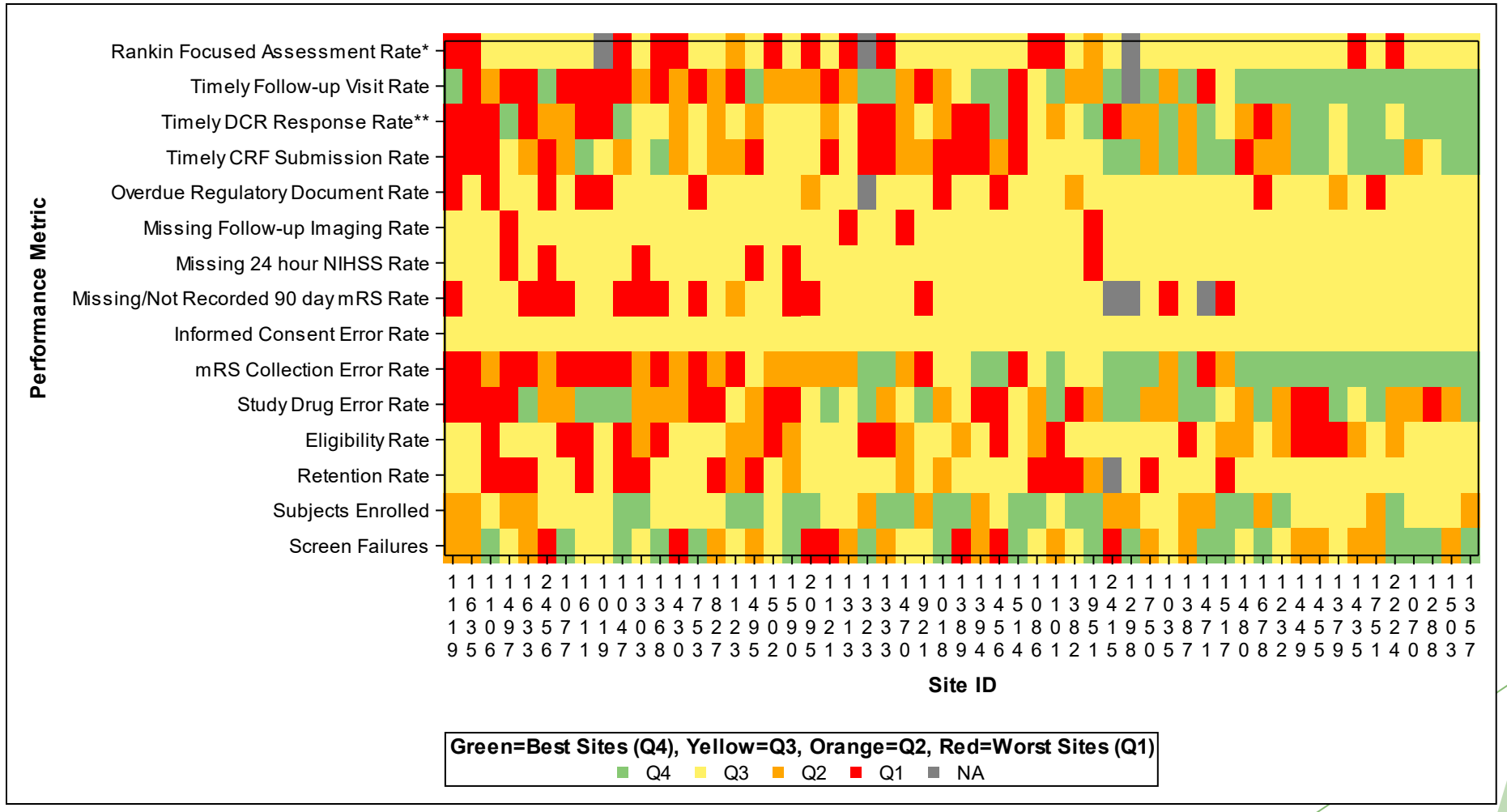
Statistical Risk Based Monitoring

- Monthly the biostatistical team conducts analyses of site characteristics and performance metrics in order to identify “high-risk” sites.
- Aggregated statistical analyses of study data used to identify sites that are outliers relative to other sites.
- High-risk sites discussed with study team.
- Sites will be contacted for retraining and/or prioritized for a remote or on-site monitoring visit by the NDMC.

Sloppiness/Poor Performance

- Sites flagged as “high-risk” if consistently ranked poorly for the performance metrics compared to other sites.
- Monthly heatmaps, funnel plots, and data listings of site performance of the following performance metrics.
- Sites will be ranked on the following performance metrics based upon their performance over the whole study period (cumulative) and most recent period (to account for changes in practice). These performance metrics reviewed to see if sites are improving or worsening.
- Consideration will be given for sites’ performance in other, similar StrokeNet studies.

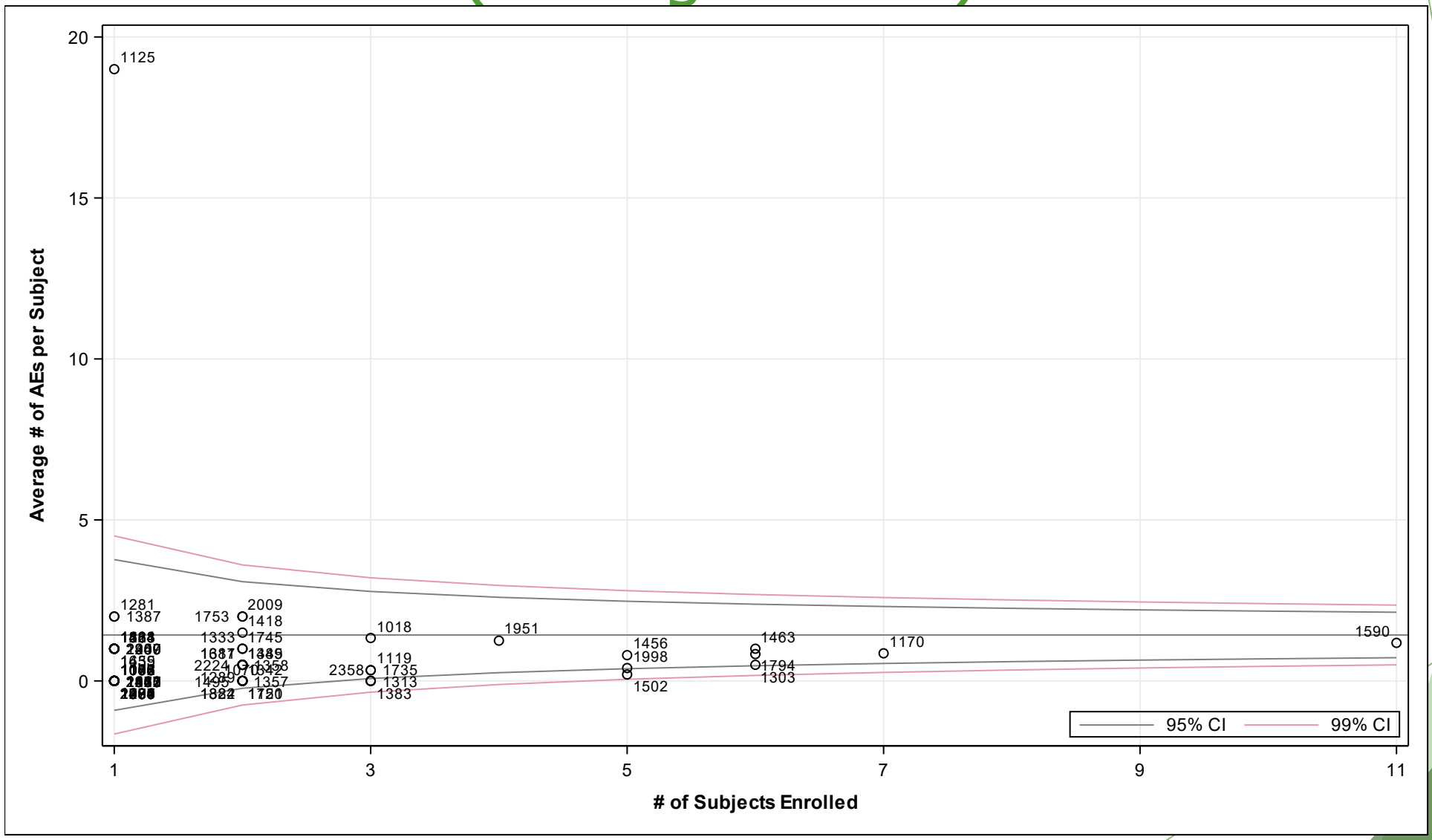
Site Performance Heat Map



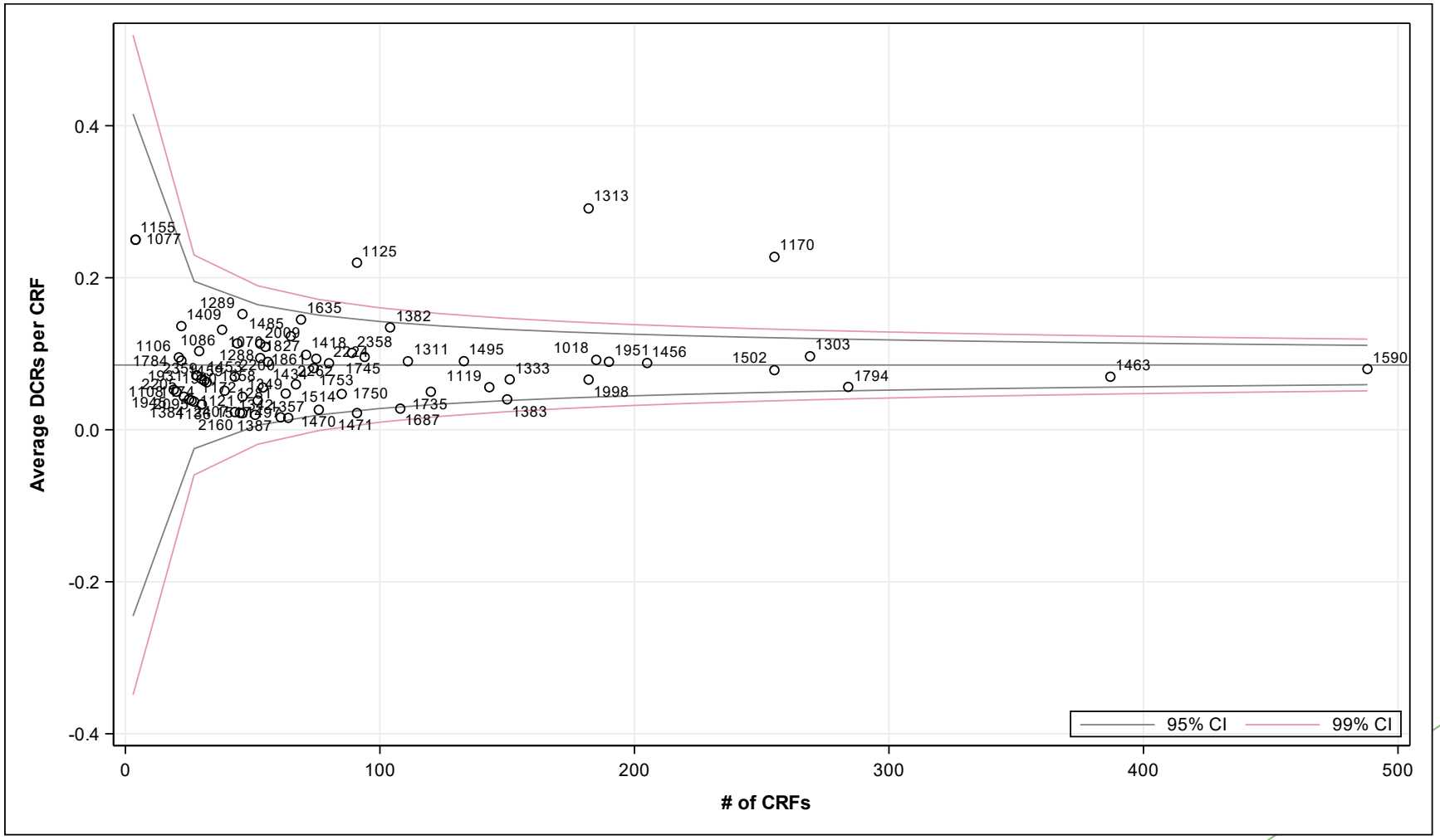
Site Performance

Site ID	Subjects enrolled	Average Screen Failure	Average Subject Enrollment	Subject Retention Rate (% of enrolled subjects)	Subject Eligibility Rate (% of enrolled subjects)	% of Subjects without study drug administration errors	% of Subjects without mRS errors	% of enrolled subjects with informed consent	% of study completed subjects with 90 day mRS data collected and recorded	% of subjects with 24 hour NIHSS data	% of subjects with follow-up imaging data	% of regulatory documents submitted on time	% of CRFs submitted on time	% of DCR responses timely	% of Day 30 and Day 90 Visits Timely	% of follow-up mRS assessments used Rankin Focused Assessment*
		Month	Month													
1018	23	3.7	0.7	95.7	100	69.6	91.3	100	100	100	100	96.9	70.8	34.1	94.7	100
1019	2	0.9	0.1	100	100	100	50	100	100	100	100	96.9	87.8	33.3	75	.
1035	3	1.4	0.1	100	100	66.7	100	100	.	100	100	100	100	90.9	100	100
1047	7	4.9	0.2	71.4	57.1	100	14.3	100	60	100	100	100	78.2	66.7	54.5	66.7
1070	4	2.1	0.1	100	100	75	100	100	100	100	100	100	79.3	81	100	100
1077	2	2	0.1	100	100	50	0	100	0	100	100	100	87.2	50	33.3	100
1078	0	1.7	0	.	.	.	.	.	.	.	.	100	.	.	.	.
1086	13	1.1	0.4	91.7	84.6	76.9	84.6	100	100	100	100	100	86.6	57.8	95.2	90
1101	1	0.1	0	.	100	100	100	100	.	100	100	94.9	100	50	100	100
1106	3	1.8	0.1	66.7	100	100	66.7	100	100	100	100	95.9	76.3	26.9	80	100
1119	2	0.4	0.1	100	100	0	50	100	50	100	100	92.9	69.1	26.7	100	50
1121	2	0.2	0.1	100	100	100	100	100	100	100	100	100	63.2	50	100	100
1122	0	0	0	.	.	.	.	.	.	.	.	.	.	.	.	.
1123	43	1.4	1.3	96.6	97.7	90.7	67.4	100	100	100	100	89.8	81.3	38.6	73.1	97.1

Funnel Plots (Average # AEs)



Funnel Plot of Data Quality (Queries/CRF)



Fraud detection

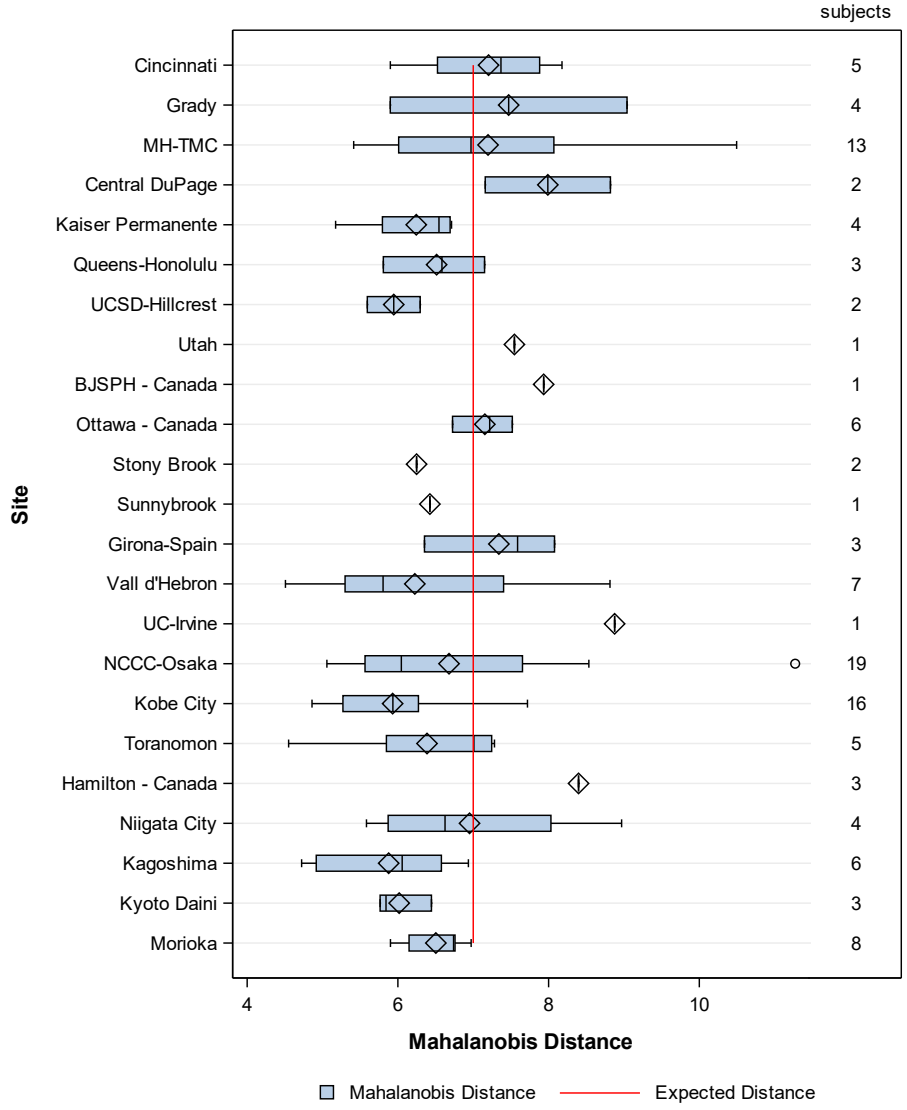
- If there is fabrication of data, then there is often
  - too little variability within subjects, (*Duplicate same values with only slight variations)
  - too low of correlation between variables collected on the same subject,
  - a digit-preference,
  - data are “too perfect” (inliers not outliers).
- Fraud may be occurring at the level of the site or at the level of the study team member. Both sites and study team members will be considered.
- Once there is sufficient data, statistical approaches can be applied.

Mahalanobis distance

- Fraudulent data will not have the expected correlation between variables
  - Multivariate-correlation is too low

- Multivariate Method for Fraud Detection
- Mahalanobis Distance Box Plot by site
  - shows how the Mahalanobis distances are distributed at each enrolling site.
  - Short boxes homogeneous population (subjects of similar characteristics) being recruited at a site.
  - Long boxes indicate a more heterogeneous population (subjects of different characteristics)

Mahalanobis distance box plot

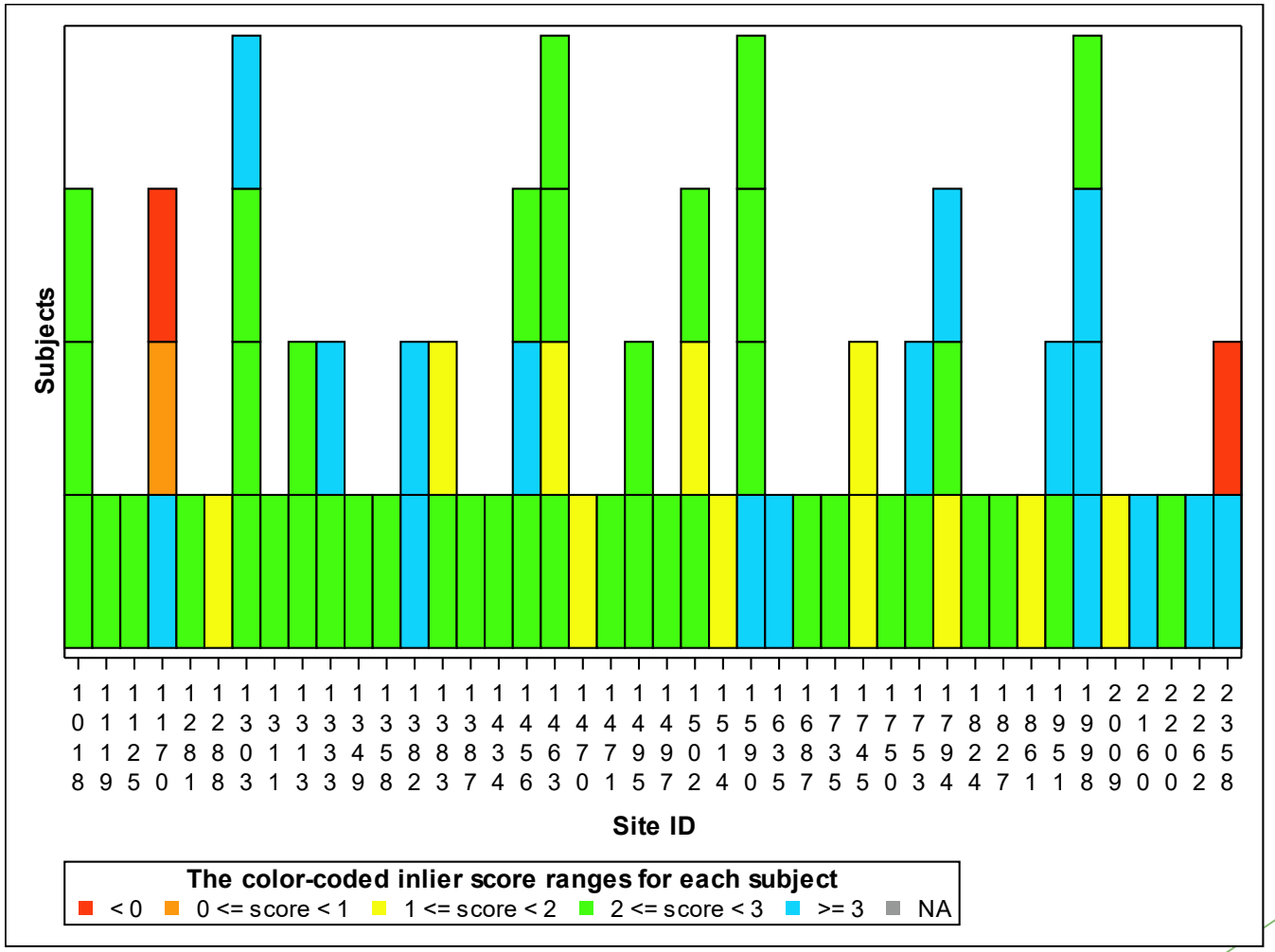


Low Variability due to Inliers

- What is an Inlier?
  - inlier is an erroneous data value which lies in the interior of a statistical distribution, making it difficult to distinguish it from good data values.**
- Inlier scores:
  - Variables are standardized (subtract sample mean and divide by SD). Then for each patient, each standardized variable is squared and summed (across all variables) and take the natural log. Then plot scores (y-axis) by site/study team member (x-axis). Sites with too little variability will have negative scores or scores smaller than their expected value. (Weir, Murray 2011)

** https://ec.europa.eu/eurostat/statistics-explained/index.php

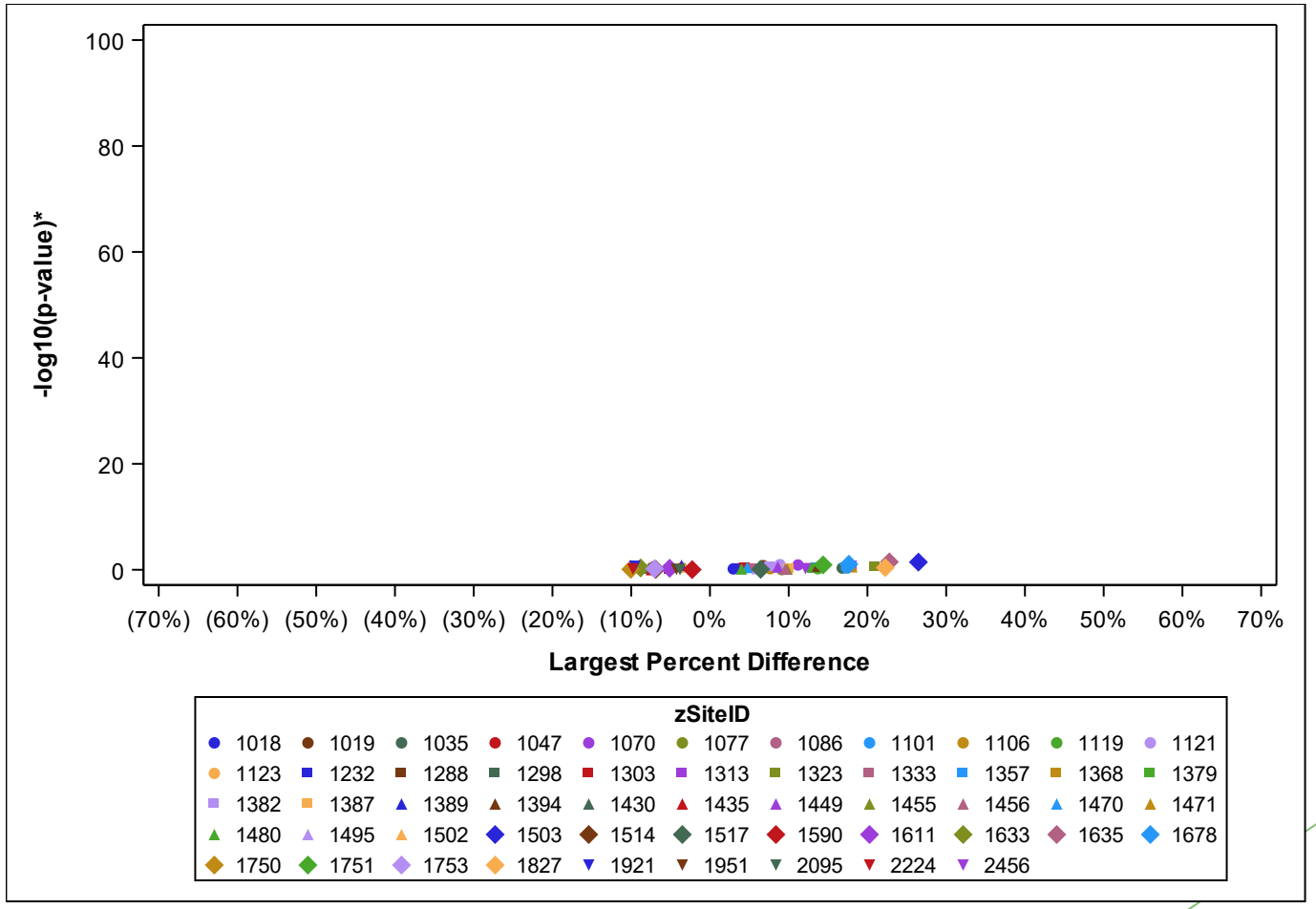
Heat Map of Inlier Scores for each subject (grouped by site)



Trailing Digit

- Trailing Digit Analysis compares the distribution of the LAST digit of all numeric variables (without regard to the distribution of the numeric variables) of each individual site to all other sites combined via a Cochran Mantel-Haenszel row mean score test.
- A volcano plot is used to visualize the data where the data points represent the individual sites, the y-axis is the p-value from the row mean score test, and the x-axis is the largest percent frequency difference (positive or negative) between the individual site and all other sites from any of the last digits 0-9.
- Data points close to the upper corners of the plot indicates a site's trialing digit distribution is very different from that of all other sites, a potential indication of data fabrication.
- Better for Clinical data than Benford's law (first digit follows exponential dist/better for financial data) due to restriction on ranges.

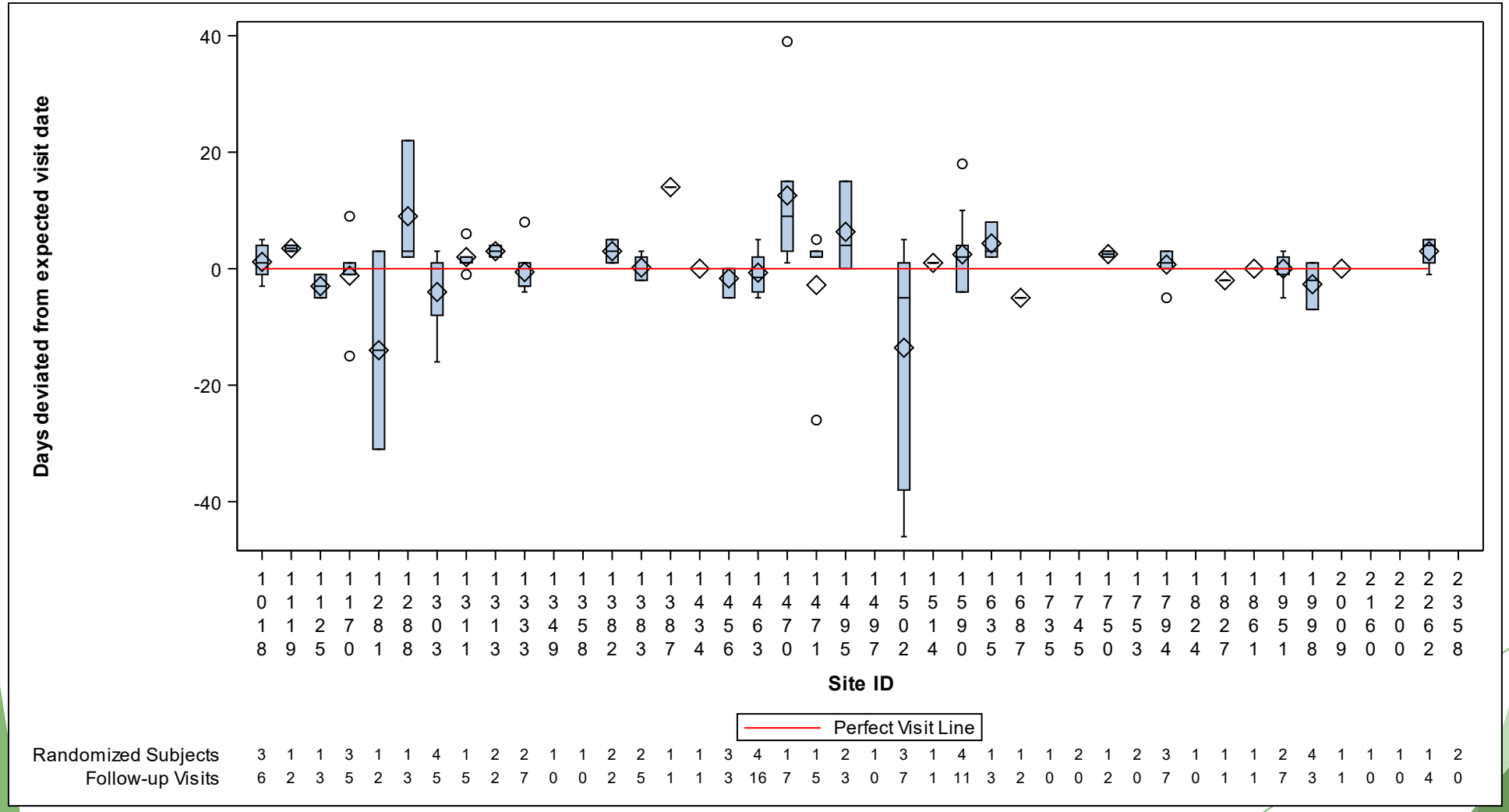
Trailing Digit Preference



Visit Scheduling is too perfect

- Perfect scheduling of study visits is suspicious.
- Study days (hours, min etc.) variables for a single site will be graphical reviewed to see whether they are too close to the expected visit (relative to other sites).
- We calculate the actual days from randomization to the visits for each participant within a site and subtracted that number from the target date for that visit. This difference is summarized in box plots, one for each site. Its noteworthy if we observe that a site always conducts visits exactly on the target date (Lindblad et al Clinical Trials 2014).
- Follow up visits will likely not occur on holidays (Christmas, July 4th). Flag any that do.

Perfect Visits/Imperfect Visits



Unusual Missing Data Patterns

- Unusually high or low frequencies of missing data may indicate fraud. Sites with very low or high missing data (relative to what is expected based upon the number of subjects enrolled) will be reviewed and compared with other sites. We compare the average number of missing observations per participant at each site in order to identify any sites with unusually high or low frequencies of missing data (Lindblad et al Clinical Trials 2014). Restrict this to all patients who have been enrolled for the expected study period for all required CRFs (not optional CRFs). Calculate the number of data points completed versus number expected x number of subjects.

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USES & CHALLENGES OF RISK-BASED MONITORING WITHIN NEURONEXT

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May 22, 2023

THE UNIVERSITY OF IOWA

THE UNIVERSITY OF IOWA
CT DMC
Clinical Trials Statistical and Data Management Center

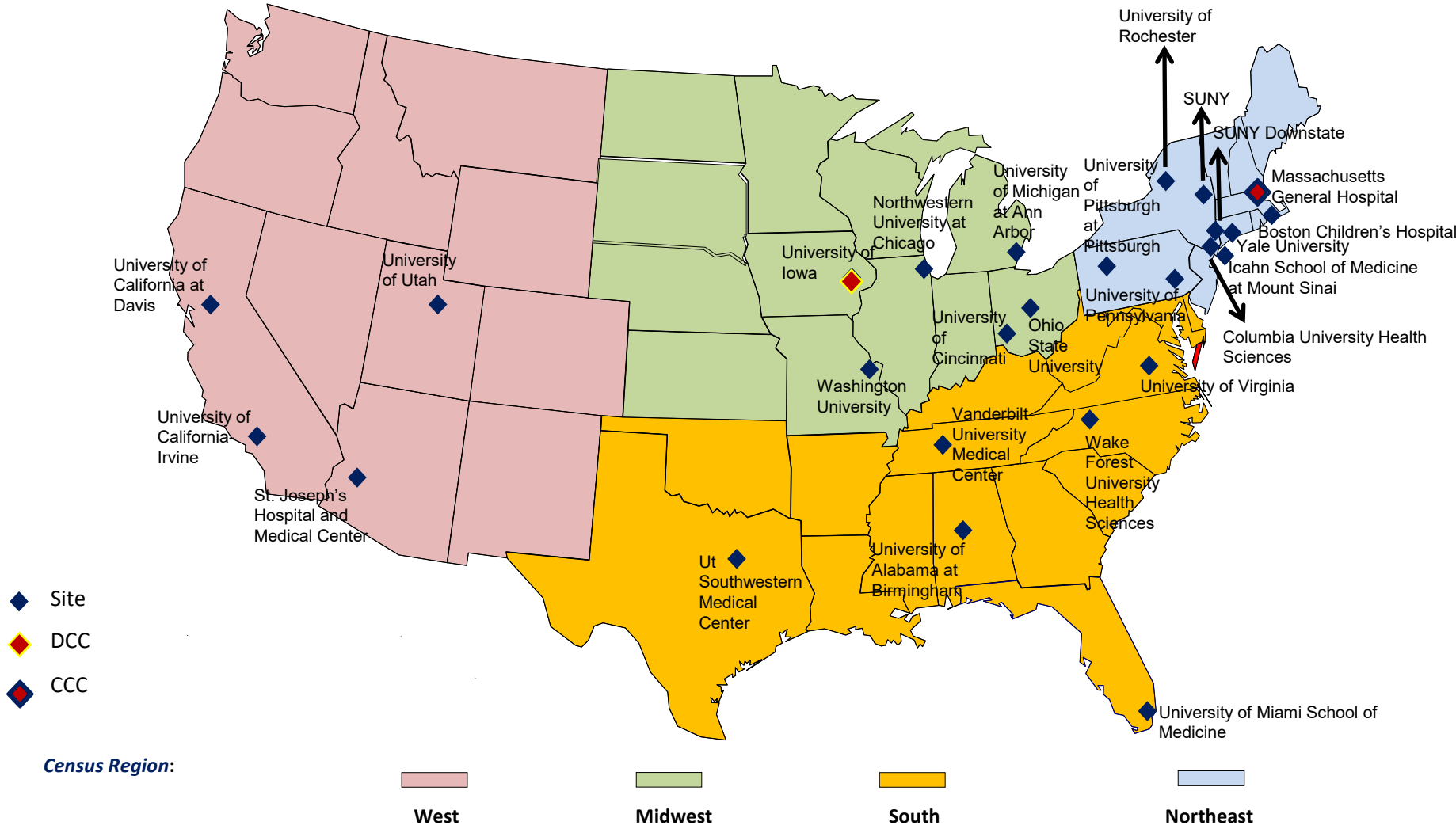
NEURONEXT

NeuroNEXT was designed to conduct studies in neurological diseases through partnerships with academia, private foundations, and industry in order to expand NINDS capabilities to:

- Test promising new therapies
- Increase efficiency of clinical trials
- Respond quickly as new opportunities arise to test promising treatments for people with neurological diseases

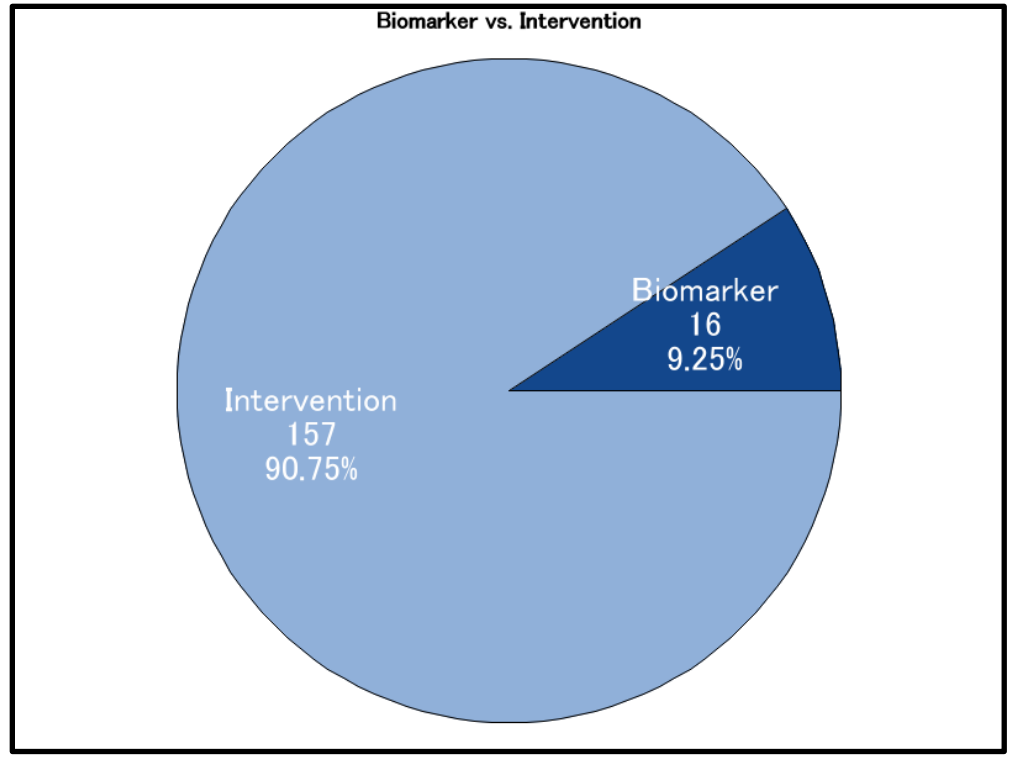
NEURONEXT

Network Infrastructure



NEURONEXT

Majority of proposals to date involve phase 2 clinical trials



NEURONEXT

Since the inception of NeuroNEXT in 2011, ***the Network has received 178 proposals from 90 different institutions/companies covering 65 different diseases!***

NEURONEXT

Completed Studies:

- NN101 **Spinal Muscular Atrophy**
- NN102 **ALS**
- NN103 **Alzheimer's Disease**
- NN104 **Rhapsody**
- NN105 **Sprint-MS**
- NN107 **Huntington's Disease**

- NN106 **Glioblastoma Multiforme** Biomarker Study

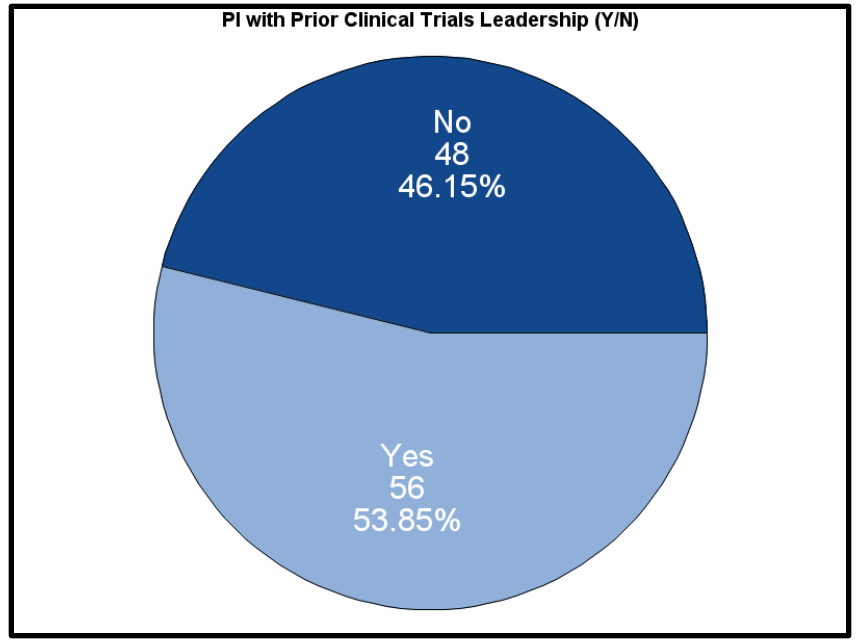
NEURONEXT

- NN107: Intervention Study in **Fragile X Syndrome**
- NN108: Intervention Study in **Cryptogenic Sensory Peripheral Neuropathy**
- NN109: Intervention Study in **GNE Myopathy**
- NN110: Intervention Study in **Parkinson's Disease**
- NN111: Intervention Study in **Anti-NMDA Receptor Encephalitis**

NEURONEXT: CHALLENGES

For 103 proposals for whom prior multicenter trial experience of PPI could be confirmed to date, 47 (46%) come from PIs with no prior multicenter trial leadership.

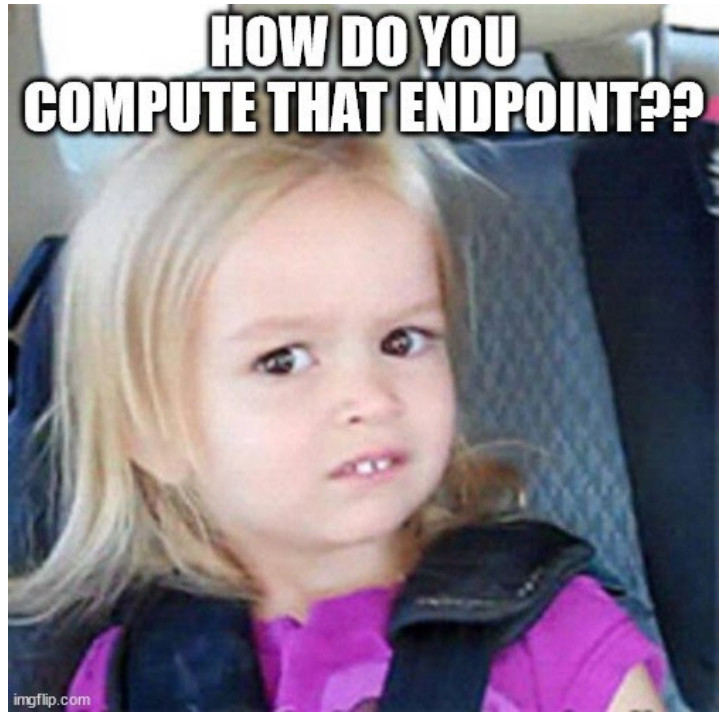
- 4 of 11 funded trials to date led by PPIs with no prior experience leading multicenter trials



NEURONEXT: CHALLENGES

DCC limited familiarity with diseases of interest

- Limited ability to proactively identify and program key variable checks
- Requires combination of analytical & process-oriented minds



NEURONEXT: CHALLENGES

"I shall not today attempt further to define the kinds of material I understand to be embraced within that shorthand description ["hard-core pornography"], and perhaps I could never succeed in intelligibly doing so. ***But I know it when I see it…"***

~ US Supreme Court Justice Potter Stewart (1964)

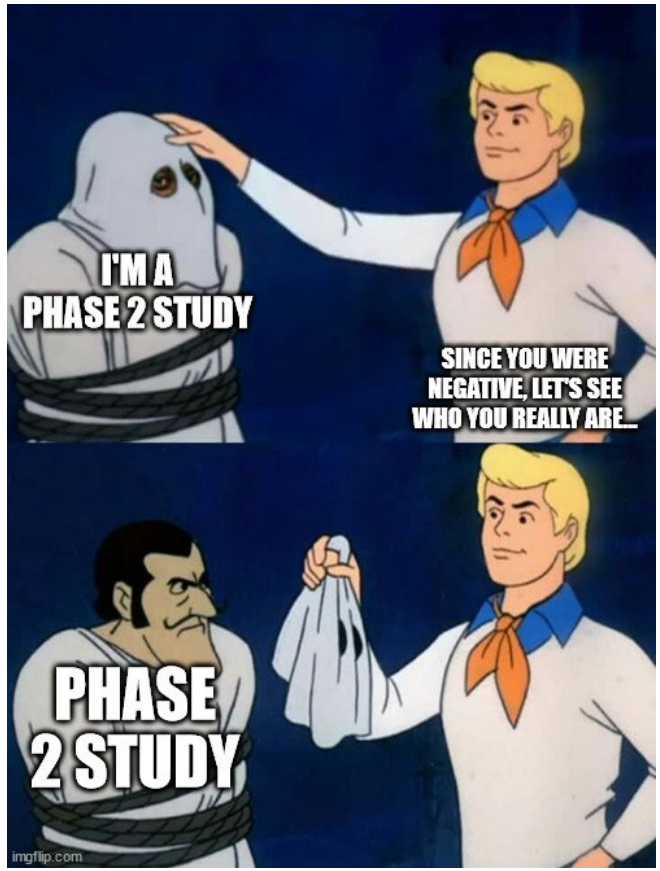
"[Risk-based monitoring] is kind of like bridging the divide between we will know it when we see it vs. we need to see it to know it."

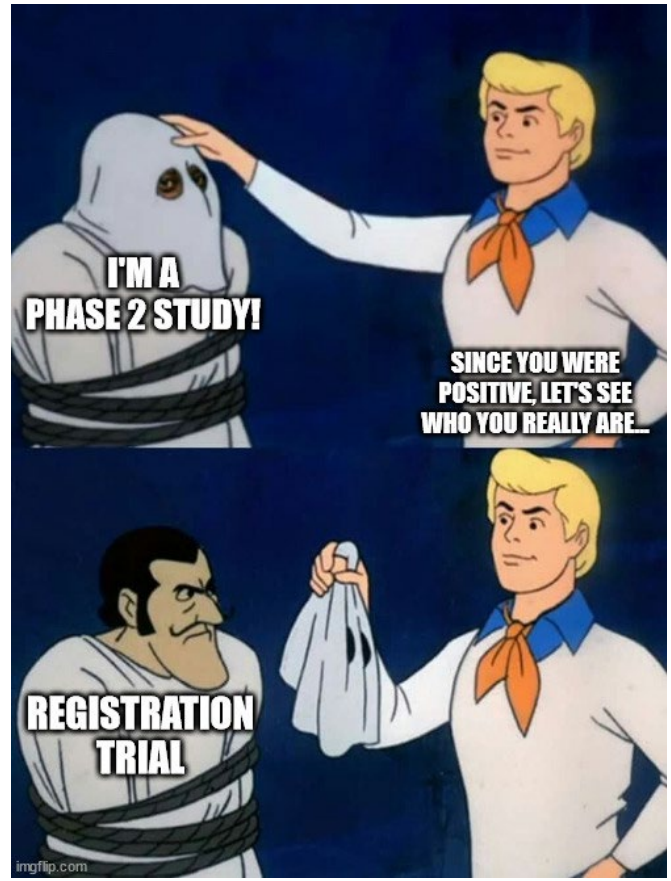
~ Dixie Ecklund (2023)

NEURONEXT: CHALLENGES

Correct level of monitoring needed?

- Phase 2 or Phase 3 in disguise??





NEURONEXT: CHALLENGES

Who should follow up with sites when statistical issues are discovered?

- Statisticians best understand the nuances of the checks implemented
- Coordinators best understand the clinical relevance of the issues and have best relationships with site coordinators

NEURONEXT: REPORT CARDS

Metrics:

- Study Startup
  - Time from site SIRB approval to site activation
  - Time from site activation to first consented participant
- Randomization
  - Total number of participants randomized
- Data Quality – Composite Measures
  - Score is on 0-4 scale
  - Higher score is better

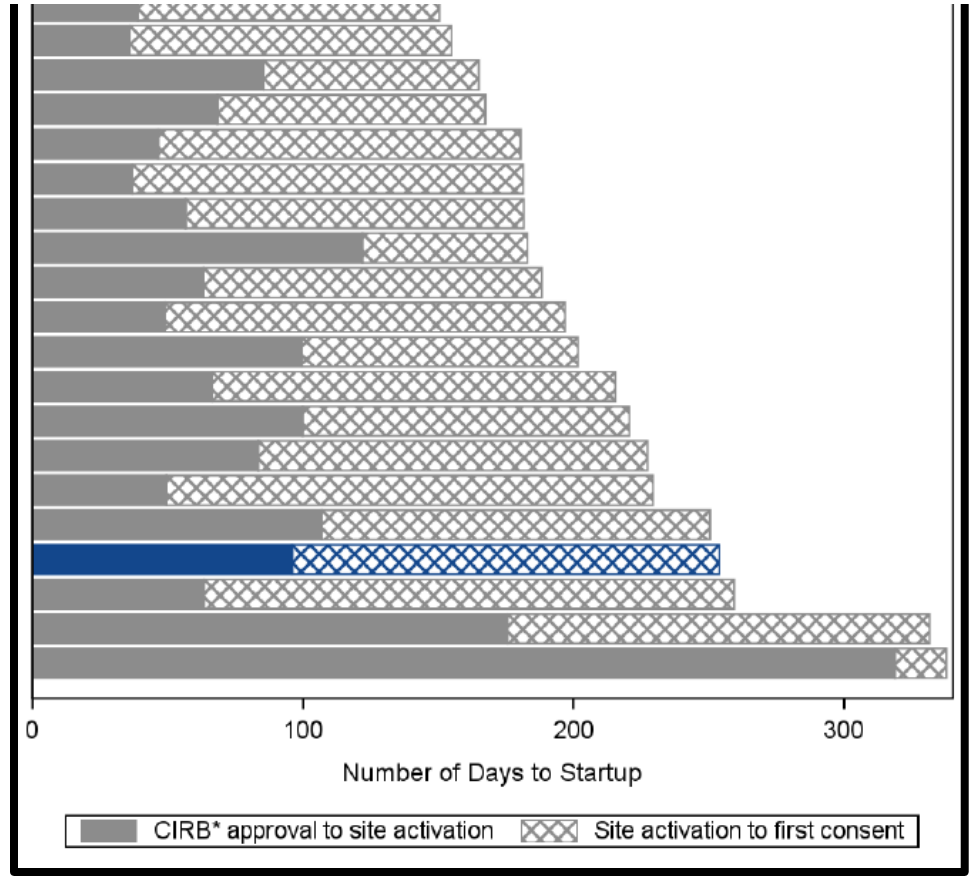
NEURONEXT: REPORT CARDS

Data Quality Metrics (All scaled 0 to 1 – higher score better):

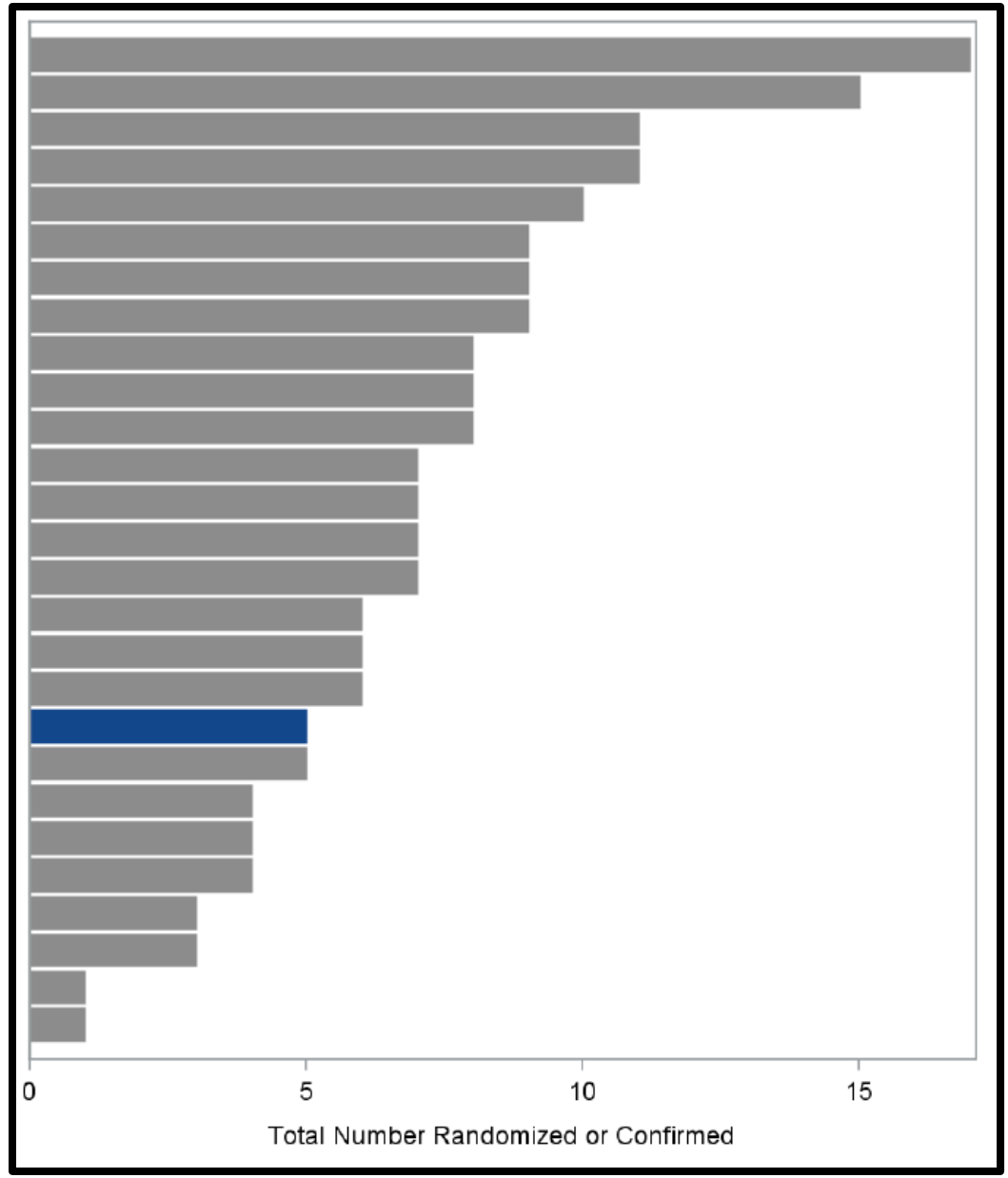
- Data Accuracy
  - Percentage of CRFs without a post-complete change (PCC) or data change request (DCR)
- Timeliness – Average of following:
  - Percentage of CRFs where data entered within 7 days
  - Percentage of CRFs where data entered within 30 days
- Protocol Deviations – Average of following:
  - Percentage of participants with no PD
  - Percentage of participants with no major PD
- Participant Retention
  - Percentage of participants without early termination

NEURONEXT: REPORT CARDS

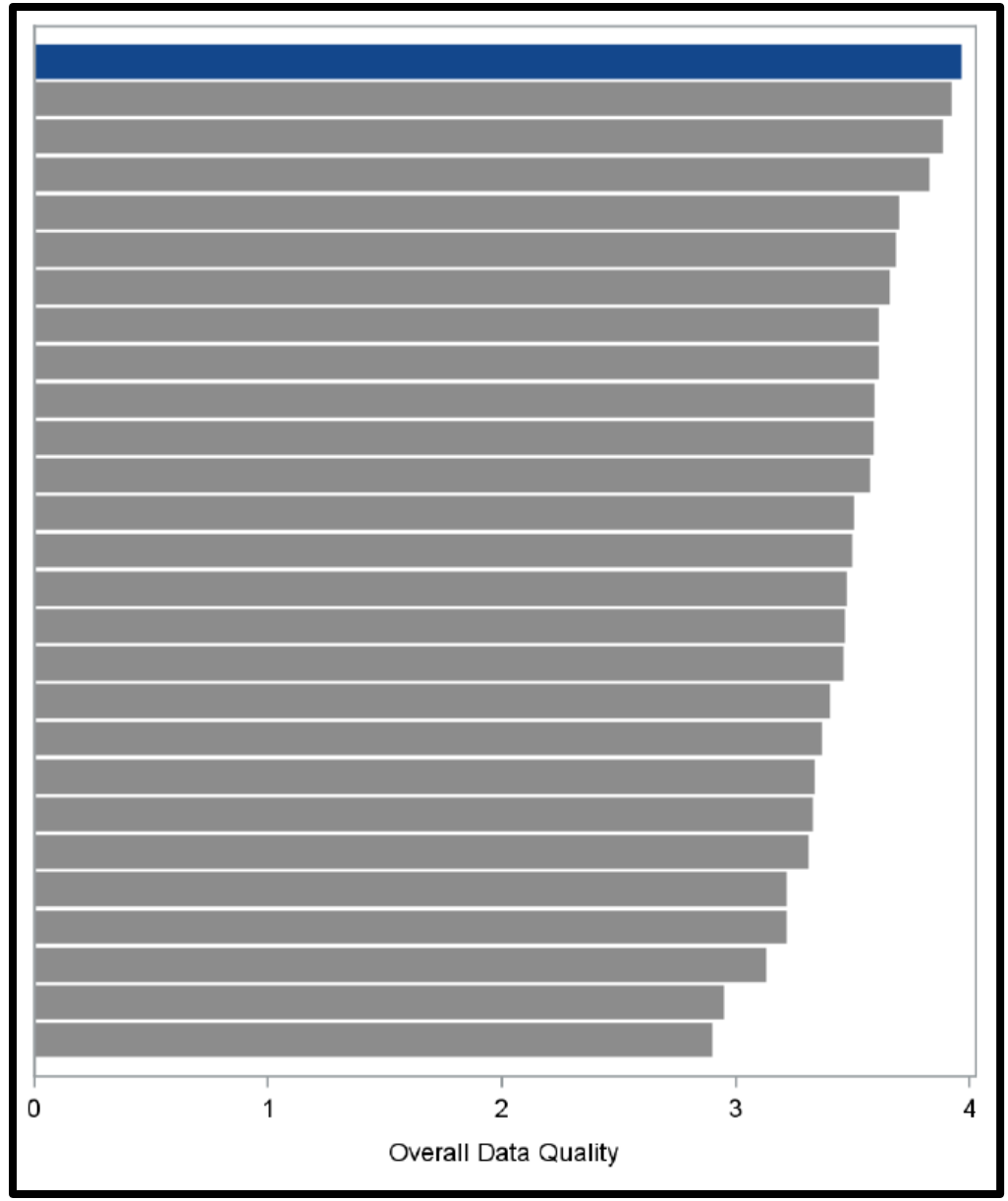
NeuroNext Startup			
Study	CIRB Approval to Site Activation (Days)	Site Activation to First Consent or End of Enrollment (Days)	CIRB Approval to First Consent or End of Enrollment (Days)
NN110	108	37	145
NN111	84	279	363
Site Average	96	158	254
Network Average	81.67	100.00	184.17



NEURONEXT: REPORT CARDS



NEURONEXT: REPORT CARDS



NEURONEXT: REPORT CARDS

Data Quality – Overall Network Metrics:

Study	Data Accuracy	Timeliness	No Deviations	Retention	Composite Score
A	0.92	0.86	0.75	0.50	3.08
B	0.94	0.85	0.55	0.88	3.13
C	0.96	0.82	0.50	1.00	3.23
D	0.85	0.90	0.00	0.88	2.66
E	0.91	0.92	0.50	1.00	3.22
F	0.78	0.54	0.94	1.00	3.10
G	0.92	0.73	0.50	1.00	2.99
H	0.94	0.89	0.50	0.94	3.16
I	0.97	0.99	1.00	1.00	3.90

NEURONEXT: NEC METRICS

- All Feasibility Reviews
  - Median: 1.5 months (Range: 0.5 to 5 months)
- 'Final' Feasibility Reviews
  - Median: 2 months (Range: 1 to 4.5 months)
- NEC Feasibility to ESC Review
  - Median: 7 months (Range: 1.5 to 10.5 months)
- ESC Review to Grant Submission
  - Median: 6 months (Range: 4 to 8 months)
- ***Initial Receipt to Grant Submission***
  - ***Median: 17.5 months (Range: 14 to 33 months)***

NEURONEXT: NEC METRICS

For completed studies, NEC has performed exploratory analyses comparing participant expectations based on site feasibility surveys to actual enrollment.

- Remarkably consistent across a diverse range of studies
- On average, sites recruit about 67% (two-thirds) of the amount the indicate they ‘expect’ to recruit
- Has major implications on interpretation of feasibility surveys – especially in rare studies that are difficult to review


RUNNING UP THAT HILL:
Navigating the Upside Down World of Coordinating Clinical Trials
WELCOME TO
CT DMC
THE UNIVERSITY OF IOWA

THANK YOU!!

Centralized risk-based monitoring of Alzheimer's clinical trials using an open-source platform

Rema Raman, Ph.D.

Professor of Neurology, University of Southern California (USC)

Director, Section of Biostatistics and Section of Recruitment & Retention
USC Alzheimer's Therapeutic Research Institute (ATRI)

Co-lead, Biostatistics, Recruitment, Engagement & Retention, & IDEA-CT Units
Alzheimer's Clinical Trials Consortium (ACTC)

May 22, 2023

Keck School of Medicine of USC

Alzheimer's Therapeutic Research Institute

ACTC ALZHEIMER'S CLINICAL TRIALS CONSORTIUM

Disclosures

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Board Chair (Unpaid):	Alzheimer's Association San Diego/Imperial Chapter

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This is joint work with:

ACTC Coordinating Center PI:	Paul Aisen, MD
ACTC Biostatistics Unit co-lead:	Michael Donohue, PhD
ACTC Informatics Unit lead:	Gustavo Jimenez-Maggiora, MBA
ACTC Medical and Safety Unit lead:	Michael Rafii, MD, PhD

Outline

- Introduction
- Approach and Implementation
- Examples
- Summary and next steps

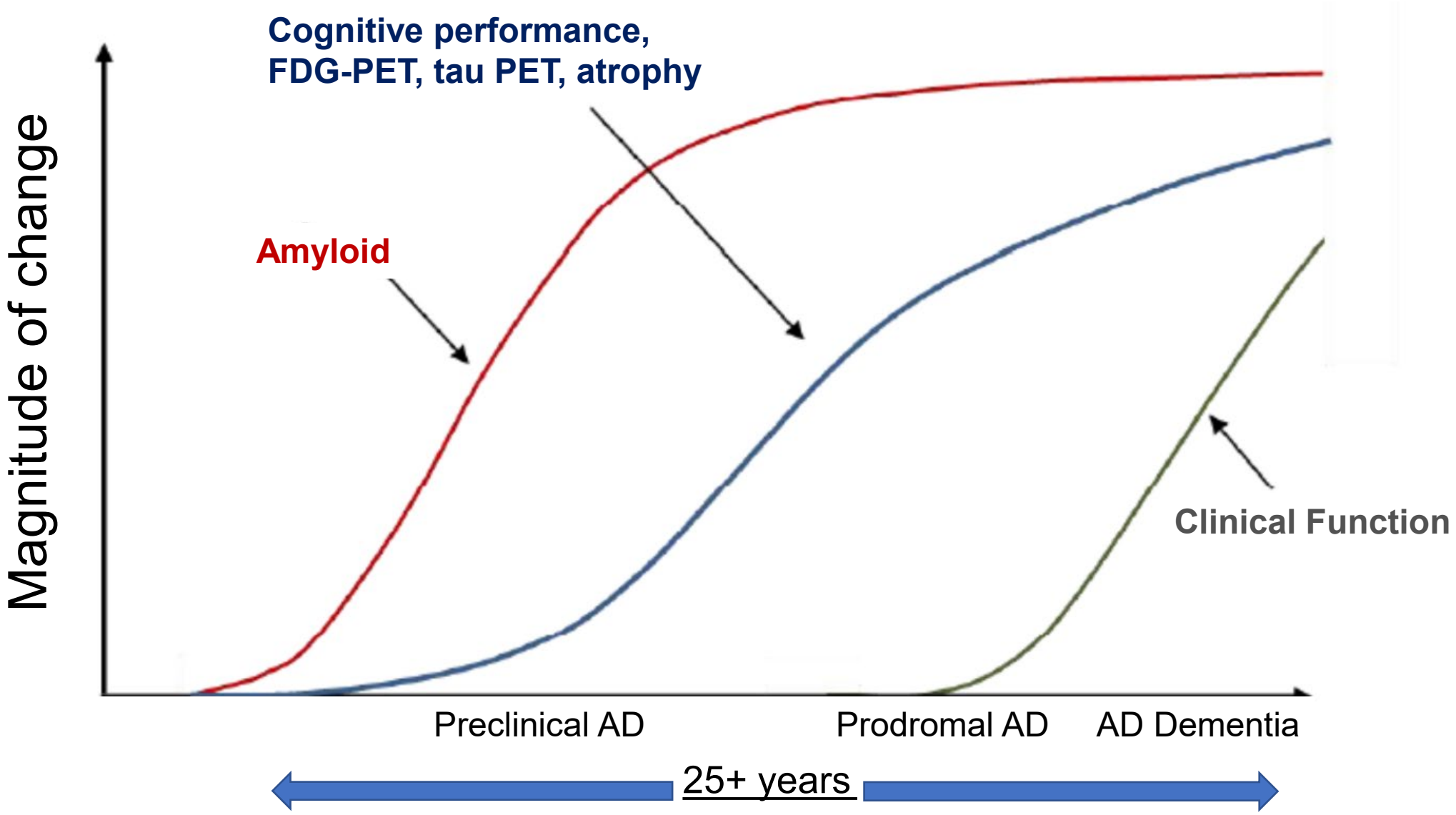
General Study Design for AD Clinical Trials

- Double-blind, placebo controlled, parallel group trials
- Cognitive and Functional outcomes

PACC	Preclinical Alzheimer Cognitive Composite
ADAS-Cog	Alzheimer`s Disease Assessment Scale cognitive portion
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating Sum of Boxes
ADCS-CGIC	Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change
ADCS-ADL	Alzheimer`s Disease Cooperative Study-Activities of Daily Living

- Long follow-up
- 30-70 sites across the United States and Canada
- Rater training and re-training critical to administration of instruments to minimize the rater variability in outcome scoring

New concept of the AD continuum



Aisen P. et al. *Alz Res Ther.* ,2017

Alzheimer's Clinical Trials Consortium

Leadership Team: Paul Aisen, Ron Petersen, Reisa Sperling, Laurie Ryan

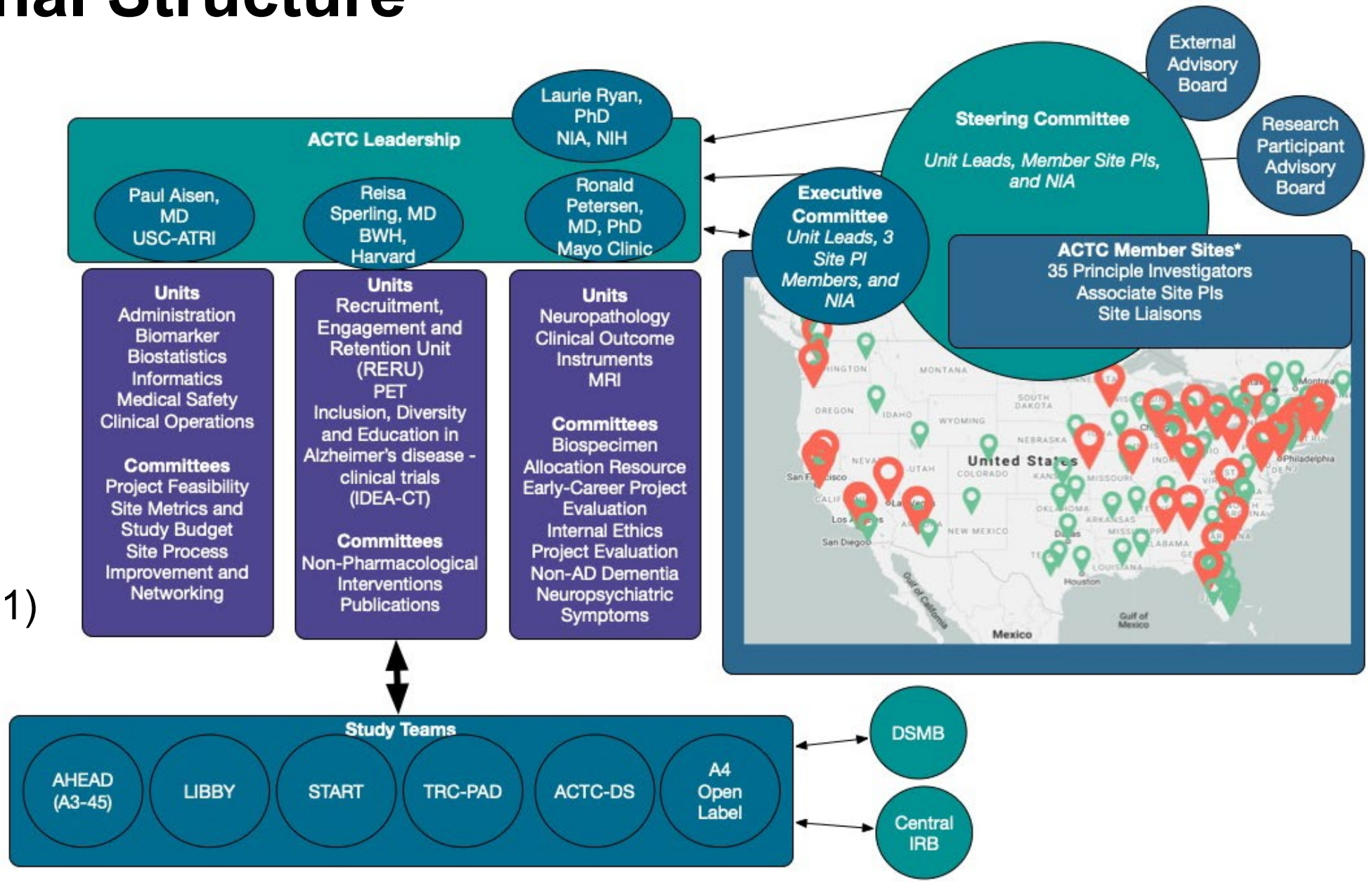
To provide an optimal infrastructure, utilizing centralized resources and shared expertise, to accelerate the development of effective interventions for Alzheimer's disease and related disorders.

- Collaboration
- Efficiency
- Diversity
- Transparency

Organizational Structure

- 3 MPIs
- 12 Units
- 10 committees
- 35 members sites

Trials:
- Preclinical (2)
- Early AD (1)
- End-of-life (1)
- Down Syndrome (1)



Issues specific to ACTC trials

- Rater training and re-training critical
- A site participates in several studies
- A monitor is assigned to a cluster of sites
- Monitoring needs to be done by participant, site, and study level to maximize impact
- Wide range of trials:
  - registration/non-registration
  - preclinical, prodromal AD, early AD and end-stage of disease
  - large, medium and small
  - amount of funding available for coordinating center varies

ACTC Monitoring Paradigm

- Adaptive and targeted study monitoring using
  - close to real-time data from all sources
  - statistical approaches (simple and highly complex) to visualize and inspect data
  - data capture technology and data analytics to generate easy-to-read suite of reports
  - expertise from a multi-disciplinary team to review and determine potential issues or follow-up actions.

Approach

General approach to evaluate data centrally across all study sites, both within a study and across studies being conducted at the coordinating center

Goal: Assess important study parameters to determine and monitor

- ❑ clinical trial conduct
- ❑ data quality
- ❑ participant safety
- ❑ efficacy

to inform the study clinical monitoring plan and target monitoring effort and site visits

Guiding Philosophy

- Emphasis on providing centralized monitoring support to sites through the study monitoring team with a focus on data and study quality
- General framework for all ACTC managed studies, with study-specific components included
- Functionality built using the open-source R (www.r-project.org) platform with interactive visualization graphs and tables
- Adaptive process to incorporate site and monitor feedback to improve utility and efficiency

Implementation

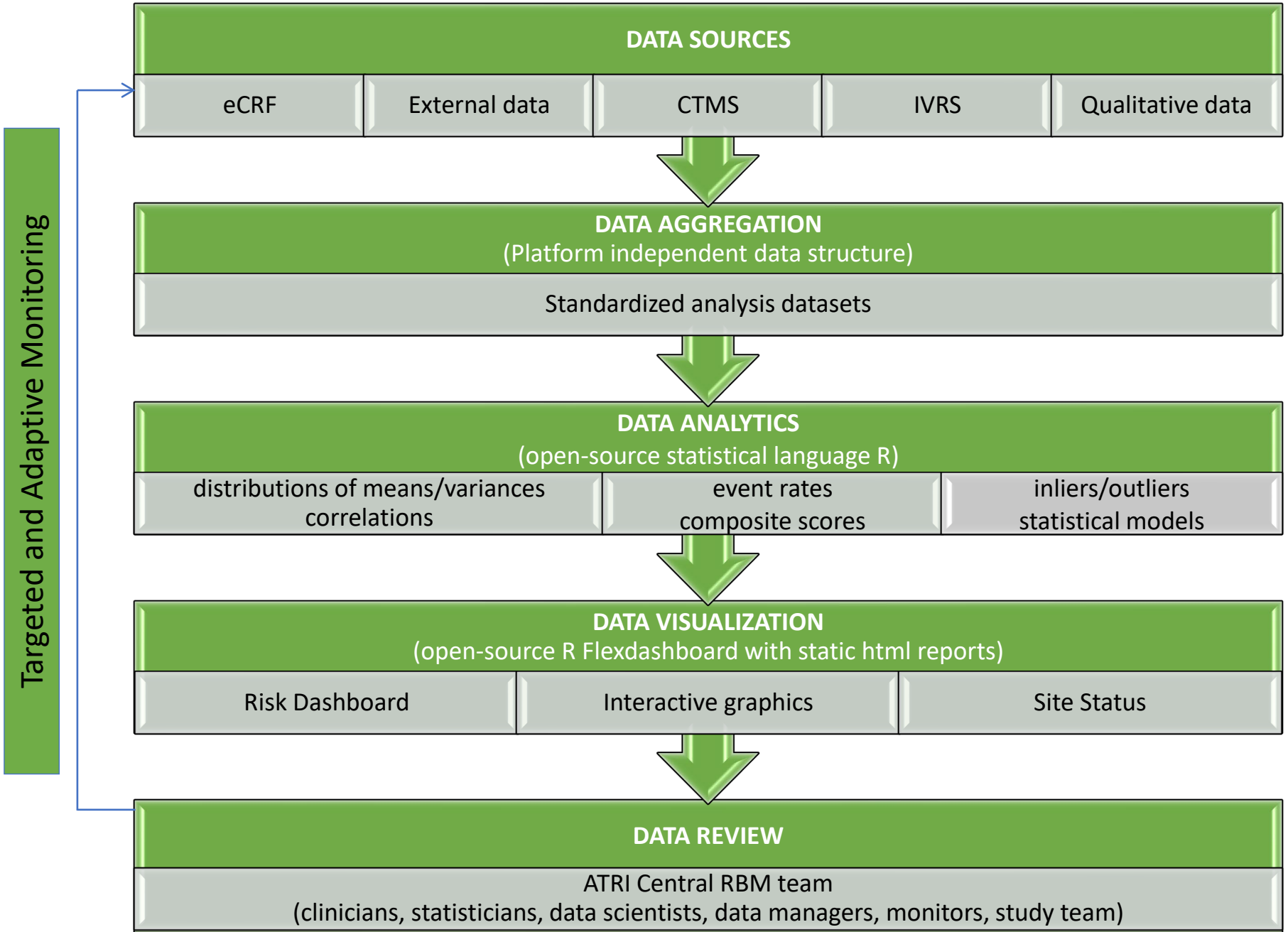
- Define KPI across key risk areas with thresholds defining three levels of risk: Green (low), Yellow (medium) and Red (high)

- KPI thresholds established at study start
  - Pre-specified fixed thresholds
  - Variability metrics evaluating each site relative to study average

- Clinical monitoring team reviews study data and site performance on an ongoing basis to inform study monitoring plan

- Combine “statistical" and “clinical" thinking into the review and monitoring of data.

ACTC Centralized RBM Model



Reports for clinical trial conduct

Enrollment	Screening, screen fail, randomization rates by site
Protocol Deviation	Rates by site accounting for site randomizations
Early Discontinuation	Rates by site and type

Reports for data quality

Completeness	Visit completion, missing item scores, late visits, time to data entry
Queries	Query rate by site, time to query completion, open queries
Randomization	Time to randomization, overdue randomization

Reports for safety

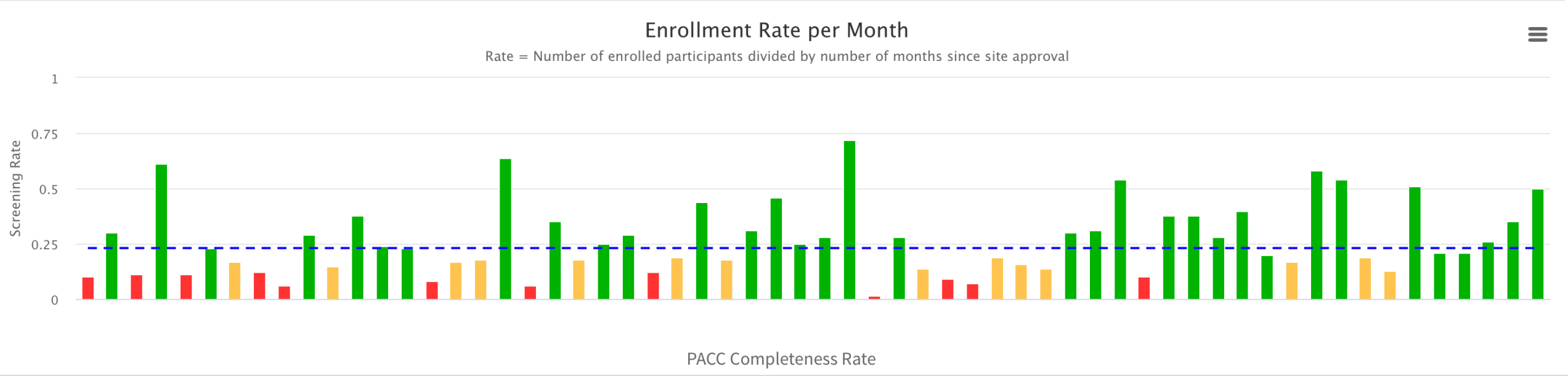
Adverse Events, SAEs	Event rates adjusted for time in study
Significant Protocol Deviation	Rates by site and type
Deaths	Rates by site

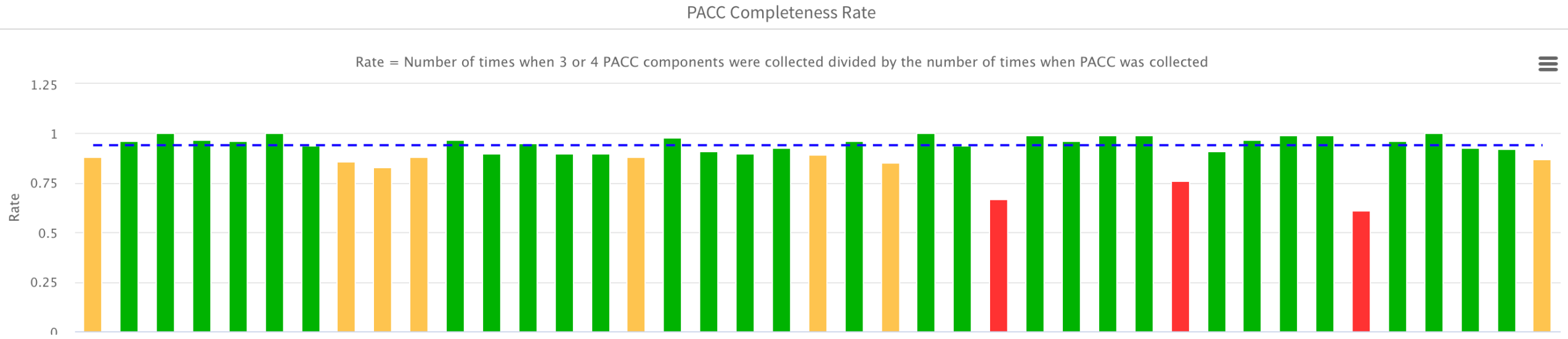
Reports for cognitive and functional outcomes

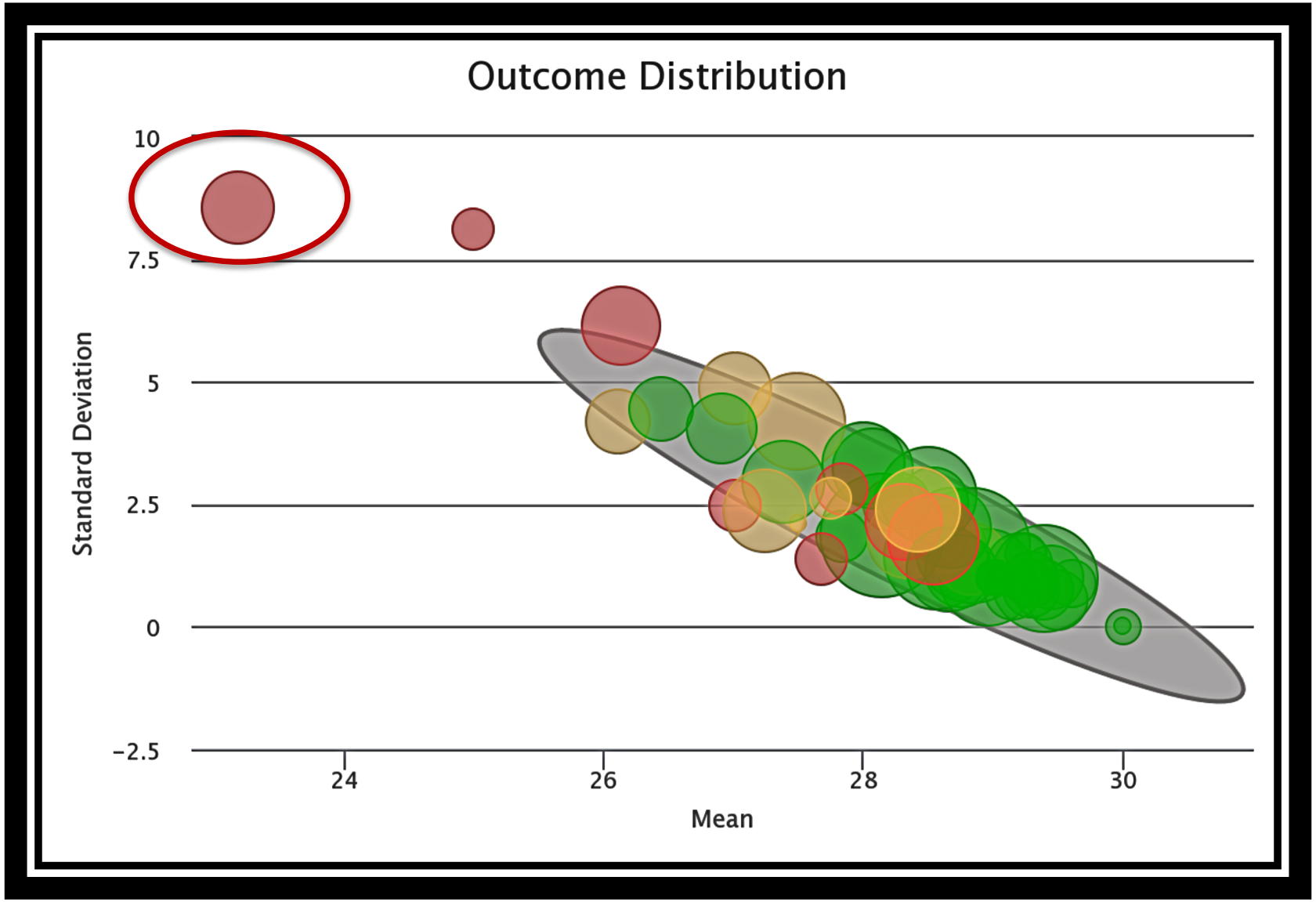
Focus: Identify variability in instrument scoring observed as a result of improper training and administration. Aggregate review only.

Screening vs. Baseline	Participants with large changes in score
Baseline Score Distribution	Mean scores across sites
Baseline score variability	Bivariate normal distributions of outcome means and variances

Examples for demonstration purposes only







Each circle indicates a site; size of circle indicates numbers of participants at that site. Grey region is the 95% C.I of the bivariate normal distribution of site mean and standard deviation

Study Conduct	Safety	Data Quality	Overall
High Risk	Low Risk	Low Risk	Low Risk
Low Risk	Low Risk	Low Risk	Low Risk
Low Risk	Low Risk	Low Risk	Low Risk
High Risk	Low Risk	Low Risk	High Risk
Low Risk	Low Risk	Medium Risk	Low Risk
Low Risk	High Risk	Low Risk	Low Risk
Low Risk	Low Risk	Low Risk	Low Risk
Low Risk	Low Risk	High Risk	High Risk
Low Risk	Low Risk	Low Risk	Low Risk
Low Risk	Low Risk	Low Risk	Low Risk
Low Risk	Low Risk	Low Risk	Low Risk

Main Dashboard View

- One row per site
- Weighted risk score per risk category
- Weighted risk score across categories
- Can be changed during the trial

Limitations

- Reports are not reliable until there is substantial data
- Possible introduction of bias in looking at outcome data; however, this can be controlled with a structured review.
- Output from a single report does not provide evidence of an irregularity at a site.
  - reports reviewed collectively to identify possible deviations that need corrective action.
  - takes a period of observation to get a sense of the variance in cognitive measures before calling them inliers/outliers and initiating modification in study conduct/procedures.

Strengths

- Study monitoring plan is proactive and responsive to study needs and conduct
  - Data errors are corrected on an ongoing basis.
  - Procedural errors identified and corrected during the trial
- Use of statistical methods augments existing monitoring strategies to allow a comprehensive monitoring approach
- Monitoring teams are now multidisciplinary and include clinical monitoring, data, and statistical perspectives.
- Adaptive approach has substantially enhanced data quality and given the potential to detect fraud and enable more selective in-person monitoring.

Survey of RBQM tools and the experience of a new DCC

Zhongyang (Caitlin) Ma

NYU Grossman School of Medicine

SCT
SOCIETY FOR CLINICAL TRIALS

Disclosures

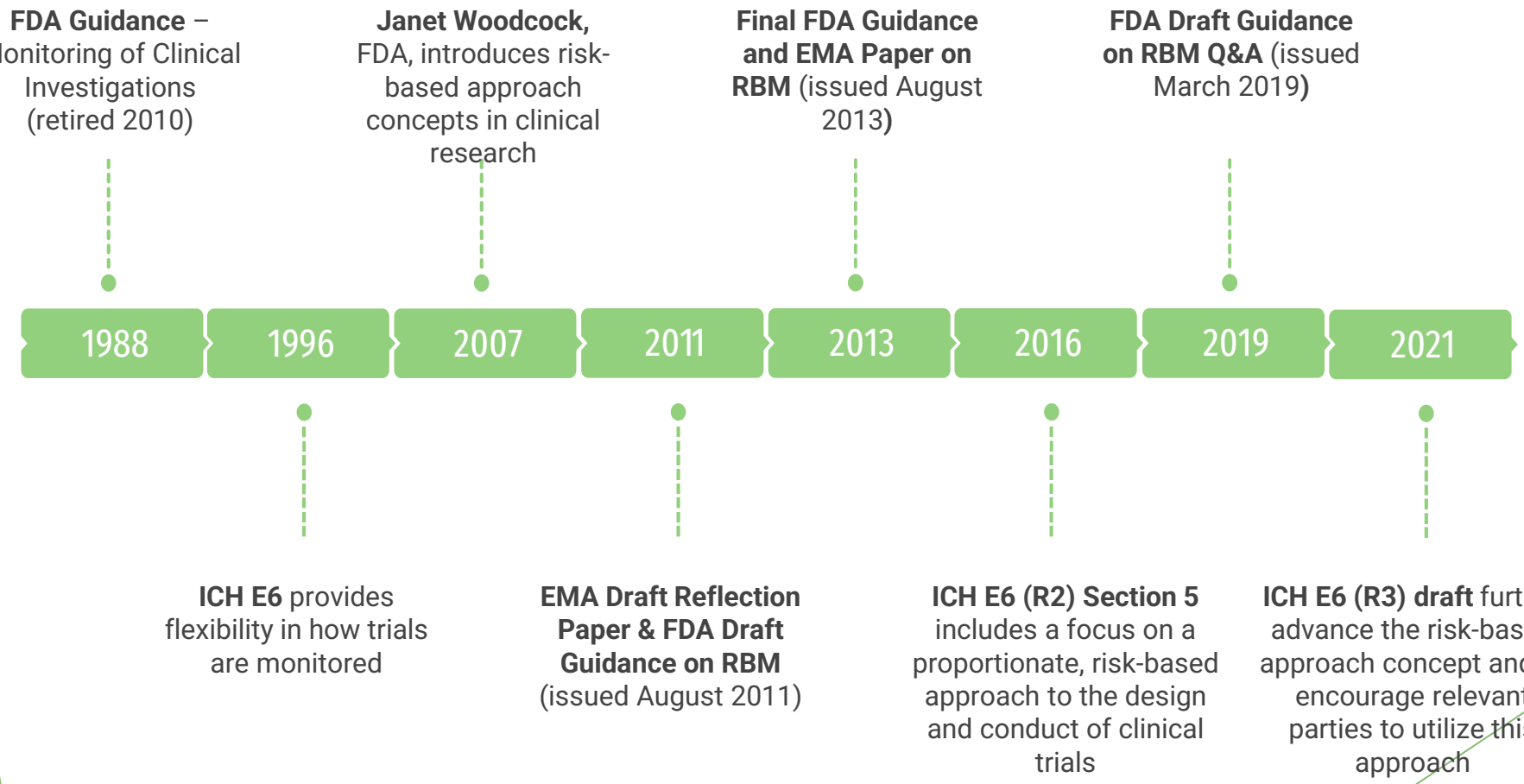
- No Relevant Disclosures

EPPIC-Net

- NIH National Institute of Neurological Disorders and Stroke (NINDS) established the Early Phase Pain Investigation Clinical Network (EPPIC-Net) as a part of the NIH HEAL (Helping to End Addiction Long-term) Initiative.
- EPPIC-Net seeks to enhance the treatment of acute and chronic pain and reduce reliance on opioids by accelerating early-phase clinical trials of non-addictive treatments for pain.
- The Data Coordinating Center (DCC) will manage data from the trials conducted in EPPIC-Net and other parts of the NIH HEAL Initiative's pain research program. The DCC will make these data available to pain researchers. The DCC will also provide expertise and leadership on statistical design and analysis of studies conducted within EPPIC-Net.

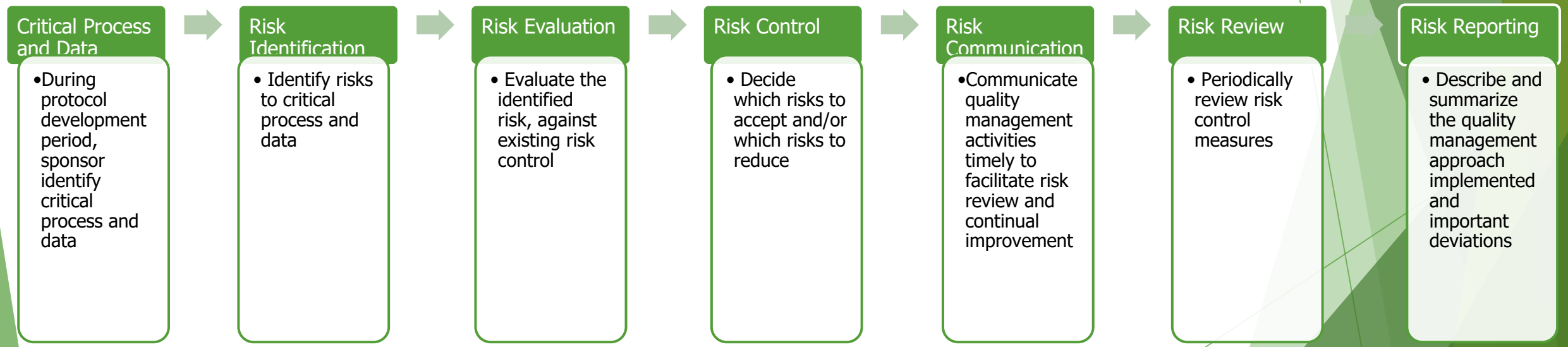
https://www.ninds.nih.gov/current-research/trans-agency-activities/ninds-role-heal-initiative/early-phase-pain-investigation-clinical-network-eppic-net

Risk-based quality management (RBQM)



Risk-based quality management (RBQM)

- ICH E6 (R2) Good clinical practice Section 5.0 Quality Management



INTEGRATED ADDENDUM TO ICH E6(R1): GUIDELINE FOR GOOD CLINICAL PRACTICE E6(R2)

Risk-based quality management (RBQM)

- **Benefit**
  - Shift the focus and resources to the most critical data and process, which are more likely to ensure subject protection and overall quality[1,2]
  - Reduce source data verification (SDV)
  - Reduce source document review (SDR)
  - Key risk indicators (KRIs) helps assess site performance
  - Centralized monitoring can remotely review the electronic data capture (EDC) data and perform appropriate data analysis
  - Reduce cost
  - Ensure the trial integrity and data quality

Risk-based quality management (RBQM)

- **Implementation rate of RBM**

  Association of Clinical Research Organizations (ACRO) conducted a landscape survey among its member companies across 6,513 clinical trials ongoing at the end of 2019 (Barnes et al, 2021)

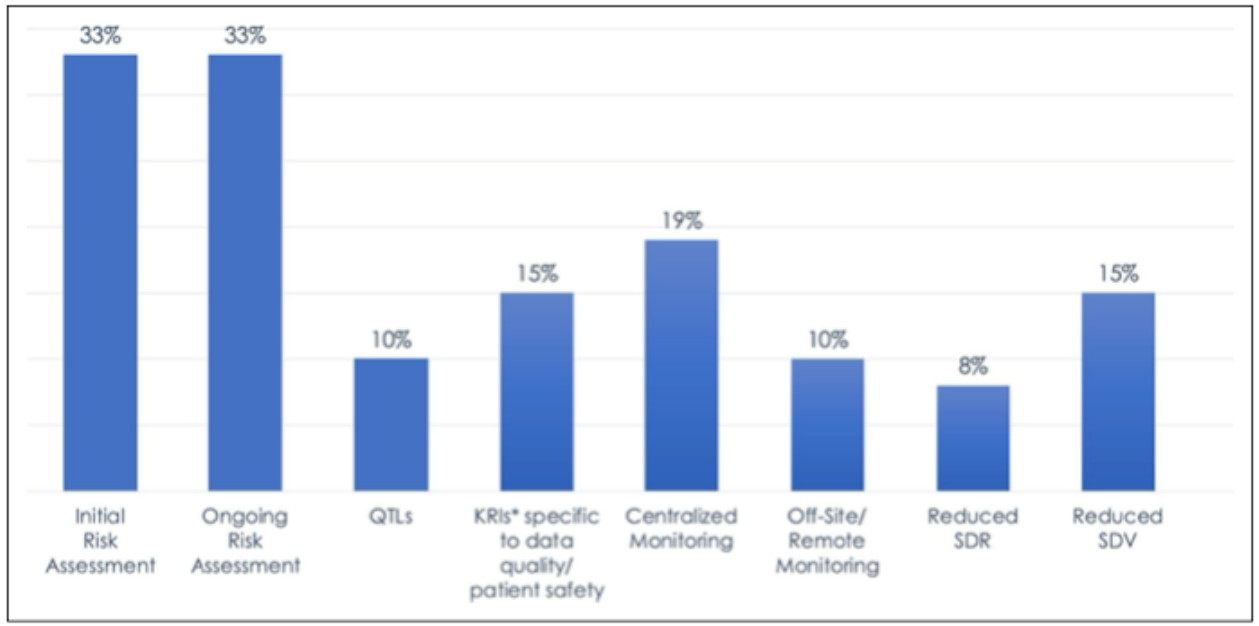


Fig. 1 2019 Landscape of RBM/RBQM Components in Clinical Trials. Data represent the percentage of all 6,513 trials included in the survey, not just the subset of studies that have at least one RBM component. *The KRI percentage does not include KRIs related to operations or performance.

Vendors

- **Considerations**
  - Vendor has different KRI libraries
  - Different standard operating procedure (SOP)
  - Efficiency / response rate
  - Have RBM capabilities
  - Alignment with regulatory agencies
  - Flexibility and transparency
  - Budget
  - Study complexity

CluePoints

IMS Health & Quintiles are now IQVIA™

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MEDPACE

In-house RBQM tools

- **Benefit**
  - DCC teams already have deep understanding of the studies and data; we can apply the statistical models directly
  - More efficient and high response rate
  - The experience of in-house RBQM tools can be extended and applied to future studies
  - Handle complex trials
  - Reduce cost

Approach

- Related **regulatory documents**

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 November 2013
EMA/269011/2013
Compliance and Inspection

Reflection paper on risk based quality management in clinical trials

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

16 June 2017
EMA/729273/2016
Committees and Inspections

Final summary record – EDC systems and risk-based monitoring in Clinical Trials

E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1)

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

March 2018
Procedural

OMB Control No. 0910-0843
Current expiration date available at https://www.reginfo.gov
(Search ICR and enter OMB control number 0910-0843)
See additional PRA statement in section 9 of this guidance.

Guidance for Industry

Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring

A Risk-Based Approach to Monitoring of Clinical Investigations
Questions and Answers
Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Ansalan Stewart, 240-402-6631, ansalan.stewart@fda.hhs.gov; (CBER) Outreach and Development, 800-835-4709 or 240-402-8010; (CDRH) Office of the Center Director, CDRHClinicalEvidence@fda.hhs.gov; Office of Good Clinical Practice, 301-796-8340; or Office of Regulatory Affairs (ORA) ORAHQBIMOInspectionPOC@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biological Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Office of Good Clinical Practice (OGCP)
Office of Regulatory Affairs (ORA)

March 2019
Procedural

Approach

- Consult with other **NINDS DCCs** for advice

Thanks **Dr. Christopher Coffey, Dr. Janel Fedler, Ms. Dixie Ecklund** from NeuroNEXT studies at The University of Iowa for sharing their risk-based monitoring experience and related documents.

Approach

- **Published papers** related to RBQM or centralized statistical monitoring
  - Kirkwood et al. Application of methods for central statistical monitoring in clinical trials, 2013
  - Fneish et al . Improving Risk Assessment in Clinical Trials: Toward a Systematic Risk-Based Monitoring Approach, 2021
  - Afroz et al. Risk-based centralized data monitoring of clinical trials at the time of COVID-19 pandemic, 2021
  - Hatayama, T. Yasui, S. Bayesian central statistical monitoring using finite mixture models in multicenter clinical trials, 2020
  - Koji Oba. Statistical challenges for central monitoring in clinical trials: a review, 2016
  - David Venet et al. A statistical approach to central monitoring of data quality in clinical trials, 2012

Approach

- Using **R Shiny** to build interactive web apps for **in-house RBQM**
  - Identify critical data/process and their potential risk
    - Site enrollment performance (enrollment rate or Poisson-gamma enrollment model)
    - Site protocol deviation rate
    - Primary and secondary endpoints – potential outliers, inliers etc.
    - Site adverse event/ serious adverse event
    - Check the correlation matrix for efficacy endpoints or vital signs
  - Apply appropriate statistical analysis methods to evaluate the risk
  - Control the potential risk by adding additional monitoring to problematic sites, SDV, initiating on-site visit

Centralized statistical monitoring

- **Supervised statistical monitoring**
  - Key risk indicator (KRI) clinical data variables identified as important, and monitored throughout the trial against pre-specified thresholds (Valdés-Márquez E, 2011)
  - KRI focus on relatively small number of variables and most likely to affect reliability/ safety
    - Generalizable
    - Trial-specific
    - Data availability
    - Finding driven
  - Each KRI, create a measure, find the extreme sites and calculate the summary score for each site based on all the KRIs
  - Drawbacks
    - Not suitable for longitudinal KRIs
    - Threshold is subjective and not generalizable
    - Require sites to have sufficient data

Centralized statistical monitoring

- **Unsupervised statistical monitoring**
  - Exploratory and data dependent (Hypothesis-free)
    - Check consistency between sites
    - Plausibility (outliers, inliers, patterns)
    - Statistical tests generate large number of p-values and summary score is calculated

      Data inconsistency score (DIS) (Buyse et al., 2020)

      $$DIS_i = \exp\left(\frac{1}{\sum_{j=1}^{N} w_j} \sum_{j=1}^{N} w_j log P_{ij}\right)$$

      w_j is the weight that accounts for the correlation between the tests

      P_{ij} is the p-value from the jth statistical test in center i

Unsupervised statistical monitoring

- Mahalanobis distance to detect **multivariate outliers or inliers**

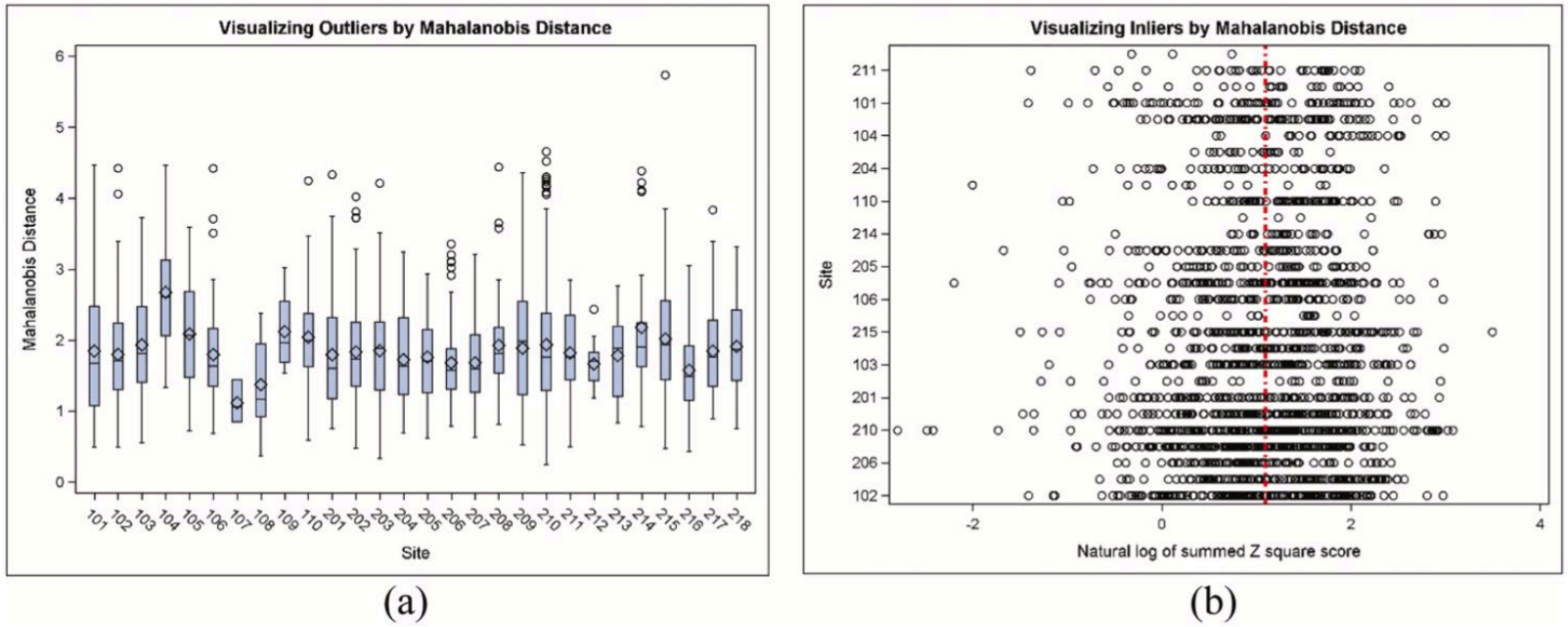


Fig. 5. Mahalanobis distance by study sites. (a) Large distance identified outliers, (b) Small distance determined inliers.

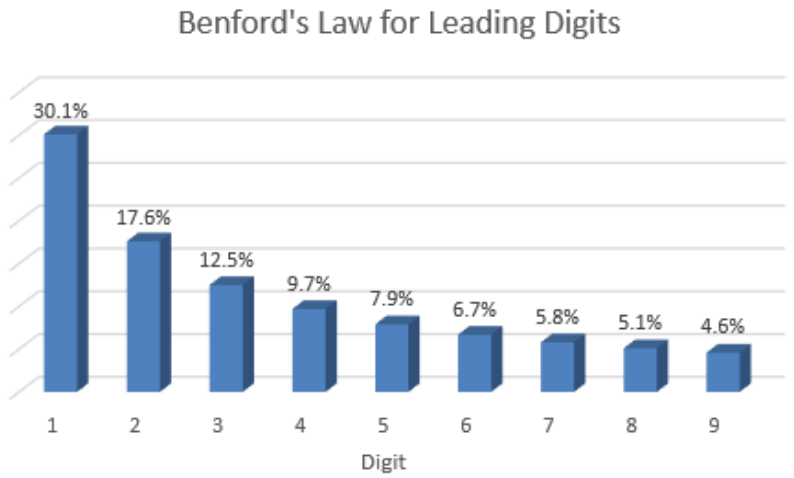
Afroz MA, Schwarber G, Bhuiyan MAN. Risk-based centralized data monitoring of clinical trials at the time of COVID-19 pandemic. Contemp Clin Trials. 2021;104:106368. doi:10.1016/j.cct.2021.106368

Unsupervised statistical monitoring

- **Digit preference**
  - Human nature favored specific digits during data fabrication.
  - When a terminal digit, either first or last, appeared more frequently than the other, it may be because of rounding to the nearest digit or data fabrication. Terminal digit analysis could help monitor the data quality and avoid data fraud or data errors.[1]
  - Chi-square goodness of fit
    - Benford's law p(d) = log10(1/d)

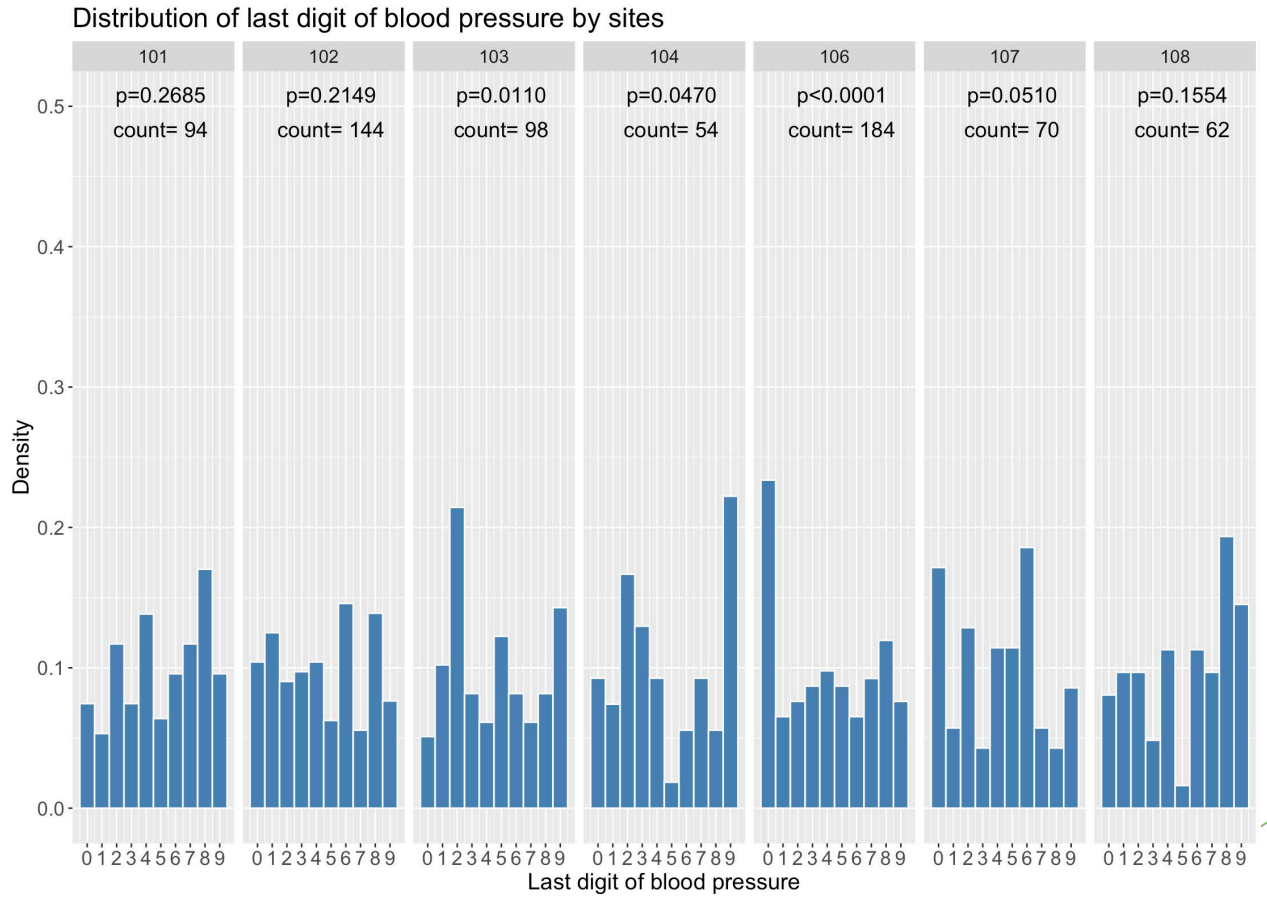
      Leading digits with smaller values

      occur more frequently than larger values.
    - Uniform distribution



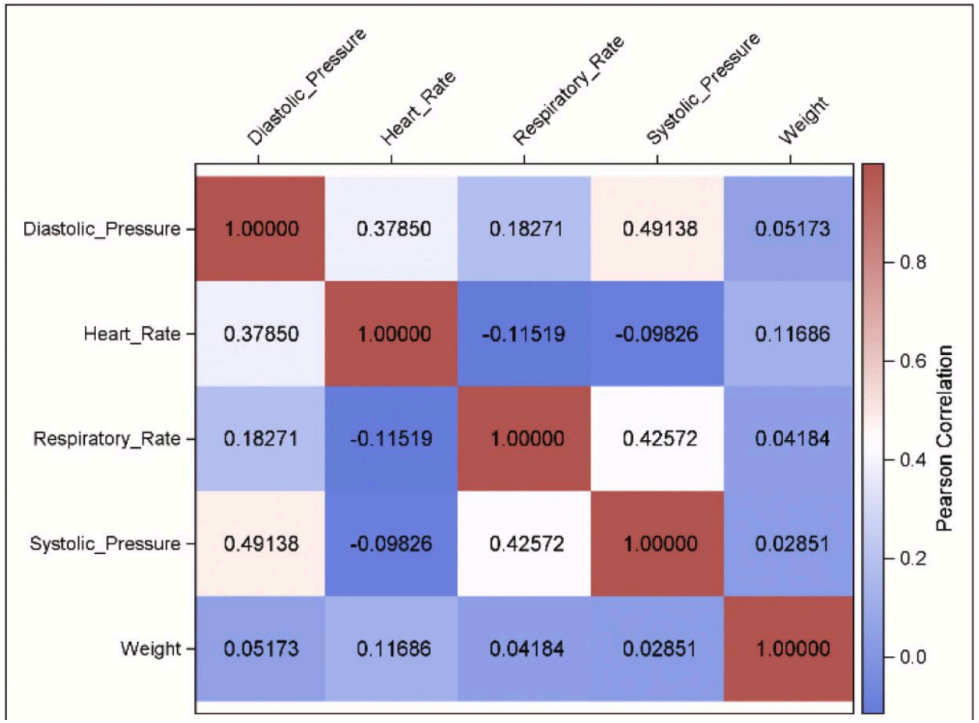
Unsupervised statistical monitoring

- **Digit preference**



Unsupervised statistical monitoring

- **Correlation checks -** compare the correlation matrix between sites or visits



Afroz MA, Schwarber G, Bhuiyan MAN. Risk-based centralized data monitoring of clinical trials at the time of COVID-19 pandemic. Contemp Clin Trials. 2021;104:106368. doi:10.1016/j.cct.2021.106368

Unsupervised statistical monitoring

- **Linear mixed-effect model** to compare variable mean (Desmet et al. 2014)

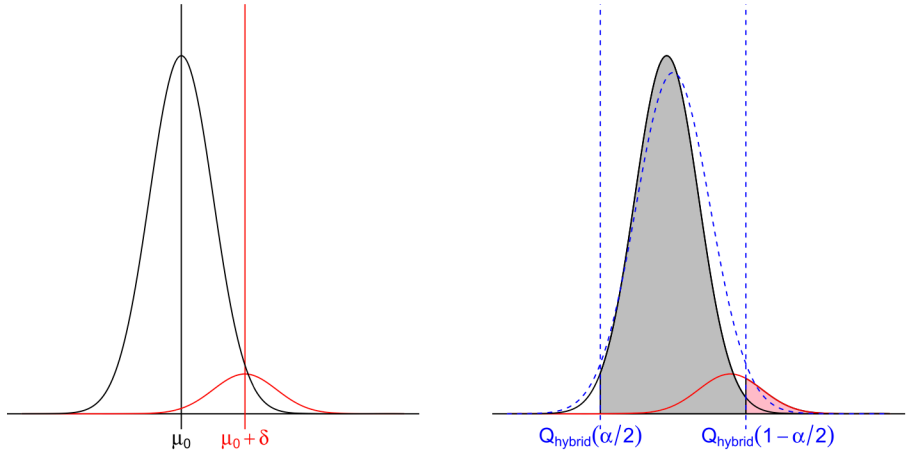


Figure 1. Left panel: densities of the null and the alternative models, each scaled according to their weight in the mixture (90% and 10%, respectively, in this example). Right panel: same, with hybrid density added (dashed line); the vertical lines are the 0.025 and 0.975 quantiles with respect to this density; power and specificity are the shaded areas under the alternative density curve and the null density curve, respectively.

Desmet L, Venet D, Doffagne E, et al. Linear mixed-effects models for central statistical monitoring of multicenter clinical trials. Stat Med. 2014;33(30):5265-5279. doi:10.1002/sim.6294

Unsupervised statistical monitoring

- **Linear mixed-effect model** to compare variable mean
  - Linear mixed-effect model for clustered data

$$y_{ij} = \mu + \gamma_i + \epsilon_{ij}$$

y_{ij} variable from site i and subject j

μ fixed effect

γ_i random site effect, $i.i.d.N(0, \sigma_s^2)$

ϵ_{ij} random residual error, $i.i.d.N(0, \sigma_r^2)$

  - $For\ each\ site, \bar{y}_{i\bullet} = \frac{1}{N_i}\sum_{j=1}^{N_i} y_{ij} \sim N(\mu, \sigma_s^2 + \frac{\sigma_r^2}{N_i})$
    - Estimation step: estimate the hybrid model from all data, using linear mixed effect model
    - Evaluation step: assign a p-value to each site using $\bar{y}_{i\bullet} - \hat{\mu}_{hybrid} \sim N(0, \hat{\sigma}_{s,hybrid}^2 + \frac{\hat{\sigma}_{r,hybrid}^2}{N_i})$
    - Detection step: flag sites according to the decision rule.

Desmet L, Venet D, Doffagne E, et al. Linear mixed-effects models for central statistical monitoring of multicenter clinical trials. Stat Med. 2014;33(30):5265-5279. doi:10.1002/sim.6294

Unsupervised statistical monitoring

- **Linear mixed-effect model** to compare variable mean
  - Cardiology trial, 2364 patients were recruited in 235 centers
  - Center 511, $p = 1.4 \times 10^{-6}$, and Center 815, $p = 5.5 \times 10^{-7}$

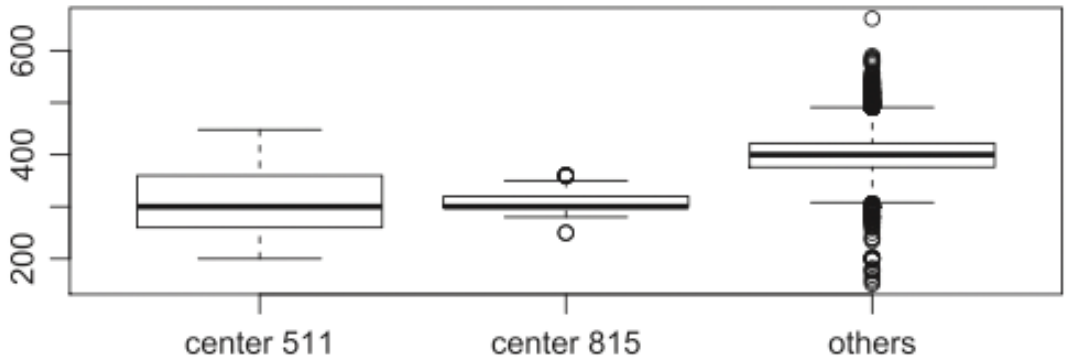


Figure 10. Boxplot of QT interval durations (in ms) in centers 511 and 815 compared with the other centers.

Desmet L, Venet D, Doffagne E, et al. Linear mixed-effects models for central statistical monitoring of multicenter clinical trials. Stat Med. 2014;33(30):5265-5279. doi:10.1002/sim.6294

Conclusion

- Continually improve our in-house RBQM as we learn more going forward
- NYU is running more and more DCCs, hopefully we can leverage what we developed for these other DCCs
- Great opportunity to provide training to graduate students in this aspect of running clinical trials

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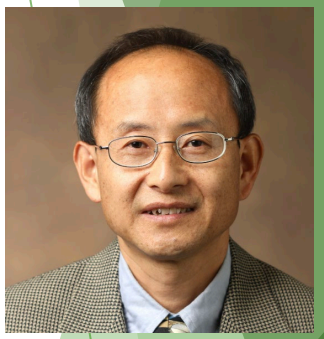
- This study was funded by NINDS
- I convey my sincere gratitude to
  - EPPIC-Net DCC team at New York University

Thaddeus Tarpey

Sharon B. Meropol

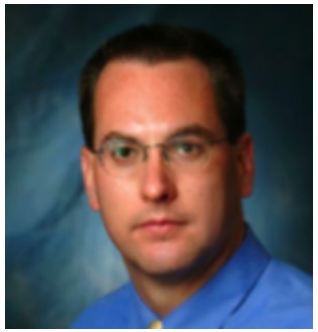
Charles Cleland

Hayley Belli



Yu Chang

  - NeuroNext DCC team at The University of Iowa



Christopher Coffey

Janel Fedler

Dixie Ecklund

Reference

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10. Desmet L, Venet D, Doffagne E, et al. Linear mixed-effects models for central statistical monitoring of multicenter clinical trials. Stat Med. 2014;33(30):5265-5279. doi:10.1002/sim.6294

Thank you!