



## **Analytical Risk-Based Monitoring (ARBM) – How Central Monitors Detect the Ripple in the Dataflow that Hides the Danger On Site**

Juergen Zech

07 Nov 2023



# Agenda

- Introduction to Central Monitoring
- Key Risk Indicators (KRIs) and Critical to Quality Factors (CtQ)
- Crohn's Disease Activity Index (CDAI) as CtQ in Crohn's Disease Studies
- Management of Central Monitoring Risk Signals in a Case Study
- Conclusions
- Q&A

# Introduction to Central Monitoring

## Regulator's Guidance (EMA - 2013)

remote data analysis & review to identify unusual data patterns, missing or invalid data

### 2. Central monitoring

Document review, **data review and analysis performed remotely** from the investigator site by the sponsor to examine the data collected in order to check compliance, **identify unusual data patterns**, deviations from protocol or **missing or invalid data**. Examples of central monitoring techniques include checks of submitted documents (e.g. checklists for TMF content completed by investigators, training evidence etc.), clinical data checks (e.g. range checks, calendar checks etc., rate of reporting adverse events), compliance data/metrics checks (e.g. number of reported deviations from the protocol, rate of reporting adverse events... etc.).

## ICH E6 (R2) - 2017

in combination with on-site monitoring

### ADDENDUM

The sponsor should develop a systematic, prioritized, risk-based approach to monitoring clinical trials. The flexibility in the extent and nature of monitoring described in this section is intended to permit varied approaches that improve the effectiveness and efficiency of monitoring. The sponsor may choose on-site monitoring, a combination of on-site and centralized monitoring, or, where justified, centralized monitoring. The sponsor should document the rationale for the chosen monitoring strategy (e.g., in the monitoring plan).

## Regulator's Guidance (FDA - 2023)

systematic evaluation across multiple sites

### Q4. How can a risk-based approach to monitoring that includes centralized monitoring help minimize missing data or protocol deviations?

Centralized monitoring is a systematic analytical evaluation of study conduct across multiple clinical sites, carried out by sponsor personnel or representatives (e.g., clinical monitors, data management personnel, or statisticians). Centralized monitoring may allow sponsors to (1) review study-wide data for inconsistencies or omissions; (2) perform activities such as data checks, for completeness and consistency; (3) verify source data; (4) ensure that institutional review board and informed consent documents are current; and (5) determine which clinical sites need on-site review.

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## Regulator's Guidance (FDA - 2023)

systematic evaluation across multiple sites

### HOLISTIC VIEW

...an a risk-based approach to monitoring that includes centralized monitoring to minimize missing data or protocol deviations?

## ICH E6 (R2) - 2017

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# Introduction to Central Monitoring



**Juergen Zech, PhD**

- 3 years' experience as Central Data Scientist with ICON Strategic Solutions, assigned to work for a global pharmaceutical company as a Central Monitoring Manager
- 2 years' experience as an In-House CRA, performing remote site monitoring and Key Risk Indicator (KRI) review.
- 15+ years in Academic Research, focused on Cancer & Cell Cycle research, with 10+ peer reviewed research publications

# Key Risk Indicators (KRIs) and Critical to Quality Factors (CtQ)

## How do Central Monitors Provide a Different Perspective on the Study ?

### **CRA**

#### Focus on the Site

(Many Datapoints are Reviewed Once and On-Site)



### **Central Monitor**

#### Focus on the Study

(Few Datapoints are Reviewed Repetitively and Study-Wide)



# Key Risk Indicators (KRIs) and Critical to Quality Factors (CtQ)

## Key Components of Risk-Based Monitoring (RBM)

1. Initial Cross-functional Risk Assessment
2. Ongoing Cross-functional Risk Assessment
3. Quality Tolerance Limits (QTLs)
  - Predetermined limits for specific trial parameters
4. **Key Risk Indicators (KRIs)**
  - *Metrics used to assess site performance*
5. **Centralized Monitoring**
  - *Remote review and analysis of aggregated data*
6. Remote-site Monitoring
7. Reduced SDV
8. Reduced SDR

Barnes B et al.

Risk-Based Monitoring in Clinical Trials: Past, Present, and Future.  
Therapeutic Innovation & Regulatory Science (2021) 55:899-906

# Key Risk Indicators (KRIs) and Critical to Quality Factors (CtQ)

Is there evidence that central monitoring of KRIs add value in 2023 ?

*Non-COVID-related protocol deviation did not drop significantly during pandemic when the majority of site visits shifted to an off-site model*

Barnes B et al.  
Risk-Based Monitoring in Clinical Trials: Past, Present, and Future.  
Therapeutic Innovation & Regulatory Science (2021) 55:899-906

*There is **statistical evidence that central monitoring is efficient** in detecting data quality issues, when it is properly implemented and risk signals are followed up and clearly communicated.*

de Viron S et al.  
Does Central Monitoring Lead to Higher Quality? An Analysis of Key Risk Indicator Outcomes.  
Therapeutic Innovation & Regulatory Science (2023) 57:295-303

# Key Risk Indicators (KRIs) and Critical to Quality Factors (CtQ)

## Critical to Quality Factors (CtQ)

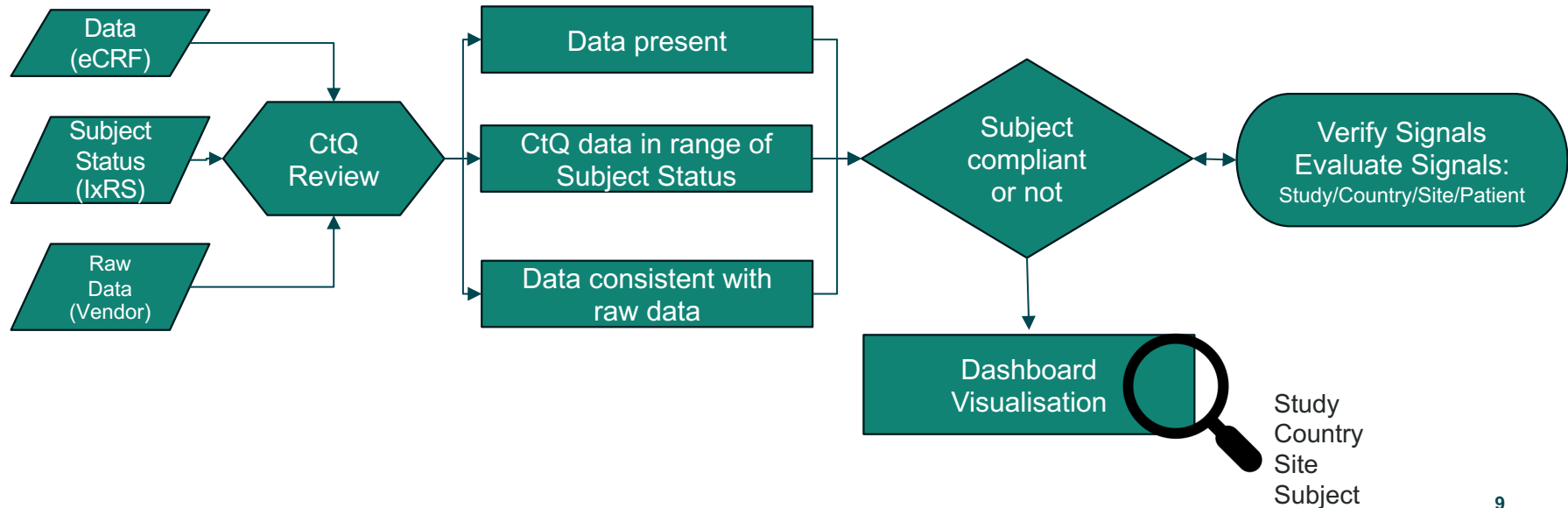
- relevant to the *integrity and reliability of study data* conclusions are based on.
- relevant to the *safety* of study participants.
- strongly *influenced by trial* design and objectives in their significance.

CtQs might be

- Based on protocol design:
  - Eligibility criteria
  - Data Quantity
  - Endpoints
- Based on Patient Safety:
  - Informed Consent
  - Withdrawal Criteria
  - Safety Reporting

# Key Risk Indicators (KRIs) and Critical to Quality Factors (CtQ)

Central Monitoring can use technology to keep oversight over CtQs as data is accumulated during the life cycle of a study.



# Use of the Crohn's Disease Activity Index (CDAI) score metrics to Centrally Monitor CtQs in Crohn's Disease Studies

## CDAI score-related CTQs identified for the Case Study

### Eligibility:

- CDAI (baseline)  $\geq 220$
- CDAI (baseline)  $\leq 450$

### Stratification:

- CDAI (baseline)  $< 300$
- CDAI (baseline)  $\geq 300$

### Crohn's Disease Activity Index (CDAI):

- Most common index in Crohn's Disease Research Literature
- Complicated and error-prone measure

| CDAI Calculation |                      |                      |     |                 |     |
|------------------|----------------------|----------------------|-----|-----------------|-----|
| Data             |                      | Treatment & Symptoms |     | Patient Ratings |     |
| Hematocrit       | <input type="text"/> | Fistula              | Y/N | Liquid Stools   | 0-2 |
| Sex              | <input type="text"/> | Fever                | Y/N | Well-Being      | 0-4 |
| Weight           | <input type="text"/> | Inflammatory         | Y/N | Pain            | 0-3 |
|                  |                      | Anti-diarrhea        | Y/N |                 |     |

Kishi et al.

A review on the current status and definitions of activity indices in inflammatory bowel disease: how to use indices for precise evaluation. J Gastroenterol (2022) 57:246–266

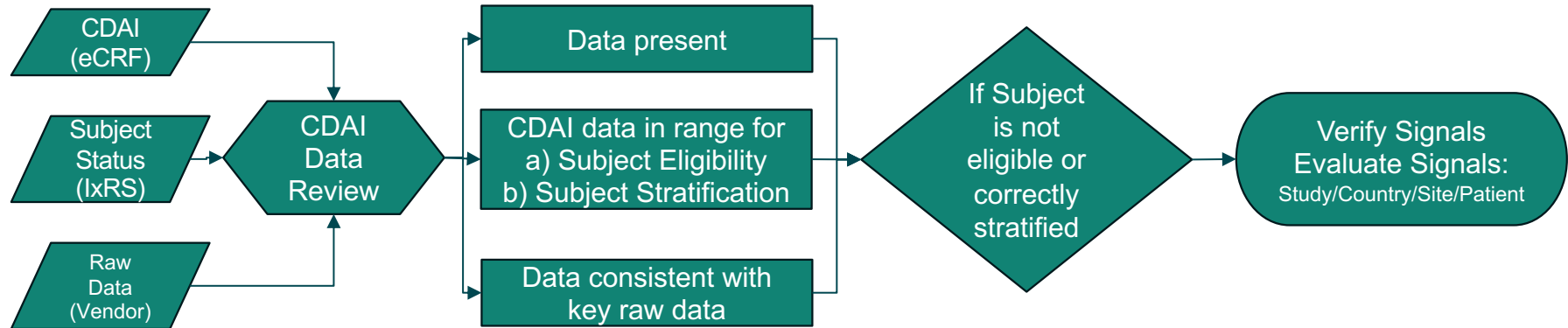
# Use of the Crohn's Disease Activity Index (CDAI) score metrics to Centrally Monitor CtQs in Crohn's Disease Studies

## Central Monitoring Oversight over Correct Enrollment and Stratification

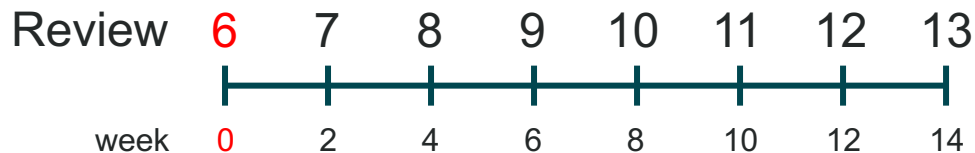
Randomized Subjects (Simplified Sample):

- Site A – Subject 1
- Site B – Subject 2
- Site B – Subject 3

## Central Monitoring Review (Eligibility/Stratification Compliance)

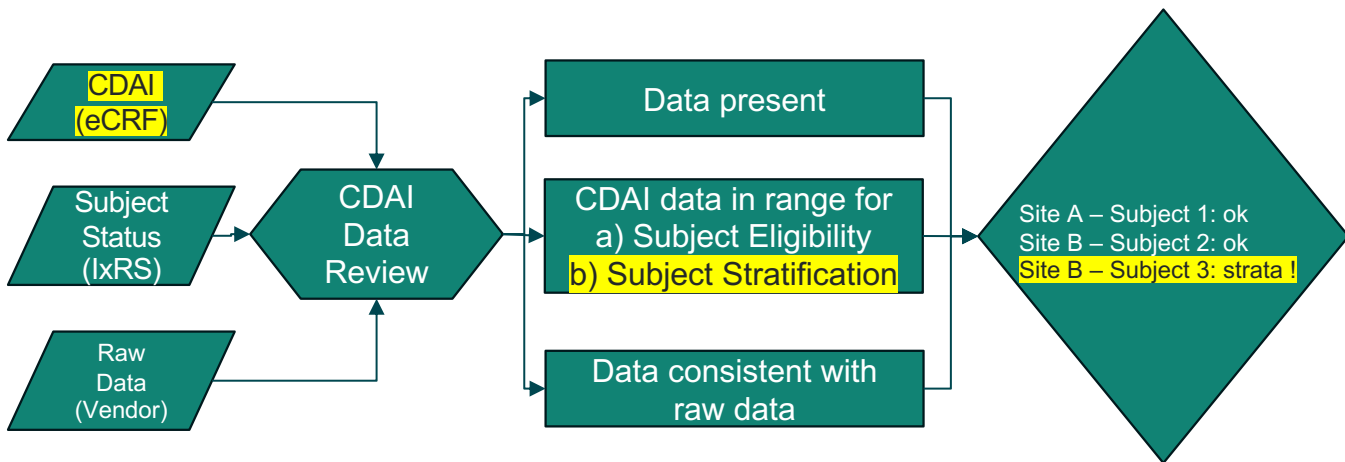


# Identification of Central Monitoring Risk Signals (Example from a Crohn's Disease Case Study)



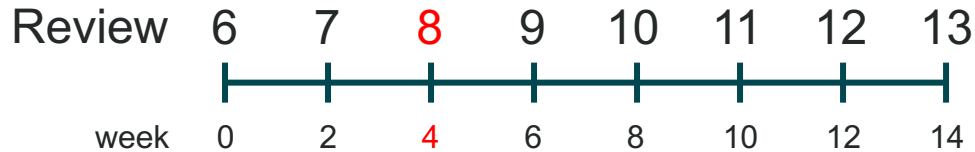
## Central Monitoring Review 6

CM: Incorrect CDAI entered Site B  
CRA B: Incorrect CDAI entered Site B



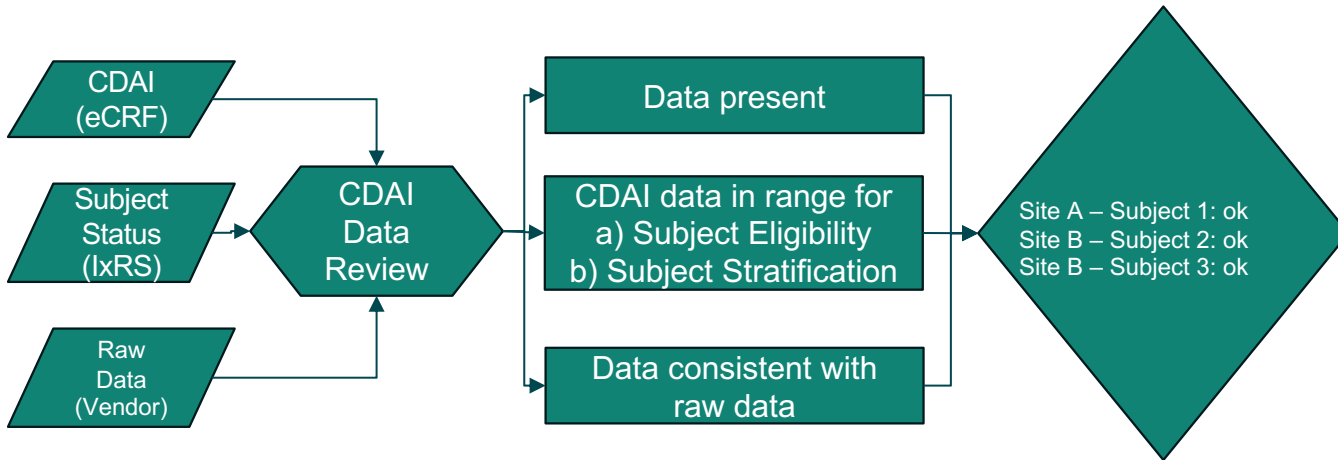
Central Monitoring Review 6 (Week X)

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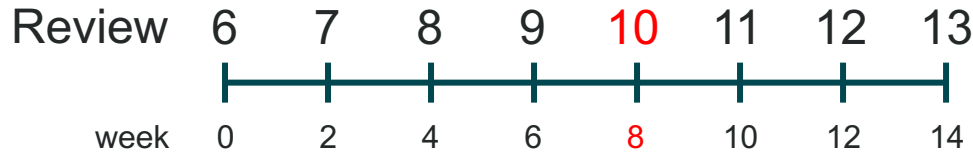


**Central Monitoring Review 6**  
CM: Incorrect CDAI entered Site B  
CRA B: Incorrect CDAI entered Site B

**Central Monitoring Review 8**  
CM: CDAI corrected at Site B  
CRA B: CDAI corrected at Site B



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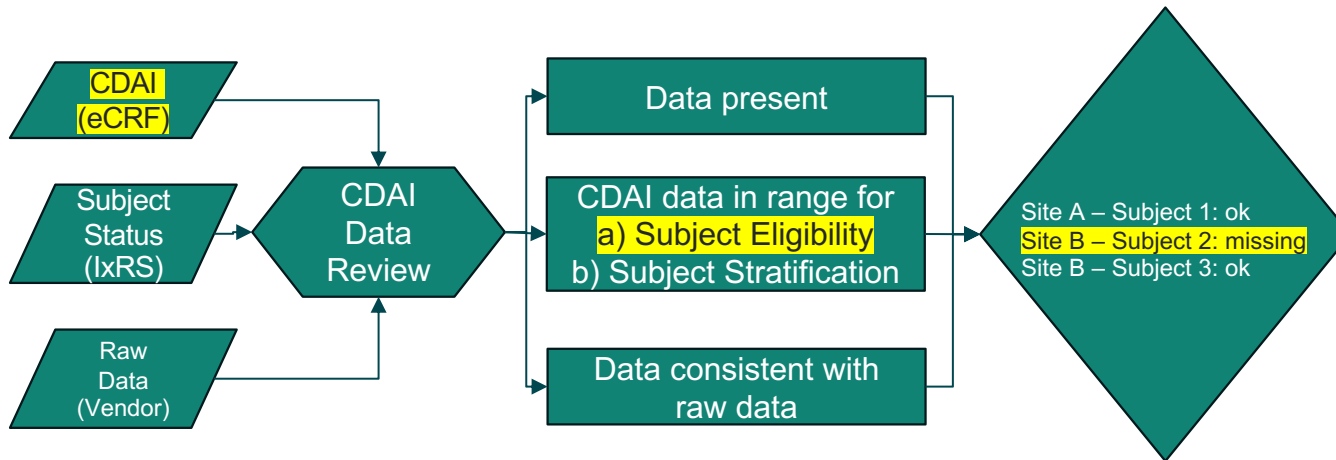


## Central Monitoring Review 6

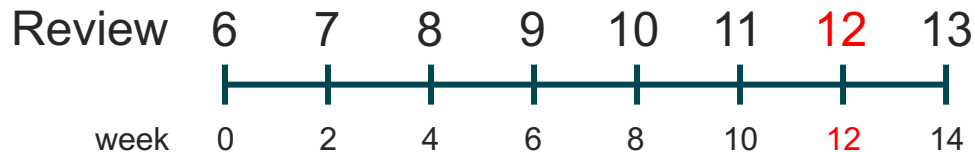
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Central Monitoring Review 6

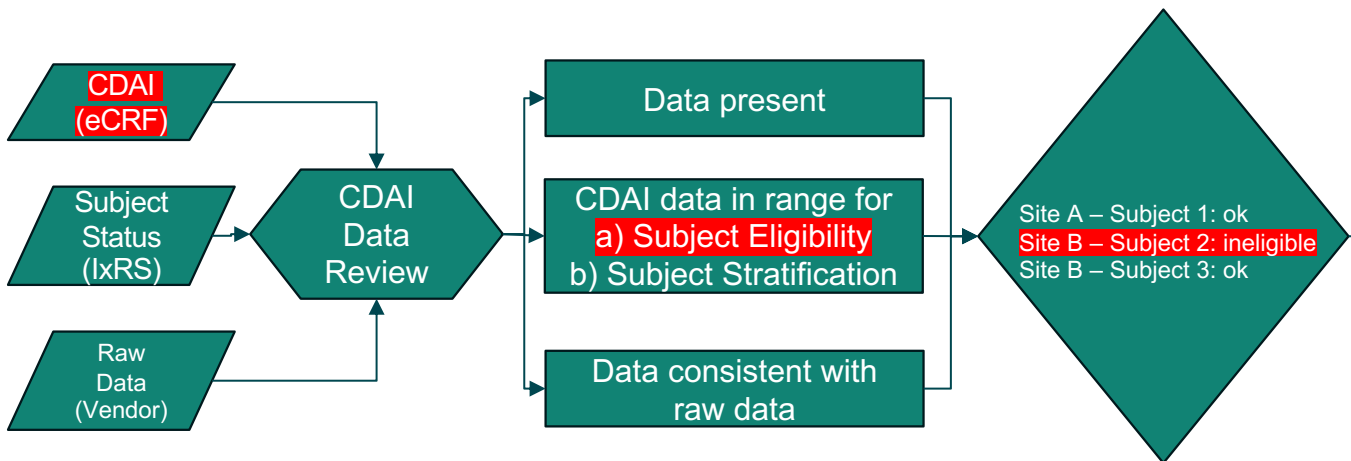
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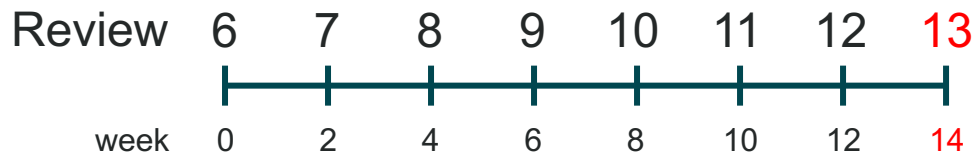
CM: CDAI corrected at Site B  
CRA B: CDAI corrected at Site B

Central Monitoring Review 12

CM: Corrected CDAI changed Site B  
CRA B: Retrain Site B on CDAI



# Identification of Central Monitoring Risk Signals (Example from a Crohn's Disease Case Study)

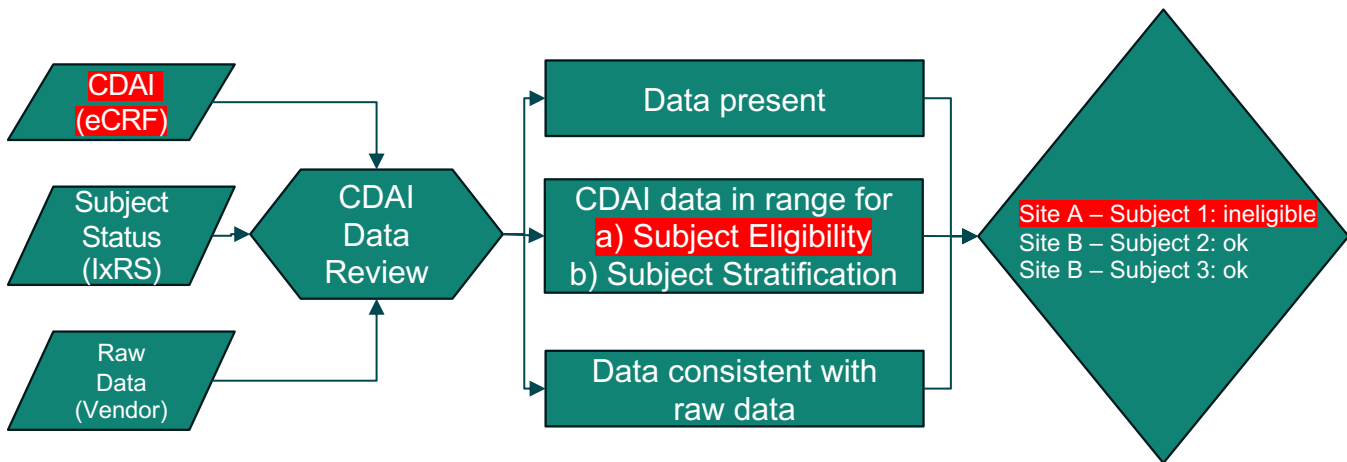


**Central Monitoring Review 6**  
CM: Incorrect CDAI entered Site B  
CRA B: Incorrect CDAI entered Site B

**Central Monitoring Review 8**  
CM: CDAI corrected at Site B  
CRA B: CDAI corrected at Site B

**Central Monitoring Review 12**  
CM: Corrected CDAI changed Site B  
CRA B: Retrain Site B on CDAI

**Central Monitoring Review 13**  
CM: Incorrect CDAI entered at 2 Sites  
CRA A: Incorrect CDAI entered Site A  
CRA B: Retrained Site B on CDAI



# Follow-up & Communication of Central Monitoring Risk Signals (Example from a Crohn's Disease Case Study)

## Central Monitoring Follow-Up of Risk Signal

**Central Monitoring Review 13**  
CM: Incorrect CDAI entered at 2 Sites

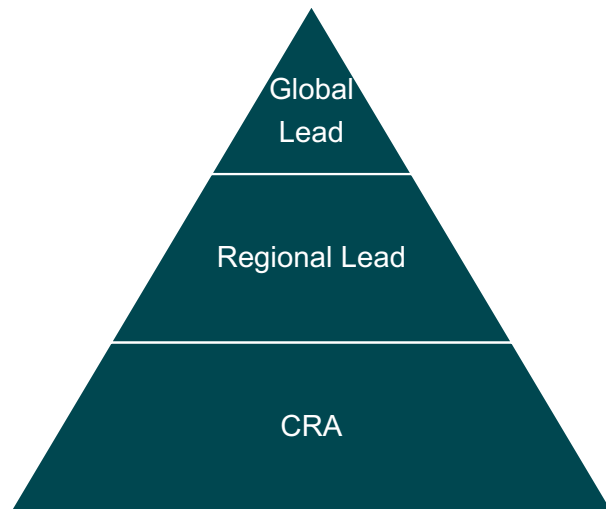


**Analysis of detailed Central Review Output:**  
Laboratory data are not the cause of incorrect CDAI entry



**Ad hoc analysis of baseline CDAI entry history (all sites):**

## Clinical Operations Follow-Up of Risk Signal



**Central Monitoring Review 8**  
CRA B: Retrained Site B on CDAI

**Central Monitoring Review 6**  
CRA A: Incorrect CDAI entered Site A

# Follow-up & Communication of Central Monitoring Risk Signals (Example from a Crohn's Disease Case Study)

## Central Monitoring Follow-Up of Risk Signal

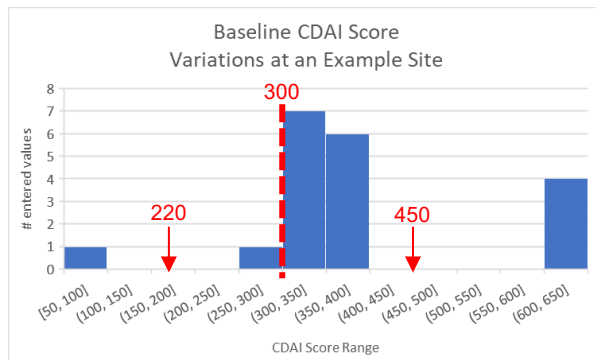
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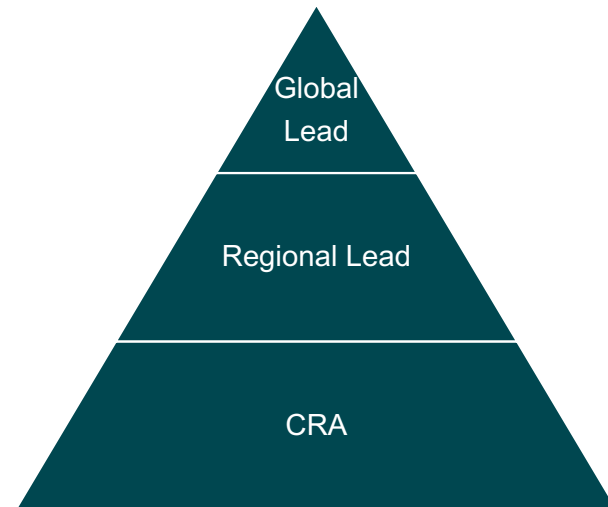


**Ad hoc analysis of baseline CDAI entry history (spot checks):**



Stratification  
Eligibility limits

## Clinical Operations Follow-Up of Risk Signal



**Central Monitoring Review 8**  
CRA B: Retrained Site B on CDAI

**Central Monitoring Review 6**  
CRA A: Incorrect CDAI entered Site A

# Follow-up & Communication of Central Monitoring Risk Signals (Example from a Crohn's Disease Case Study)

## Central Monitoring Follow-Up of Risk Signal

**Central Monitoring Review 13**  
CM: Incorrect CDAI entered at 2 Sites



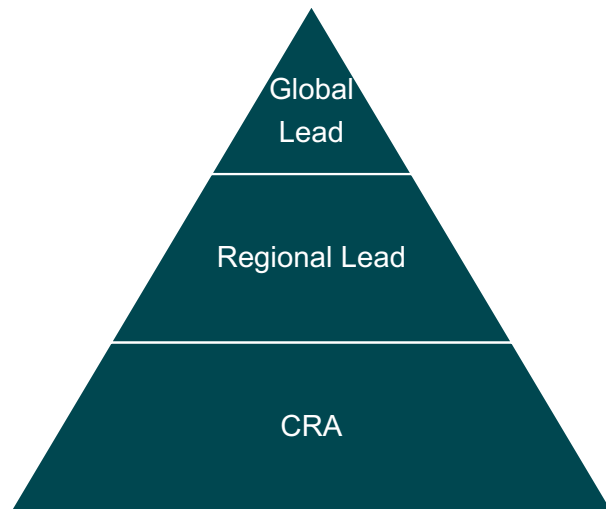
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**Ad hoc analysis of baseline CDAI entry history (all sites):**

**Conclusion: Several sites are not confident  
calculating the CDAI score**

## Clinical Operations Follow-Up of Risk Signal



**Central Monitoring Review 8**  
CRA B: Retrained Site B on CDAI

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CRA A: Incorrect CDAI entered Site A

# Follow-up & Communication of Central Monitoring Risk Signals (Example from a Crohn's Disease Case Study)

## Follow-Up of Central Monitoring Risk Signal

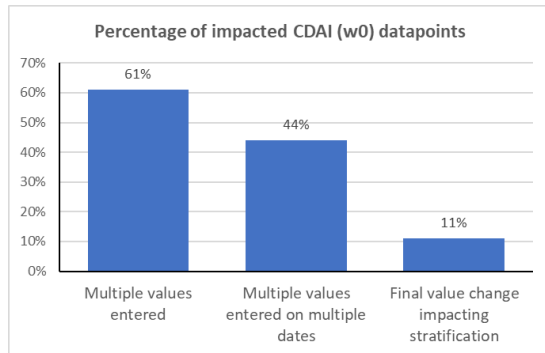
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**Analysis of detailed Central Review Output:**  
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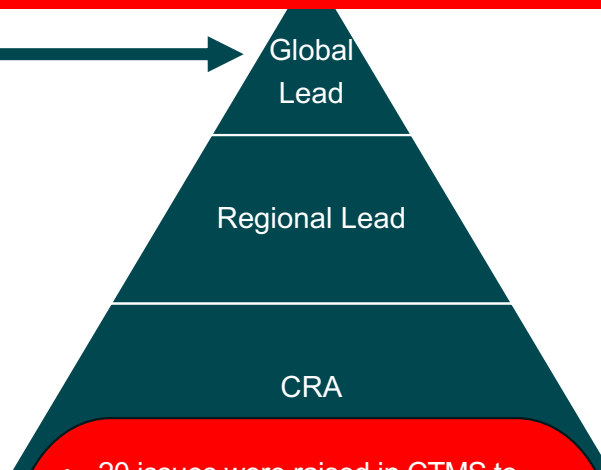


**Ad hoc analysis of baseline CDAI entry history (all sites):**



## Clinical Operations Follow-Up of Risk Signal

**Conclusion: Several sites are not confident calculating the score**



- 20 issues were raised in CTMS to check CDAI and/or lead to site retraining
- 15 of 28 sites in 6 countries effected
- 3 protocol deviations raised

# Conclusions

## Is there evidence that central monitoring of KRIs add value in 2023 ?

Yes, but there are factors critical for the added value Central Monitoring can provide to clinical trials:

- Proper Implementation
  - requires a good understanding of the trial
- Holistic View
  - provided by repetitive reviews of CtQs that show changes in the study data from different perspectives (study, country, site, subject)
- Documentation of Signals
- Follow-up of Signals
  - follow-up analysis of risk signals
  - clear communication
  - good cooperation between Central Monitoring and Clinical Operations



Thank you for your attention !

# Literature

Barnes B et al.

Risk-Based Monitoring in Clinical Trials: Past, Present, and Future.  
Therapeutic Innovation & Regulatory Science (2021) 55:899-906

Clinical Trials Transformation Initiative (CTTI)

Quality by Design Project – Critical to Quality (CtQ) factors principles document  
Accessed 07Sep2023

de Viron S, Trotta L, Steijn W, Young S, Buyse M

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