A Description of a Collective Team Approach to Risk Based Monitoring

OBJECTIVE AND COI

To discuss an overview of the regulations and describe the various ways the University of Utah DCC fosters a team-approach to conduct monitoring

The presenters have no relevant conflicts of interests

COMPREHENSIVE CLINICAL & DATA COORDINATING CENTER

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- Grants/Budgets & Contract

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Regulations and Study Risks

Maryse Brulotte, B.Pharm, DESS, CCRA

ABOUT ME

- Director of Regulatory Affairs & Quality Assurance for over 5 years
- Past Experience - Pharmaceutical industry for over 20 years in clinical operations & project management
- Interests:
  - Clinical trial management & compliance
  - Process development and oversight
  - Hiking, biking, skiing, and travelling

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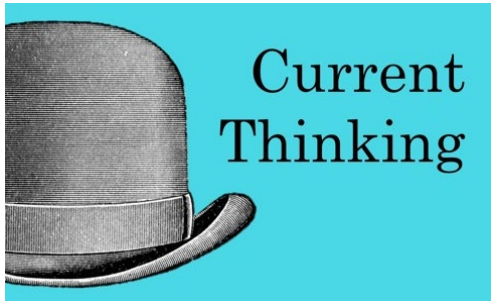
REGULATORY AGENCIES VS. ICH GUIDELINES

REGULATORY AGENCIES

U.S. **F**ood and **D**rug **A**dministration (FDA)

Code of Federal Regulations (CFRs)
legally binding procedures/requirements



Guidance Documents
recommendations

ICH GUIDELINES (Created in 1990)

International **C**ouncil for **H**armonization
of Technical Requirements
for Pharmaceuticals for Human Use

ICH's Mission: Facilitate the approval of products for human use worldwide.

Q – Quality
S – Safety
E – Efficacy
M - Multidisciplinary

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E6 GOOD CLINICAL PRACTICE (GCP)

- E6 GCPs
  - accepted by regulatory agencies worldwide
  - avoid potential approval delays of drugs globally
- Evolution of ICH & FDA guidance
  - risk-based quality management (RBQM) guidance
- DCC assessment of the overall risk of a study

ICH E6 GCPs: 1996, (R2) 2016, (R3) UNDERWAY

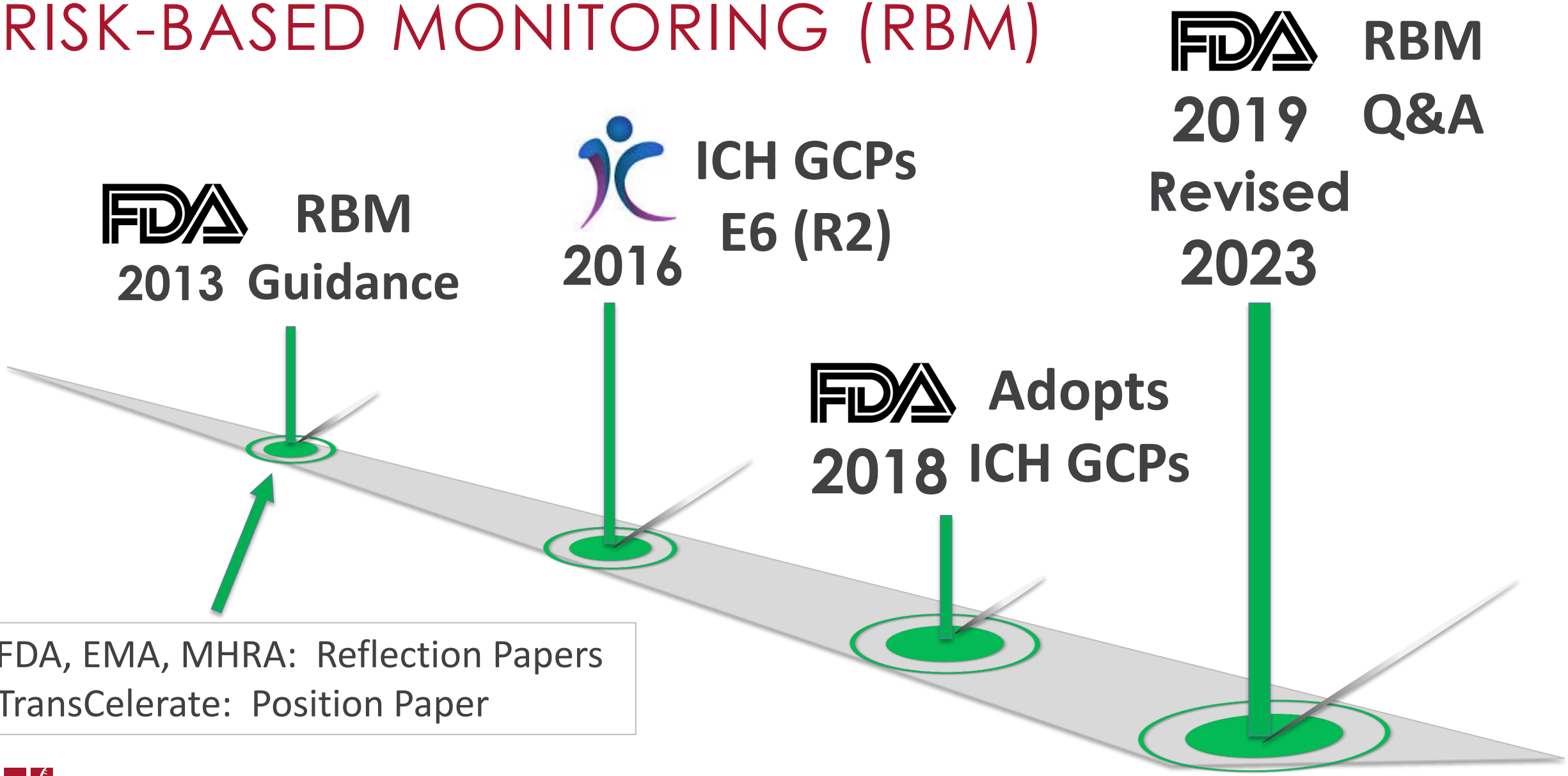
- Expert working groups
- Consensus-building process

VOTING MEMBERS	NON-VOTING MEMBERS
DEPARTMENT OF HEALTH & HUMAN SERVICES • USA FDA 厚生労働省 Ministry of Health, Labour and Welfare EUROPEAN MEDICINES AGENCY SCIENCE MEDICINES HEALTH	• Regulatory Agencies • Pharmaceutical industry • Academia • Patient / Consumer Groups • Others

U.S. NATIONAL INSTITUTES OF HEALTH (NIH)
NIH – FUNDED CLINICAL STUDIES

- NIH-funded studies conducted per E6(R2) GCPs
- 2017 NIH Policy on GCP training for NIH Awardees involved in NIH-funded clinical studies

RISK-BASED MONITORING (RBM)



FDA, EMA, MHRA: Reflection Papers
TransCelerate: Position Paper

OVERALL STUDY RISK LEVEL (SRL)

Why do we assess SRL?

To guide how much
source data monitoring should be done.

study less "risky" = less monitoring
study more "risky" = more monitoring

SRL scale (overall risk of the study) = Low – Medium – High

STUDY RISK LEVEL (SRL) TOOL WITH GUIDANCE

Study Aspect	Questions for Discussion	Role of Primary Assessor
Complexity of Study Design	Does the protocol study design increase overall study risks? Randomization? Intervention blinded? For registry studies, consider if the data will eventually be linked to higher risk studies (requiring more robust data) as well as the overall study duration and/or other complexities.	Statistician
Complexity of Procedures	Does the protocol require any complex or uncommon procedures beyond the usual standard of care (SOC) for the population being studied?	Medical

Guiding Examples Only
Up/downgrade per Study Team overa
For example, a very simple adaptive s

HIGH:
Adaptive, stratified, and/or other complex
Multi-interventional blinded investigational

MEDIUM:
Cross-over randomized study design.
Kitted blinded investigational drug; risk of

LOW:
Standard parallel RCT study design. Blinde
No randomization. No blinding; open-label

STUDY ASPECTS INCLUDED IN THE SRL

Assessment of the overall risk of the study

FDA Guidance
August 2013
Section IV.C.
&
April 2023 Q3

- **Complexity of Study Design**
- **Clinical Complexity of the Study**
- **Relative Experience of Investigators and Sponsor**
- **Adequate Staffing to Support the Investigation**
- **Electronic Data Capture**
- **Stage of the Study**
- **Quantity of Data**

RISK-BASED MONITORING STRATEGY

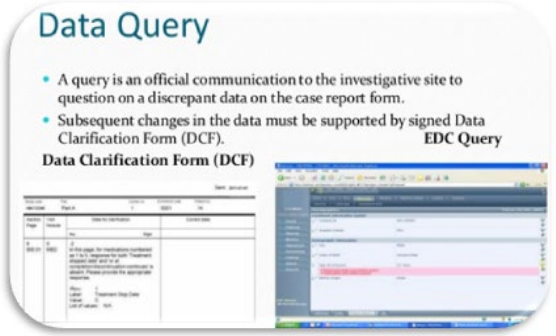
OVERALL RISK OF A STUDY
(Study Risk Level)

RISKS TO CRITICAL DATA/PROCESSES INCLUDED IN THE STUDY (RARM)

Risk-Based Monitoring Strategy/Plan

Source Document Review

Data Analysis (reports)



Database Data Query

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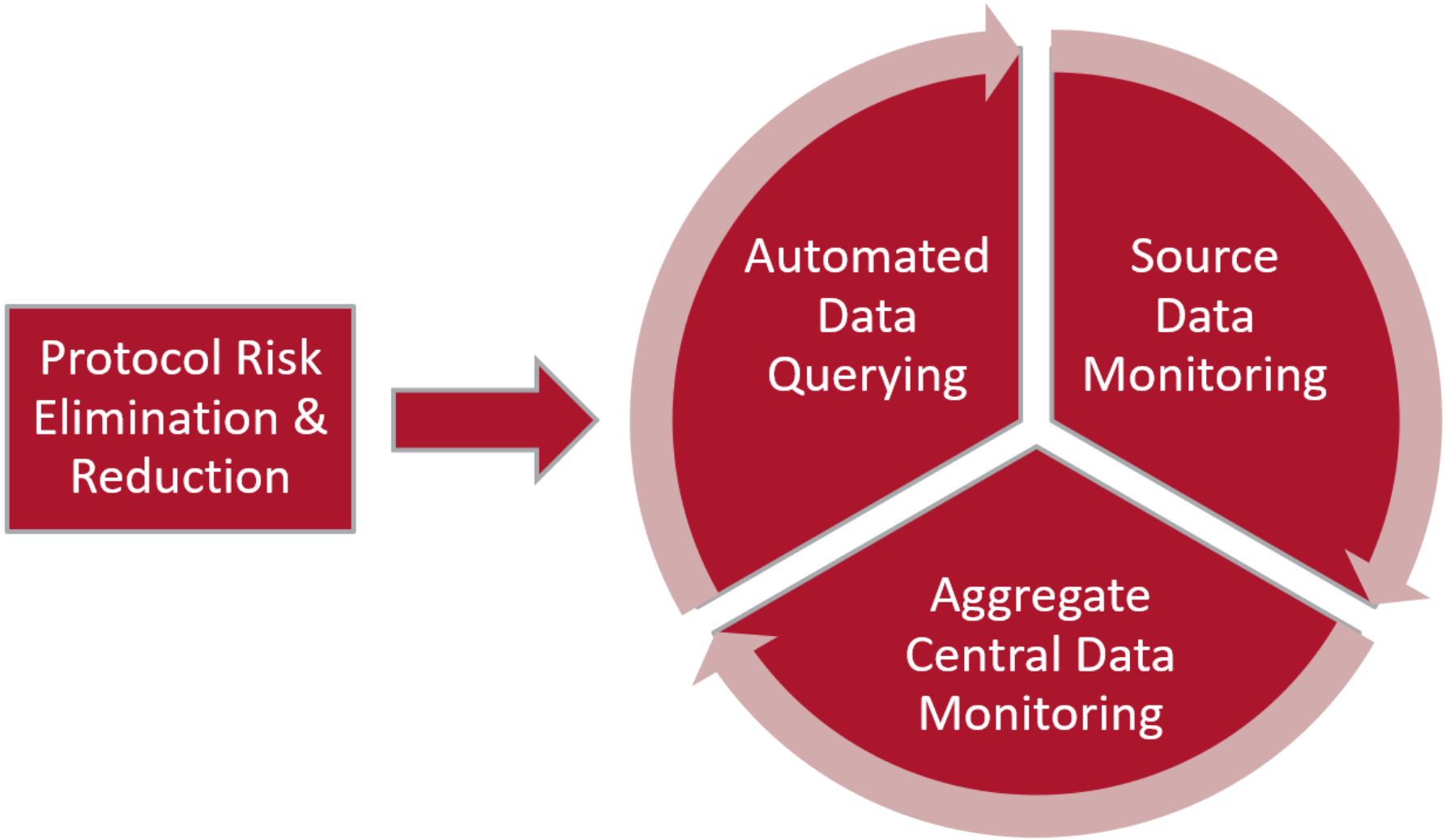
VISUAL REPRESENTATION OF ACTIVITIES



Data Discrepancies and Study Risks

Larry Cook, PhD

LARRY COOK, PHD

- Professor of Pediatric Critical Care and statistician
- CRTs, decision rules, probabilistic linkage, exact statistics
- Cycling, Arsenal, and Bayern Munich

STUDY RISKS

- Once the study risk level has been determined the next task is to identify study specific risks and threats in terms of
  - Participants
  - Data integrity
  - Study operations
- De-risking the protocol

RISK BASED APPROACH

We developed a Risk Assessment and Risk Management (RARM) tool to implement this concept

Risk Short Name	04. Low enrollment
Research Component	06. Screening and Enrollment
Risk Description	Inability to enroll at least 1,000 patients in 3 years. Enrolled patients are those who are randomized and received platelets.
Initial Risk Category	Critical
De-Risking Decision	Accept
De-Risking Summary	
Final Risk Category	Critical
Study Conduct Status	Pre Study Conduct
Risk Status	RM
Likelihood	3 Probable
Impact	5 High
Risk Score	15
Detectability	1 Highly Detectable
Key Risk Indicator	Number of randomized patients who received platelets (eligible for analysis) / expected number of randomized patients who received platelets. Expected number of patients is calculated as the current proportion of time enrolling (out of expected 3 years) * 1000

VanBuren JM, Roalstad S, Kay M, et al., (2022). Development of a risk assessment and risk management tool for an academic research organization, Contemporary Clinical Trials, 119(106812)

GOALS FOR THE RARM

- Useable by non-quality experts
- All team members can contribute regardless of role
  - Statisticians, data managers, project managers, director
- Transition of risk assessment (pre-enrollment) to risk management (post-enrollment)

As Simple as
3 : 3 : 3

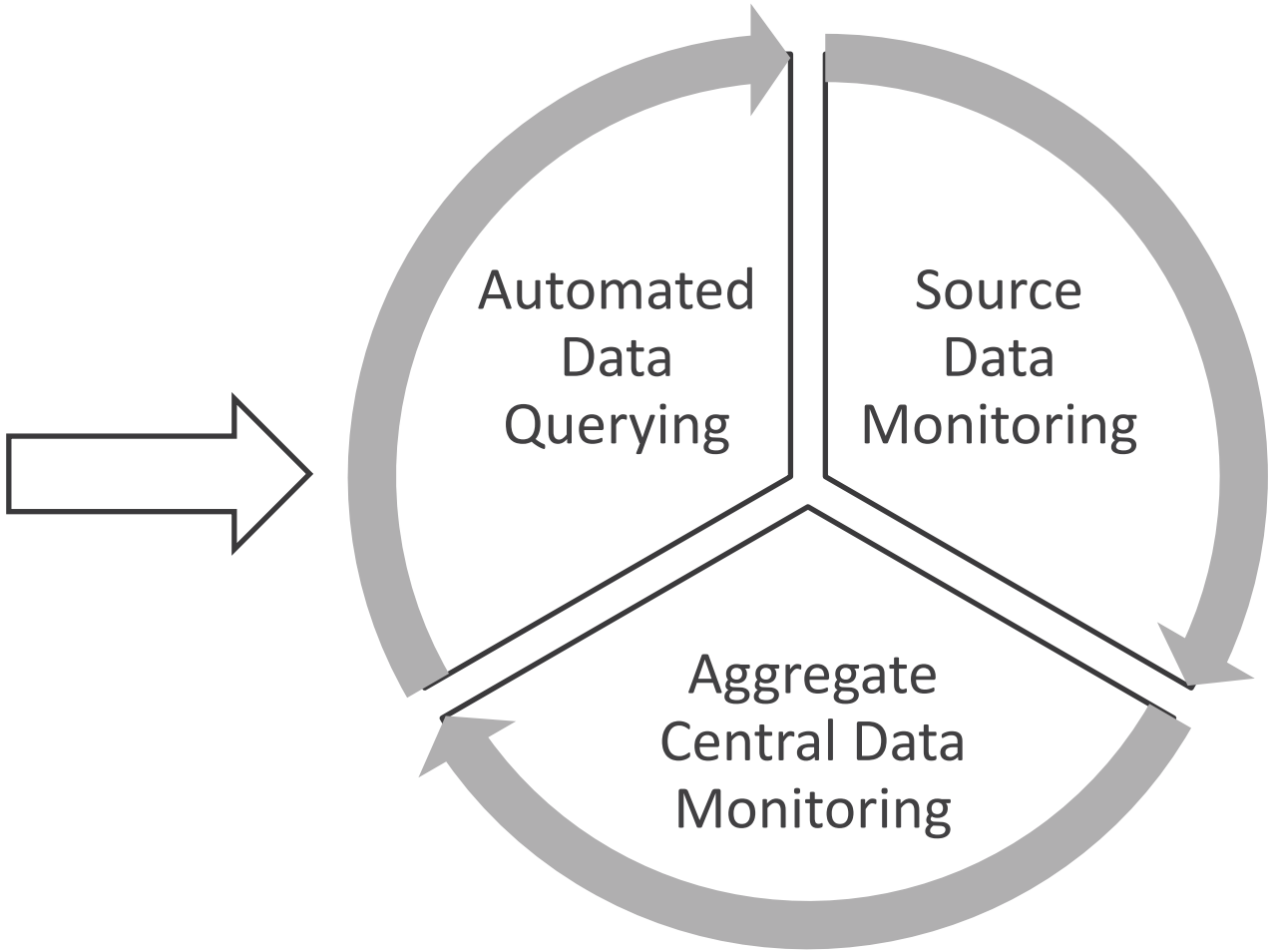

As Simple as
3 : 3 : 3
Impact
• Operations
• Subjects
• Data
Severity
• Critical
• Heightened
• Standard
Actions
• Eliminate
• Reduce
• Accept

Timing and Action

- Intervention point
  - Pre-enrollment
  - During enrollment
- Intervention Action
  - Change the protocol
  - Monitor

DE-RISKING TECHNIQUES

Protocol Risk Elimination & Reduction



EXAMPLE

- A multisite study will determine the relationship between autonomic, imaging, and blood biomarkers and the primary outcome
  - Autonomic: 70 minute protocol with specialized equipment collecting continuous streams of vital signs
  - Imaging: MRIs performed at the site
  - Blood: drawn at the site but stored at a central lab

CRITICAL RISKS

- Are there risks to the study and data related to collection of the biomarkers?
  - If testing, imaging, or draws are not done in a standardized fashion there will be added noise in the data potentially reducing power
- Can we reduce these risks in the pre-study phase?

PRE-STUDY INTERVENTIONS

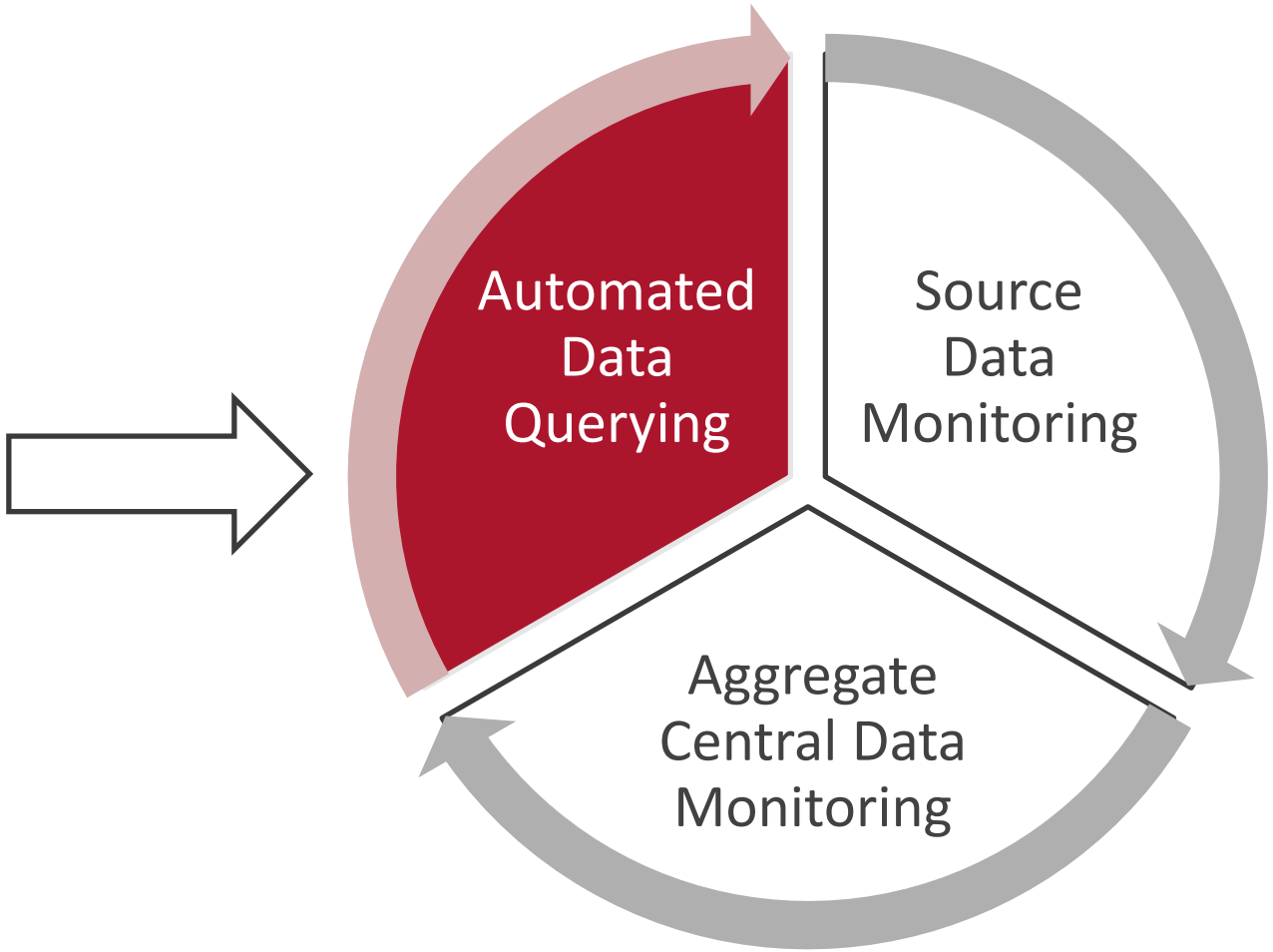
- Autonomic testing
  - Site visits to ensure correct installation of equipment
  - Each RC is required to perform five practice tests with the head of the autonomic core present
- Imaging
  - Each site required to scan phantoms
  - Central processing site
- Blood
  - Ensure the EDC collects the biorepository's Kit ID and the biorepository collects the Participant ID
- Have these risks been eliminated?

MANAGING RISKS DURING ENROLLMENT

- Autonomic:
  - RCs required to perform a minimum number of tests to remain certified
- Imaging:
  - Sites periodically submit phantom scans
- Blood:
  - Write a query to fire any time a participant is missing a kit or a kit is not connected to a subject

MONITORING TECHNIQUES

Protocol Risk Elimination & Reduction



QUERIES

- Goals
  - Identify data entry errors to reduce burden on other monitoring activities
  - Instantaneous monitoring (e.g., identify protocol deviations based on entered data)

BASIC QUERY CHECKS

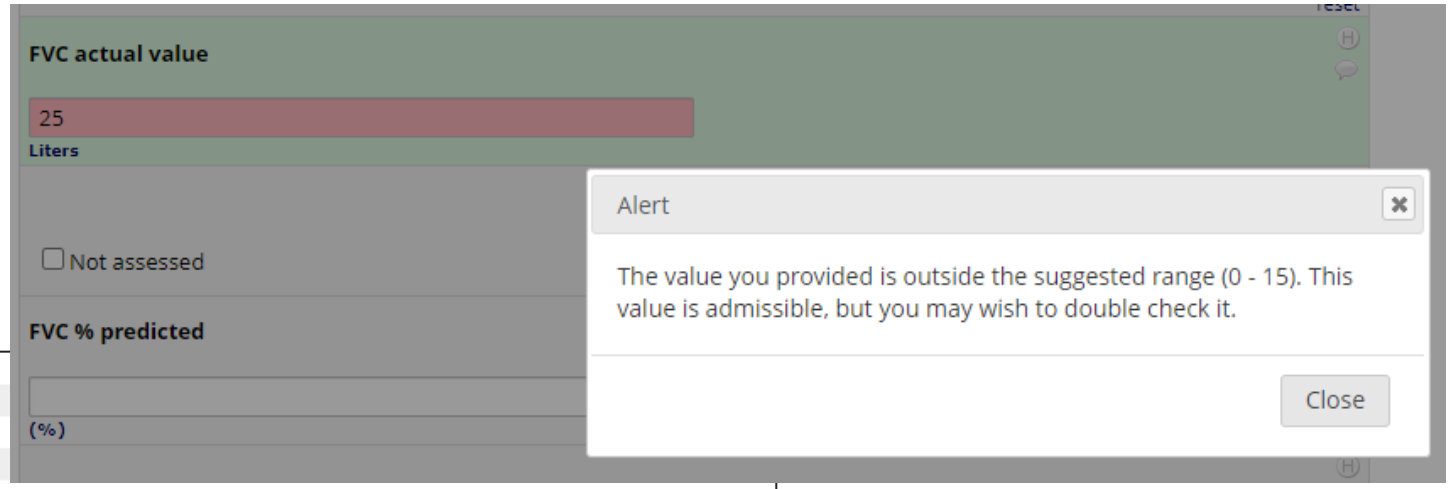
- Timeliness
  - Are data entered according to the expected timeline?
- Accuracy
  - Does the entered information match what is in the chart or EHR?
  - Is information consistent across forms?
- Missingness
  - Do required fields have data?

QUERY METHODS

- External query system
- Internal database checks
- Data checks

Missing mechanical ventilation end date/time

record_id	occurrence	Screening date	ventstopdtm
[redacted]-38	2	[redacted]	.
[redacted]-14	6	[redacted]	.



Subject ID:	160-25
QUERY ID:	1625931
SITE NAME:	UTAH
Study Event:	See query term
Form:	Rodnan Skin Score
Section:	Rodnan Skin Score
Header:	
QUERY TERM:	On the demographics and clinical characteristics form the question, [In your best clinical judgment, based on physician modified Rodnan skin score (mRSS), did this subject ever have diffuse cutaneous systemic sclerosis?] has been answered no. However, a response on the Rodnan Skin Score indicates that this subject may have diffuse cutaneous systemic sclerosis because an option other than uninvolved or unknown was selected on the upper arm, chest, abdomen, and/or thigh. Please review the Rodnan Skin Score form and update any fields if necessary. If the data is correct, request manual resolution. Do not update the demographics and clinical characteristics question. Study Event: 6 month follow-up

WHAT TO QUERY?

- Everything!
  - Huge burden on the clinical data manager
  - Time consuming
  - Delay study start/increase costs
- Can we prioritize query writing in a more systematic fashion?
  - Use the RARM

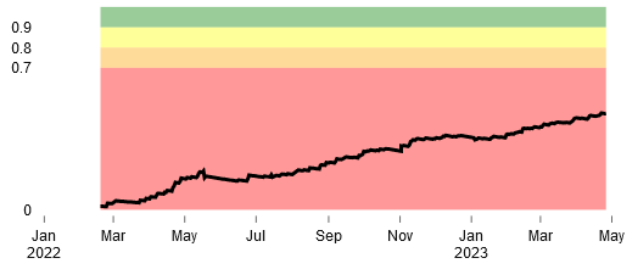
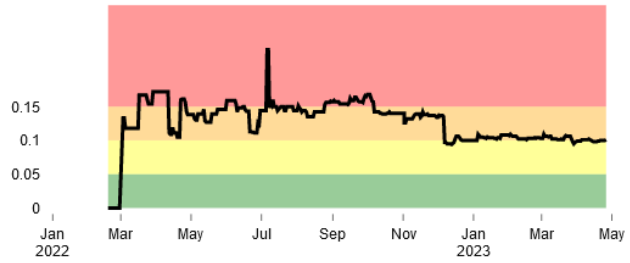
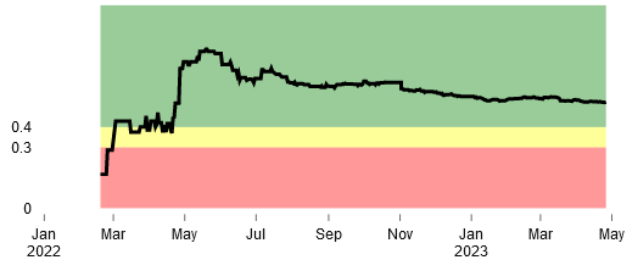
WHAT TO QUERY?

- Critical data elements
  - Protocolized items (blood collection windows, follow-up events, etc.)
  - Statistical Analysis Plan items related to primary and safety outcomes
  - Remaining risks from the RARM
- Study integrity (study procedures not before consent date and time)
- Everything else

MONITORING RISKS DURING ENROLLMENT

Define for each risk

- Key Risk Indicator
- Thresholds
- Actions for yellow, orange, and red
- Who is responsible for monitoring

Risk Description	Trend	Status
Current enrollment as a fraction of expected enrollment		0.475
Proportion of all lab draws that are out of window		0.101
Proportion of randomized subjects whose participation is not canceled who have received platelets		0.523

BENEFITS OF RARM PROCESS

- All team members are involved in the risk identification process
- Focuses attention and activities to areas most likely to impact the patient safety and the success of the study
- Develops methods for monitoring risks before enrollment
- Focuses query writing

Source Data Monitoring and Statistical Sampling Methods

Charlie Casper, PhD

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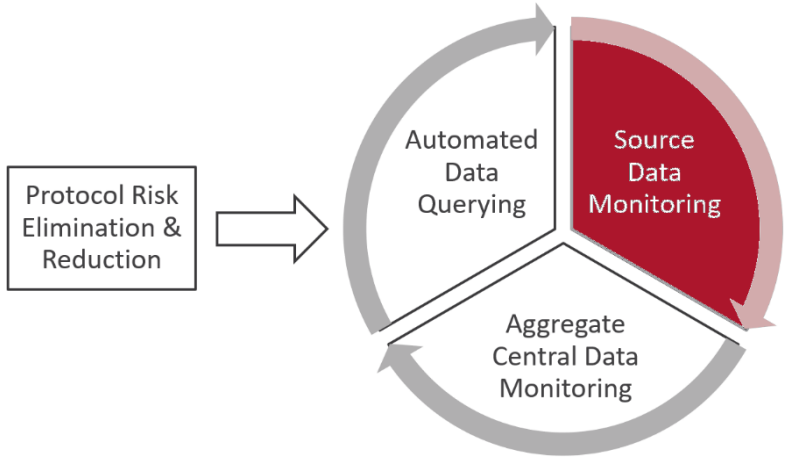
ABOUT ME

- Role at DCC: Faculty biostatistician
- Past Experience: Over 14 years with the Utah DCC, mainly with pediatric emergency medicine and pediatric multiple sclerosis networks
- Interests:
  - Clinical Trials (obviously)
  - Interim Monitoring
  - Fly fishing, tennis, and music

SOURCE DATA MONITORING



- 1988-2011: FDA guideline suggested source data verification (SDV)
  - Interpreted as a requirement for 100% SDV

Pros	Cons
Provides highest assurance of data accuracy	Time intensive and can often account for up to 30% of a trial's cost
	Likely, close to 99% of trial data are accurate
	Many inaccuracies that are present are in non-critical data points
	Unlikely to make much, if any, difference in trial conclusions

- 2011-2013: Replacement of guidance with risk-based approach

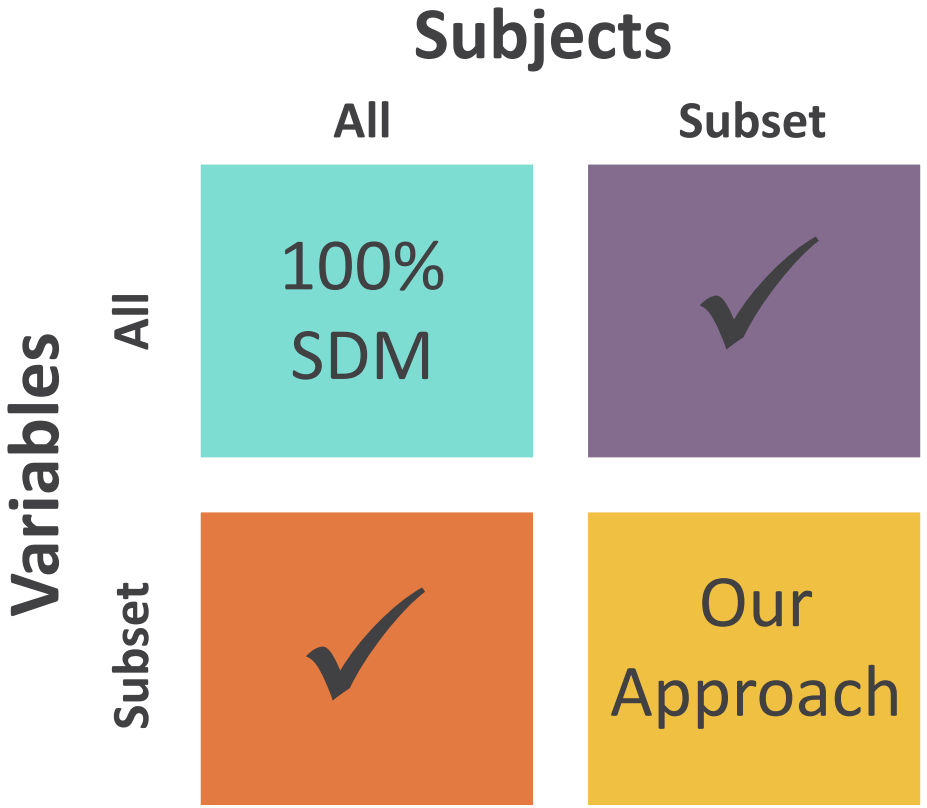
Sheets N, Wilson B, Benedict J, et al., (2014). Evaluating Source Data Verification as a Quality Control Measure in Clinical Trials, *Therapeutic Innovation & Regulatory Science,* 48(6):671-680.

INITIAL MONITORING

- Our usual approach early in the study
  - First participant (could be two, or more): 100% (or nearly) source data monitoring
    - This can identify issues that were not anticipated in trial and database design
  - If significant errors/issues identified, consider:
    - Monitoring one or more additional participants: 100%
      OR
    - Add to sampling of participants/CRFs

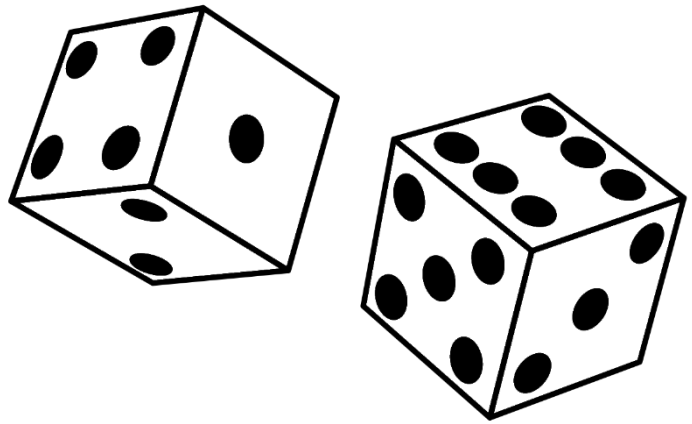
MONITORING SUBSETS

- Different approaches have been suggested:



SAMPLING

- Can be systematic or random
  - Systematic
    For example, every 10th patient
    But known patients! (sites can plan)
    And may not be representative
  - Random
    Unpredictable and representative



- Customized to fit needs of study
- Sampling is performed at set time points or "blocks" (e.g., every 6 months, or every 30 subjects at a site)
- A subject may be considered (available for sampling)
  - Only once when complete
  - At each time point when data become available

DETERMINE EXTENT OF MONITORING

Two main determining factors:

- Overall study risk level
  - Low – Medium – High

- Critical level of each variable/data element
  - From primary outcomes → down to non-critical elements

WHO ASSIGNS WEIGHTS FOR VARIABLES?

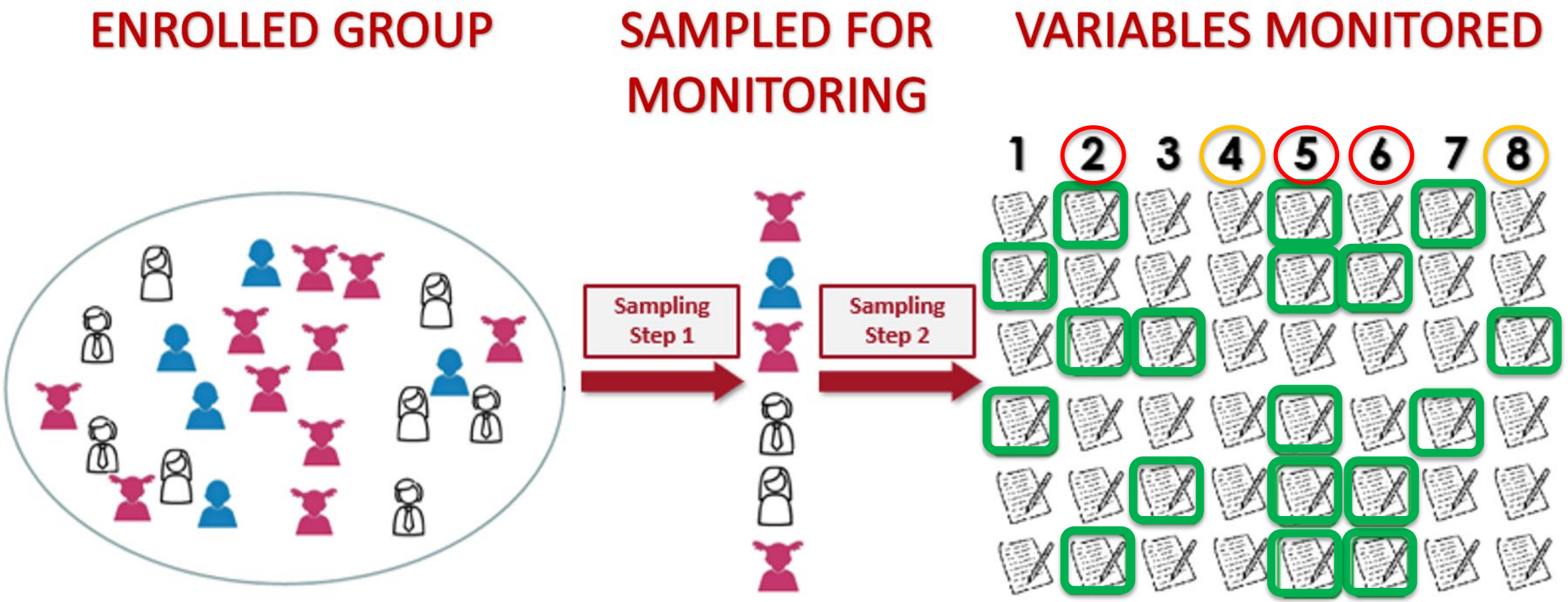
- Each project's **statistical team** is primarily given this responsibility
  - With input from other team members

- These must be based on the **Statistical Analysis Plan (SAP)**
  - Frequently, the perceived importance of items may not match what is *actually written* in the SAP

IMPORTANCE OF DATA ELEMENTS

Variable Type	Weight
Primary/secondary/safety outcome data Adverse events Eligibility Other critical data/processes	4
Exploratory outcomes Model covariates	2
Data for descriptive purposes only Only used for secondary manuscripts	1
No source to verify (e.g., patient-reported outcomes) Direct-from-source transfer No importance to trial Already planned for 100% SDV	0

SAMPLING DIAGRAM



CARRYING OUT MONITORING

- Example sample list

Subject ID	Variable 1	Variable 2	Variable 3	…
SITE-26	DepressLOC	Hypoglycemia	AbnRhythm	
SITE-30	Adherence	DepressLOC	AirIntervent	
SITE-5	TimeToDrug	Hypotension	CardArrhythm	

Variable	Data Element
DepressLOC	ED Arrival Date/Time
DepressLOC	GCS Score Baseline
DepressLOC	GCS Score Discharge
Hypotension	SBP
…	…

- May be on-site or remote-access
  - We are still talking about **source data**, not other kinds of remote monitoring
  - The benefits of on-site monitoring are
    - To observe the setting, physical access to documents, potential workflow issues
    - Have face-to-face interactions
    - On-site training

ADDITIONAL MONITORING

- If significant errors/issues identified, may
  - Monitor additional data forms/variables
    - May have extended monitoring schema
  - Investigate root causes and implement corrective actions
  - Document changes to monitoring

- Additional monitoring may also be necessary, for example, when there are staff changes or protocol amendments

NOTE: SAMPLING WITHOUT REPLACEMENT

- Our approach to monitoring:
  - Subjects are randomly selected to be monitored
  - Within each subject, variables are sampled according to assigned weights
- Statistical phenomenon due to sampling without replacement. Compared to what was intended:
  - Higher importance variables may be undersampled
  - Lower importance variables may be oversampled

A FEW EXAMPLE SIMULATIONS

Example Scenario	Number High/Med/Low Risk Variables	Relative Weight High/Med/Low Risk Variables	Prop Min/Extended Variables Monitored	Actual (bias)		
				High	Medium	Low
8	2/4/14	10/5/1	10%/20%	17.59% (-0.93%)	9.37% (0.11%)	1.95% (0.10%)
11	1/2/7	4/2/1	30%/40%	21.69% (-4.97%)	13.45% (0.11%)	7.34% (0.68%)
12	1/2/7	10/5/1	30%/40%	27.18% (-9.86%)	19.44% (0.93%)	4.85% (1.14%)
15	2/4/14	4/2/1	30%/40%	10.72% (-2.61%)	6.67% (0.00%)	3.71% (0.37%)
16	2/4/14	10/5/1	30%/40%	13.52% (-5.00%)	9.52% (0.26%)	2.49% (0.64%)

- Most of the time, this will not have a large impact
  - After all, these proportions and weights are somewhat arbitrary
  - But it is good to be aware and consider modifications

RECOMMENDATIONS

- Heavy monitoring early on to catch issues
- Sampled monitoring at subject and variable levels

Data	Participant(s) (per site)	Extent of Source Data Monitoring by Study Risk Level		
		High	Medium	Low
ICF & Consenting Process	<Enrolled, randomized, completed, other>	☐ 1st participant ☐ 1st participant with revised ICF ☐ 1st participant reconsented with a revised ICF ☐ all participants for whom Monitor is accessing medical records containing PHI ☐ other: <specify>		
All Data	<specify which participants>	100%	100%	100%
<specify data form(s) or data element(s)>	<specify which participants>	100%	100%	100%
Data Randomly Selected by Sampling	<First participant(s) <enrolled, randomized, completed, other>, or if significant errors or issues identified> **(Extended)**	75-100%	25-100%	0-50%
	<Subsequent participants> **(Minimum)**	15-40%	5-25%	0-15%

→ **RBMP**

CONCLUSIONS

- 100% source data monitoring is extremely costly and is overkill
- A risk-based approach to source data monitoring using random sampling at various levels achieves regulatory compliance
- The quantity of monitoring will depend on the risk level of the study/trial
- The ability to monitor smaller proportions of patients/variables hinges upon a multi-faceted review of data:
  - Automated data completeness and discrepancy queries
  - Central statistical and graphical monitoring
  - Coordinated effort to review aggregate automated reports

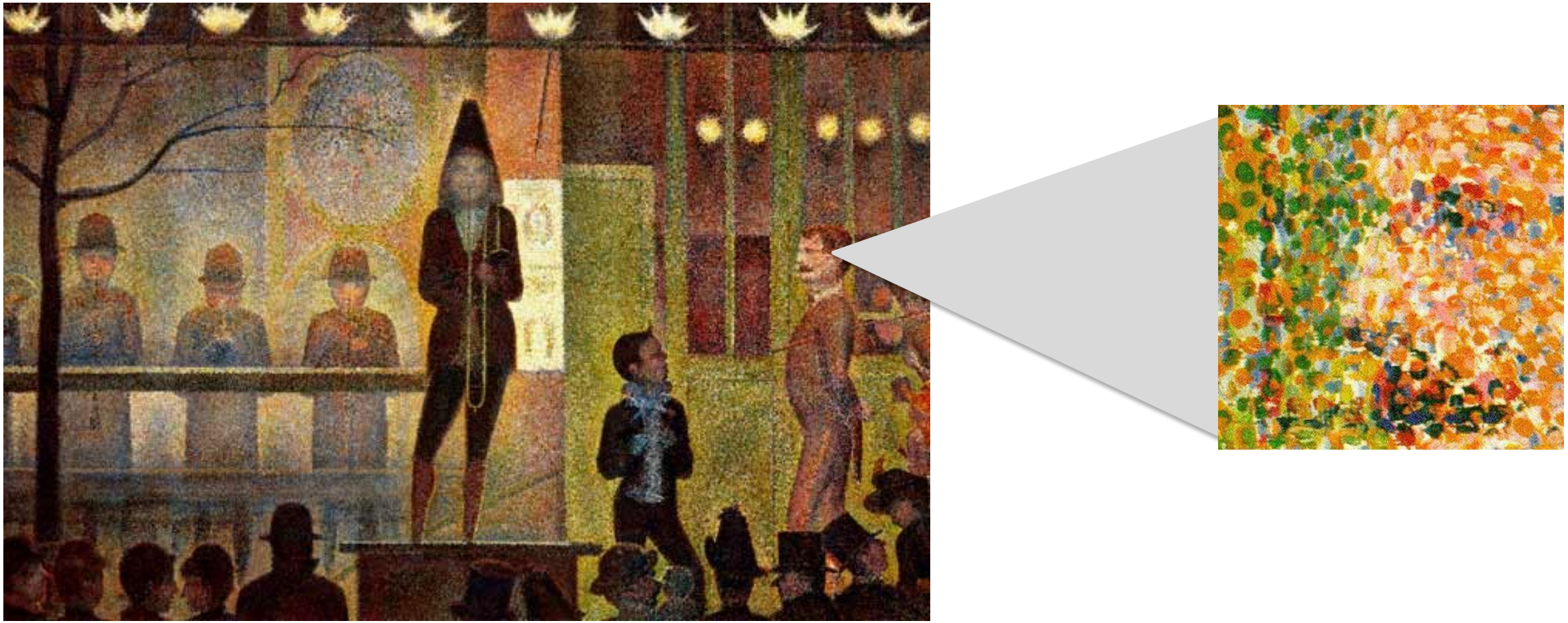
Statistical and Graphical Monitoring Methods

Jess Alvey, MS

ABOUT ME

- Biostatistician with DCC for 7 years
- Interests:
  - Clinical trial design
  - Analysis planning and execution
  - Yoga

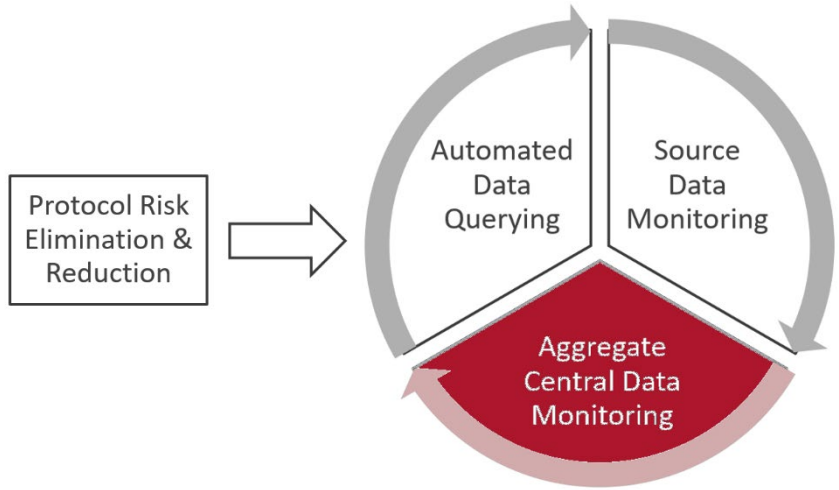
AN ANALOGY



http://www.weinerelementary.org/seurat.html; *La Parade du Cirque* by Georges Seurat

PURPOSE

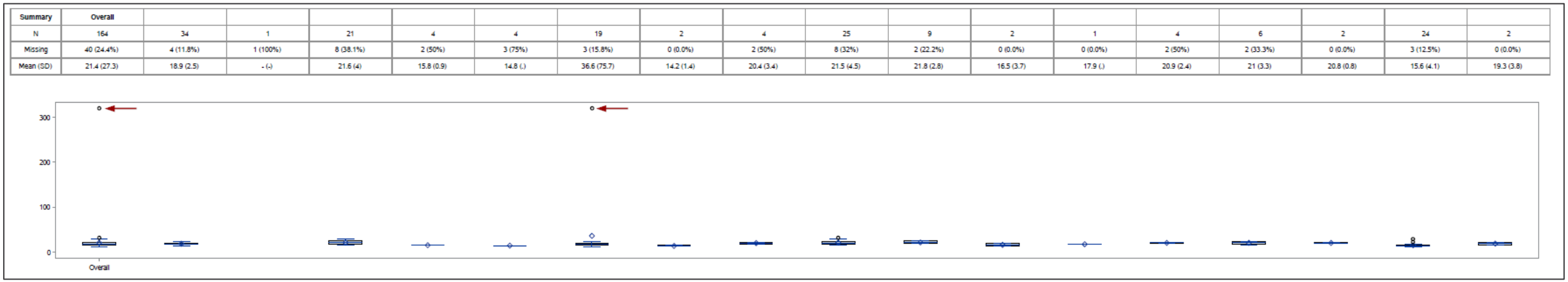
- Review data in aggregate as well as by groups of interest (e.g., clinical site) to
  - Identify outliers and systematic trends in data
  - Assess quality metrics of the study
  - Statistically evaluate data elements



OUTLIERS AND TRENDS

- Assess variables/outcomes by site
  - Determine whether outliers require further investigation
  - Identify possible trends and if they are warranted

Summary	Overall																		
N	164	34	1	21	4	4	19	2	4	25	9	2	1	4	6	2	24	2
Missing	40 (24.4%)	4 (11.8%)	1 (100%)	8 (38.1%)	2 (50%)	3 (75%)	3 (15.8%)	0 (0.0%)	2 (50%)	8 (32%)	2 (22.2%)	0 (0.0%)	0 (0.0%)	2 (50%)	2 (33.3%)	0 (0.0%)	3 (12.5%)	0 (0.0%)
Mean (SD)	21.4 (27.3)	18.9 (2.5)	- (-)	21.6 (4)	15.8 (0.9)	14.8 (.)	36.6 (75.7)	14.2 (1.4)	20.4 (3.4)	21.5 (4.5)	21.8 (2.8)	16.5 (3.7)	17.9 (.)	20.9 (2.4)	21 (3.3)	20.8 (0.8)	15.6 (4.1)	19.3 (3.8)



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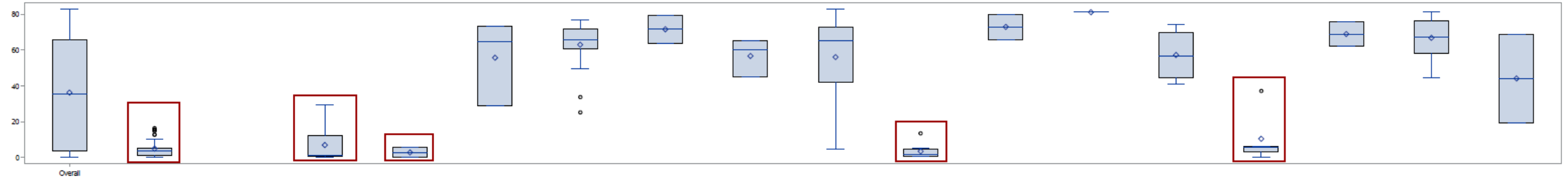
OUTLIERS AND TRENDS

Age at randomization (years)

Summary	Overall																	
N	164	34	1	21	4	4	19	2	4	25	9	2	1	4	6	2	24	2
Missing	10 (6.1%)	1 (2.9%)	1 (100%)	1 (4.8%)	1 (25%)	1 (25%)	0 (0.0%)	0 (0.0%)	1 (25%)	2 (8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (16.7%)	0 (0.0%)	1 (4.2%)	0 (0.0%)
Mean (SD)	36.2 (30.9)	5 (5.1)	- (-)	6.9 (9.6)	2.8 (2.6)	55.7 (23.5)	63 (13.6)	71.6 (11.2)	56.7 (10.5)	56.1 (20.6)	3.4 (4.1)	72.9 (10)	81.1 (.)	57.2 (15.3)	10.4 (15.1)	68.9 (9.9)	66.8 (10.7)	44.1 (35.1)



Absolute threshold of percentage difference = 40

Legend	2	10	20	30	≥ 40
Above Overall					
Below Overall					

Ethnicity	Overall																	
Hispanic or Latino	23 (14.0%)	5 (14.7%)	0 (0.0%)	0 (0.0%)	2 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (24.0%)	6 (66.7%)	1 (50.0%)	0 (0.0%)	0 (0.0%)	3 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Not Hispanic or Latino	133 (81.1%)	28 (82.4%)	1 (100.0%)	20 (95.2%)	2 (50.0%)	4 (100.0%)	19 (100.0%)	2 (100.0%)	2 (50.0%)	16 (64.0%)	2 (22.2%)	1 (50.0%)	1 (100.0%)	4 (100.0%)	3 (50.0%)	2 (100.0%)	24 (100.0%)	2 (100.0%)
Not Reported	8 (4.9%)	1 (2.9%)	0 (0.0%)	1 (4.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (50.0%)	3 (12.0%)	1 (11.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

QUALITY METRICS

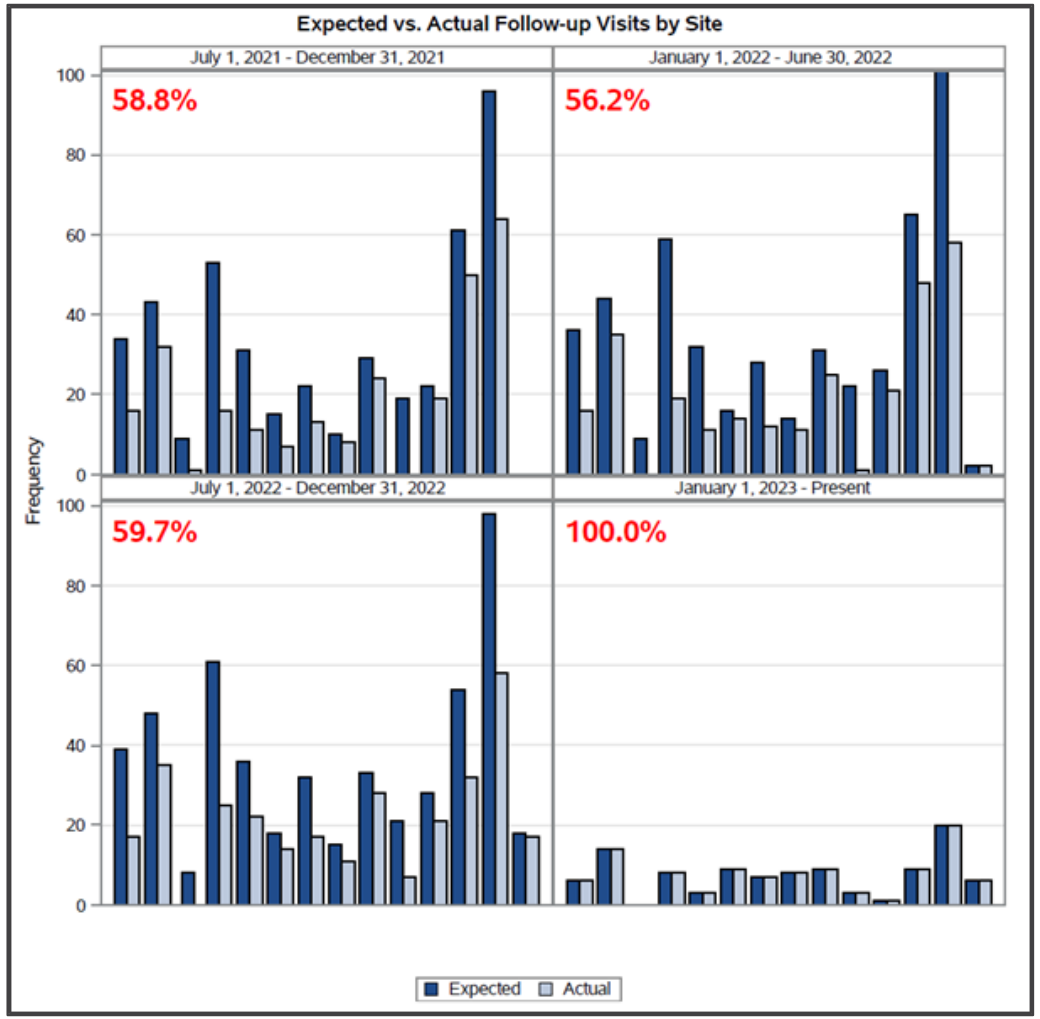
- Get a picture of study health:
  - Approach/consent rates
  - Follow-up rates
  - Protocolized procedures
  - Protocol deviations

Current Overall and Site-Level Enrollment

	Met Inclusion Criteria	Study Eligible[1]	Approached[2]	Consented[3]
Overall	755	744 (98.5%)	574 (77.2%)	377 (65.7%)
	46	46 (100.0%)	46 (100.0%)	46 (100.0%)
	100	100 (100.0%)	82 (82.0%)	38 (46.3%)
	19	19 (100.0%)	19 (100.0%)	8 (42.1%)
	15	15 (100.0%)	15 (100.0%)	15 (100.0%)
	187	185 (98.9%)	70 (37.8%)	38 (54.3%)
	14	14 (100.0%)	14 (100.0%)	14 (100.0%)
	60	55 (91.7%)	47 (85.5%)	13 (27.7%)
	0	0 (0.0%)	0 (0.0%)	0 (0.0%)
	39	39 (100.0%)	39 (100.0%)	39 (100.0%)
	33	33 (100.0%)	30 (90.9%)	20 (66.7%)
	6	6 (100.0%)	6 (100.0%)	6 (100.0%)

QUALITY METRICS

- Get a picture of study health:
  - Approach/consent rates
  - Follow-up rates
  - Protocolized procedures
  - Protocol deviations



QUALITY METRICS

- Get a picture of study health:
  - Approach/consent rates
  - Follow-up rates
  - Protocolized procedures
  - Protocol deviations

	Site 1	Site 2	Site 3	Site 4	Site 5
CBC					
Baseline					
Not completed	0 (0%)	5 (25%)	1 (5%)	1 (4%)	2 (8%)
Completed out of window	2 (5%)	3 (15%)	7 (32%)	15 (65%)	4 (15%)
15 minutes	2 (5%)	1 (5%)	3 (14%)	5 (22%)	1 (4%)
30 minutes	0 (0%)	0 (0%)	1 (5%)	2 (9%)	1 (4%)
45 minutes	0 (0%)	0 (0%)	1 (5%)	2 (9%)	2 (8%)
60 minutes	0 (0%)	0 (0%)	1 (5%)	1 (4%)	0 (0%)
> 60 minutes	0 (0%)	2 (10%)	1 (5%)	5 (22%)	0 (0%)
6 Hours					
Not completed	0 (0%)	0 (0%)	1 (5%)	0 (0%)	1 (4%)
Completed out of window	4 (10%)	2 (10%)	0 (0%)	2 (9%)	0 (0%)
30 minutes	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
1 hour	1 (2%)	0 (0%)	0 (0%)	1 (4%)	0 (0%)
1.5 hours	0 (0%)	2 (10%)	0 (0%)	0 (0%)	0 (0%)
2 hours	2 (5%)	0 (0%)	0 (0%)	1 (4%)	0 (0%)
> 2 hours	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

QUALITY METRICS

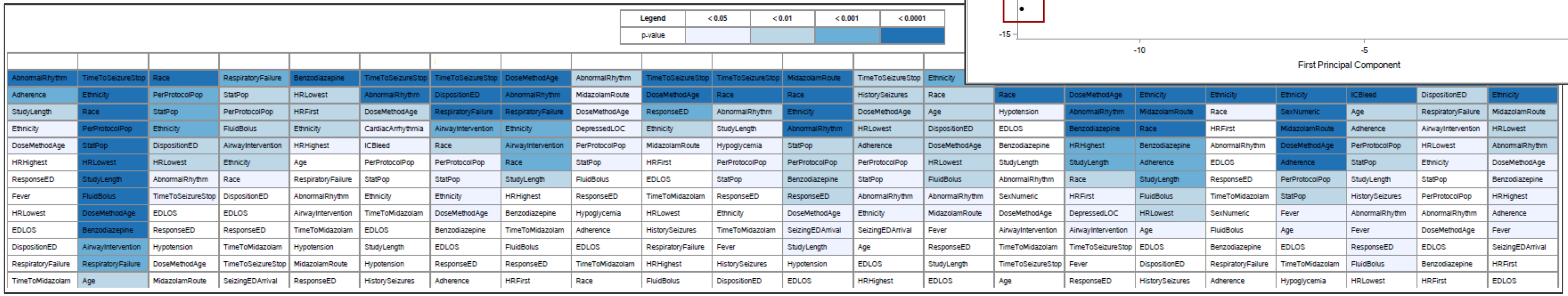
- Get a picture of study health:
  - Approach/consent rates
  - Follow-up rates
  - Protocolized procedures
  - Protocol deviations

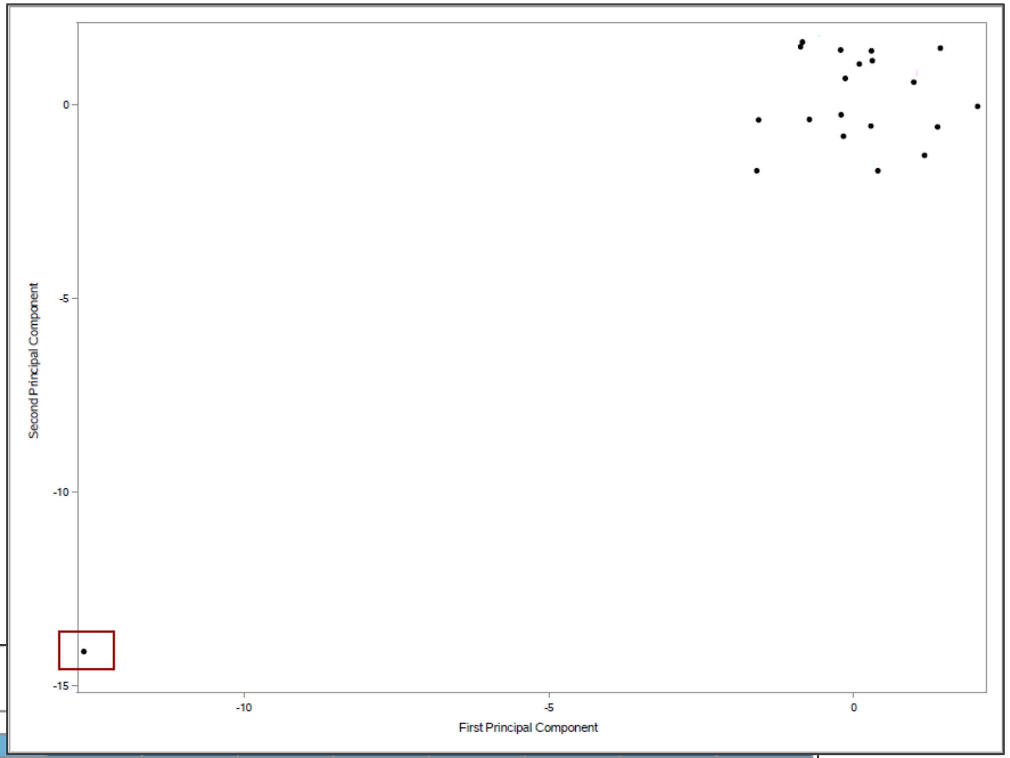
Protocol Deviations

	Grand Tot..					
	(N = 34)	(N = 0)	(N = 0)	(N = 0)	(N = 2)	(N = 0)
Significant impact to human subject protection or reliability of trial results	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (50.0%)	0 (0.0%)
Intended to eliminate apparent immediate hazard to a research participant	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Resulted in an unanticipated problem with significant or potentially significant impact on human subject protection or reliability of trial..	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (50.0%)	0 (0.0%)
Deviation type						
Blinding	2 (5.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (50.0%)	0 (0.0%)
Breach of Confidentiality	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Concomitant Medication/Therapy	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Eligibility	2 (5.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Informed Consent	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Study Platelets (Dose, administration, delivery)	3 (8.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (50.0%)	0 (0.0%)
Randomization	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Regulatory	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Safety Matter/Reporting	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Study Procedure (Labs & Samples)	26 (76.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Study Procedure (Clinical Assessments)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Visit or Visit Window Missed	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Withdrawal	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

STATISTICAL EVALUATION

- Considerations for centralized statistical monitoring (sample size, number of sites)





Pogue JM, Devereaux PJ, Thorlund K, Yusuf S. Central Statistical Monitoring: Detecting fraud in clinical trials. *Clinical Trials*. 2013;10(2):225-235. doi:10.1177/1740774512469312

Venet D, Doffagne E, Burzykowski T, et al. A statistical approach to central monitoring of data quality in clinical trials. *Clin Trials*. 2012;9(6):705-713. doi:10.1177/1740774512447898

STATISTICAL EVALUATION

- Summarize data discrepancies that are not easily evaluated by rules

Duplicate lab times - CBC

Study subject ID	Lab date/time	Screening date
4	27JAN23:16:18:00	12JAN23
4	27JAN23:16:18:00	12JAN23
7	02DEC22:00:26:00	23NOV22
7	02DEC22:00:26:00	23NOV22
15	04FEB22:02:26:00	25JAN22
15	04FEB22:02:26:00	25JAN22
10	01AUG22:09:35:00	24JUN22
10	01AUG22:09:35:00	24JUN22

Randomization date/time is after surgery start date/time

Study subject ID	Surgery start date/time	randomizedttime
33	27JAN23:09:30:00	27JAN2023:10:30:00.000

No mechanical ventilation entry that starts on the same day as surgery

Study subject ID	Surgery start date/time
2	01NOV22:09:24:00
19	13DEC22:08:30:00
31	01FEB23:08:02:00

DISSEMINATION

- When should you use a dashboard?
  - Internal vs. external audience
  - Filterability – there may be some limitations in statistical output

CONCLUSION

https://en.wikipedia.org/wiki/A_Sunday_Afternoon_on_the_Island_of_La_Grande_Jatte

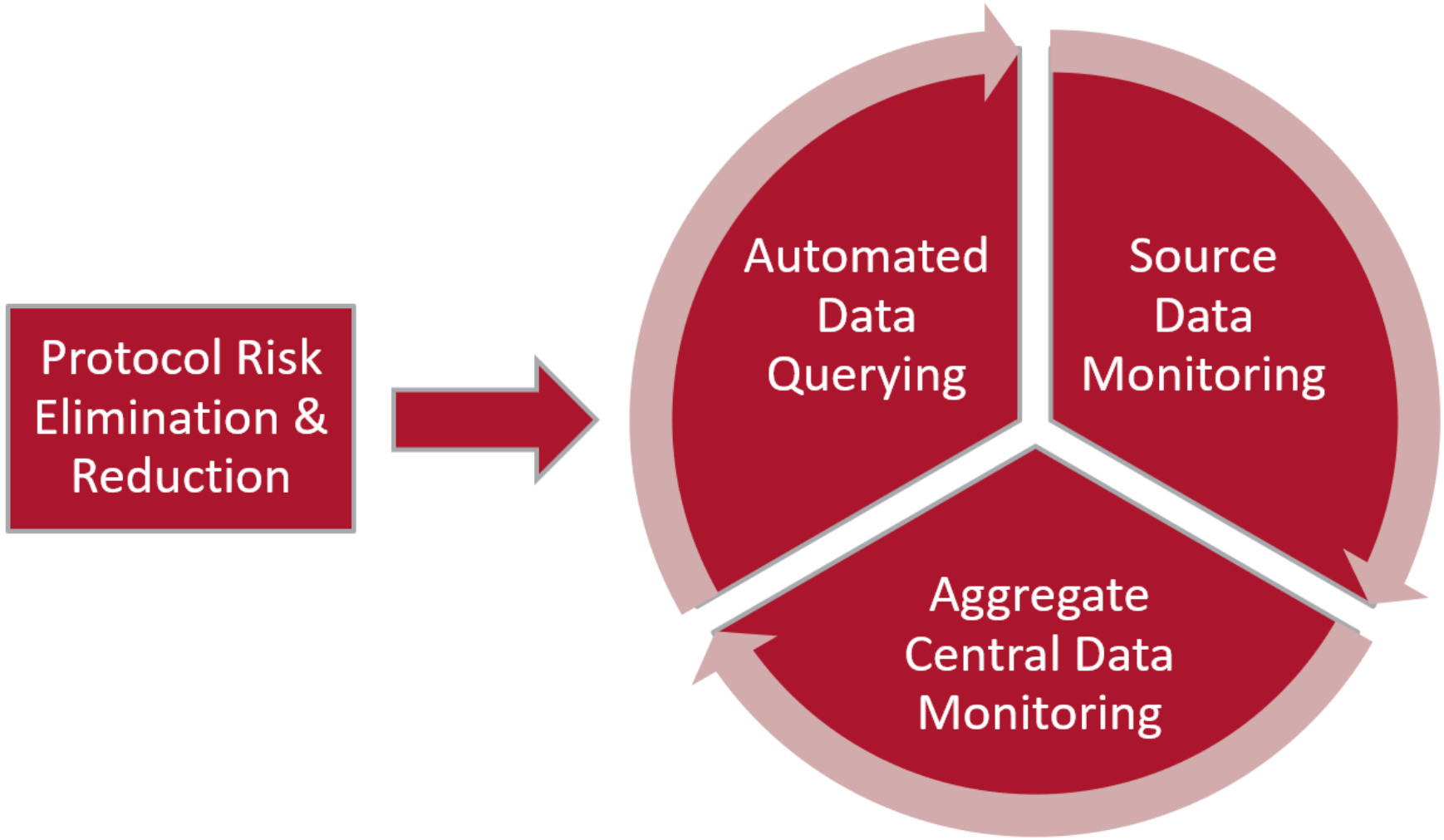
Overall Study Monitoring

John VanBuren, PhD

ABOUT ME

- Role at DCC: Faculty biostatistician
- Past Experience: Clinical trials, observational studies, rare disease registry
- Interests:
  - Adaptive designs
  - Statistical monitoring
  - Team structure and dynamics
  - Construction projects

MONITORING TECHNIQUES



STUDY REPORT LIST

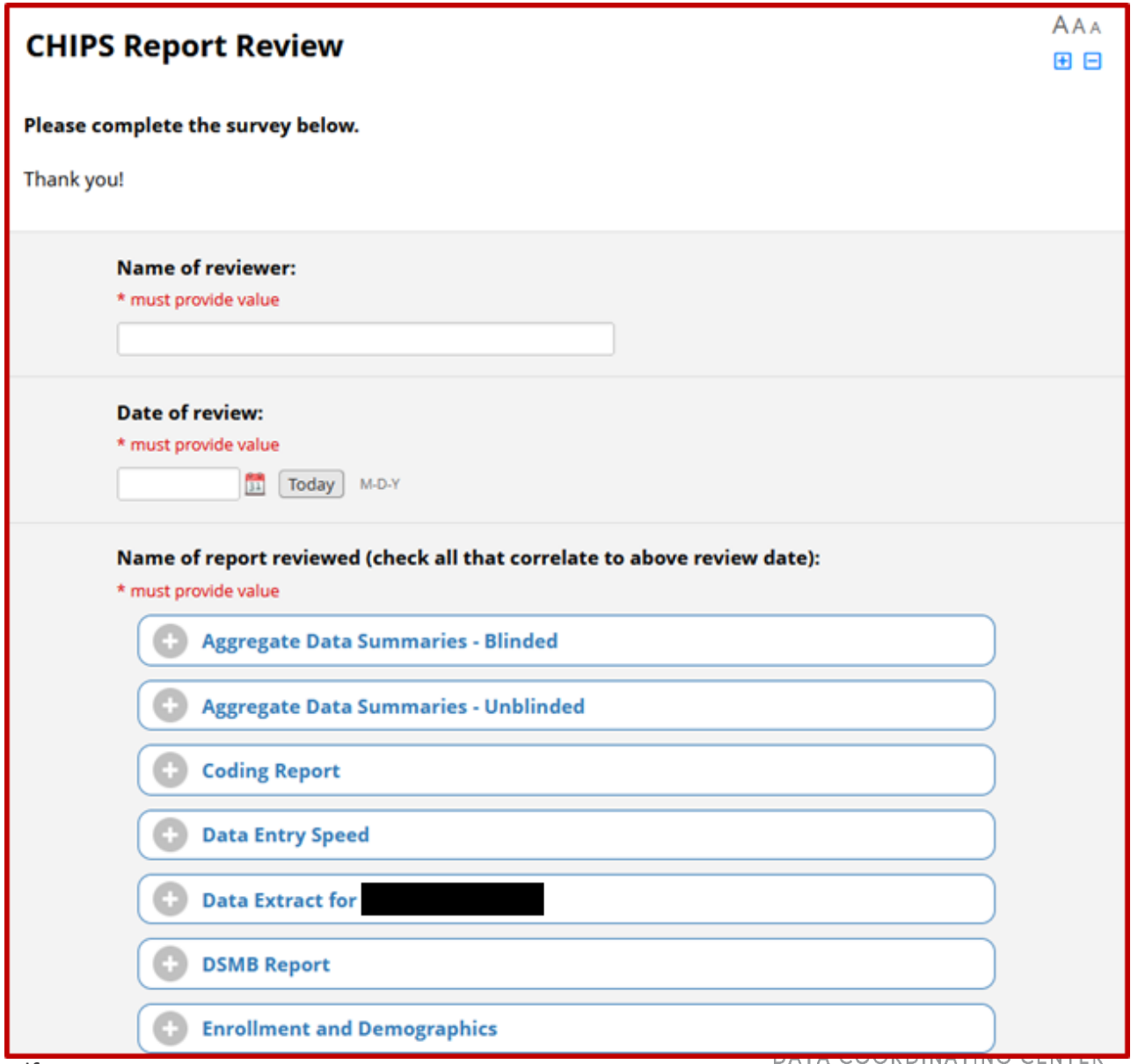
Report Name	Short Description	Developer	Point Person	Target Audience	RARM Flag	Review Frequency	Storage Location
CHIPS AE Listing	Listing of all AEs reported across all sites.	CDM	[redacted]	External	No	As needed	CHIPS AE Listing
Coding Report	A listing of coded terms for AEs within REDCap Cloud.	CDM	[redacted]	External	No	Monthly	REDCap Cloud Medical Coding Tab
Data Entry Speed	This will show a report of queries related to "Form Not Completed" so that we can quantify data entry speed by site.	Stats	[redacted]	External	No	Quarterly (or more often, if needed)	Data Entry Speed

DOCUMENTATION OF REPORT REVIEW

GCP E6 R2 Addendum – Section 5.18.6 (e)

"Results of monitoring activities should be documented in sufficient detail to allow verification of compliance with the monitoring plan"

"Reports of on-site and/or centralized monitoring should be provided to the sponsor"



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Reference: https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf

DATA COORDINATING CENTER

SUMMARY OF REPORT REVIEWS

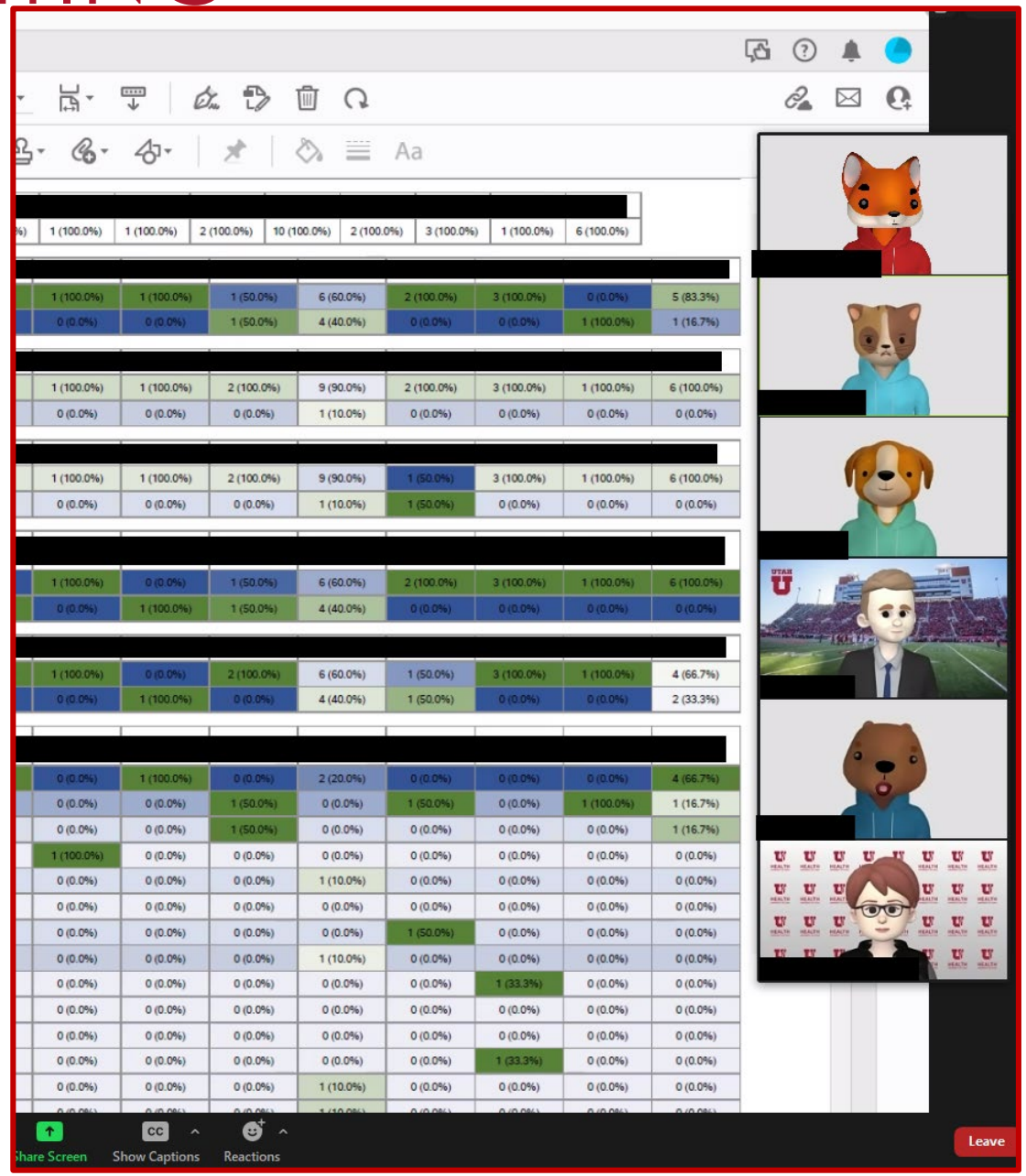
CHIPS REDCap Report Review Summary
This summary was created on February 23, 2023.

Report name	Reviewer responsible	Report review frequency	Last reviewer	Date of report review	Days since last reviewed
Aggregate Data Summaries - Blinded	[redacted]	Monthly	[redacted]	01FEB23	22
Aggregate Data Summaries - Unblinded		Monthly		01FEB23	22
Coding Report		Monthly		02FEB23	21
Data Entry Speed		Quarterly		23JAN23	31
Enrollment and Demographics		Weekly		22FEB23	1
Invoicing		Monthly		02FEB23	21
Lab Draws Summary		Weekly		17FEB23	6
Monitoring Report - Blinded		Weekly		21FEB23	2
Monitoring Report - Unblinded		Weekly		15FEB23	8
Platelet Inventory Management		Weekly		15FEB23	8
Quarterly Report		Quarterly		24JAN23	30
Query Aging Report		Weekly		09FEB23	14
RARM High-Level Summary - Blinded		Weekly		21FEB23	2
RARM High-Level Summary - Unblinded		Weekly		15FEB23	8
SUSAR Listing				23JAN23	
Subjects Randomized but Not Given Platelets		Monthly		01FEB23	22
Summary of Current EDC Roles		Quarterly		02FEB23	21

Color coding definitions (determined by number of days since last review and review frequency):
Weekly - Green: 6 days, Yellow: 7 days, Orange: 8 days, Red: > 8 days.
Monthly - Green: < 25 days, Yellow: 25-29 days, Orange: 30-35 days, Red: > 35 days.
Quarterly - Green: < 2 month, Yellow: 2-3 months, Orange: 3-4 months, Red: > 4 months.
Six Months - Green: < 5 months, Yellow: 5-6 months, Orange: 6-7 months, Red: > 7 months.

ALL HANDS ON DECK MEETING

- 1-2 hour virtual meeting once a month to review reports
- DCC employee presents report
- Summary document produced for the Sponsor



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ALL HANDS FINAL PRODUCT

[redacted] All Hands Meeting

Date: December 8 , 2022

DCC Attendees: [redacted]

Overall Findings

1. The distribution of the study cohorts is close to what we expected it to be: GRACE-2 (expected 40%, actual 36%); TRIPS (expected 50%, actual 48%), High Ferritin (expected 5%, actual 12%); Good Immune Function and Low Inflammation (expected 5%, actual 4%). This is based on a total enrolled of 25.
2. The majority of the sites are getting all of their baseline surveys completed. Of the 25 enrolled subjects, 9 (36%) do not have PEDICAT completed at baseline. For 3-month follow up surveys three subjects' windows have closed. Of those, two completed PedsQL, PedsQLFIM and FSS. No patients' 12-month follow-up windows have opened.

Overall Findings

Site Findings

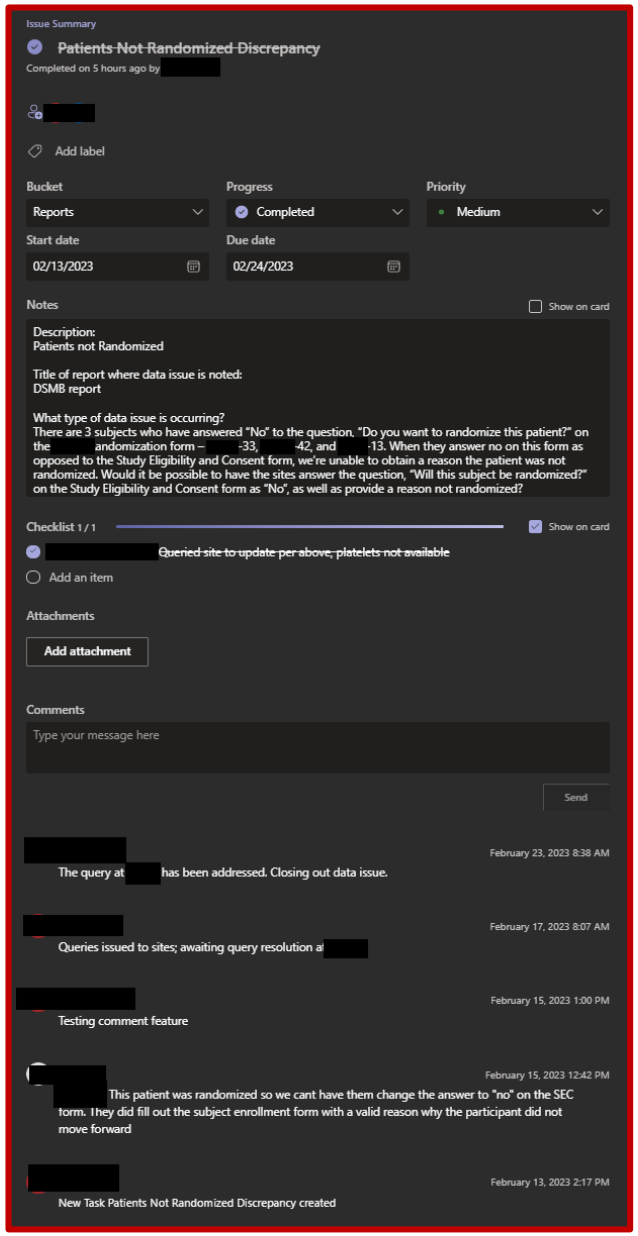
[redacted]

1. [redacted] has 13 unresolved queries that are mostly due to mean airway pressure data not being available. DCC emailed the site to clarify the data entry guidelines.
2. [redacted]-1004 was not entered with vitals data of '0' on the day of death. Data have been queried.

[redacted]

1. [redacted] has 104 unresolved queries. Approximately 1/3 of the unresolved queries are due to the missing baseline PedsQL and FIM, with the remainder being largely due to other missing data.
2. RC sent immunophenotyping samples on Friday but forgot to check Saturday delivery on the shipping label so the samples were received on Monday and no longer viable. [redacted] reeducated the site on shipment

TRACKING FINDINGS



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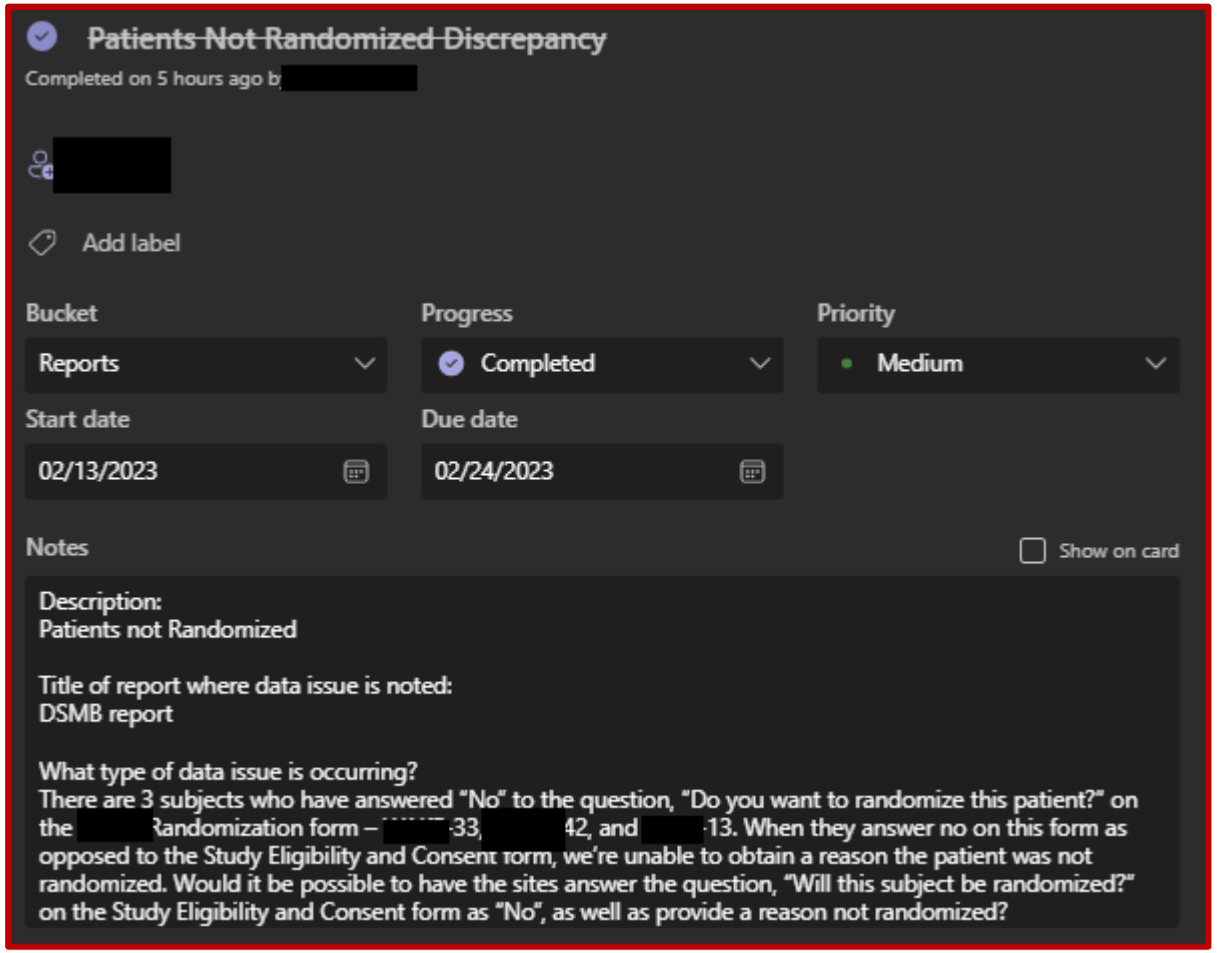
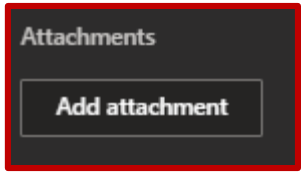
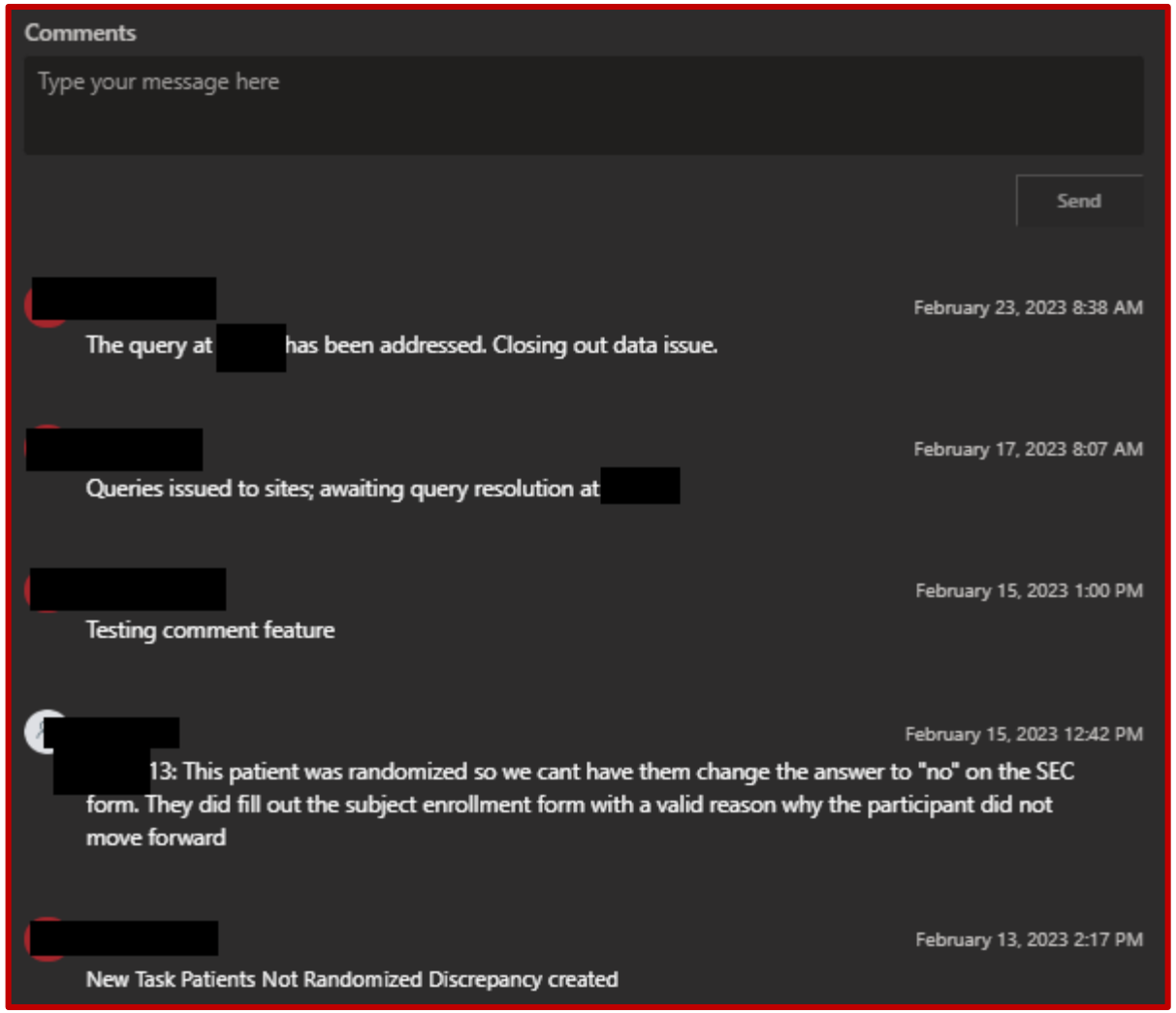
TRACKING FINDINGS







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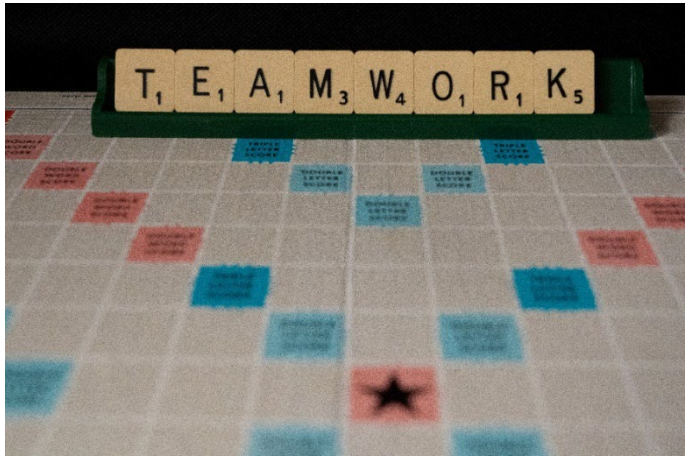
OTHER EXTERNAL MONITORING ACTIVITIES

- Data and Safety Monitoring Board
- Medical Monitor
- Institutional Review Board
- Findings from similar studies

SUMMARY

- Risk based monitoring is encouraged by the FDA
- A component of risk based monitoring is supplementing source data monitoring with other data quality activities
- Monitoring techniques should be pre-specified and study teams should work together to implement an overall strategy



QUESTIONS

SCAN ME

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