Modernizing ICH's E6 Guidelines

Sponsor: Risk Based Monitoring (RBM)

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ICH's E6 Guidelines-Updates

Sponsor – Quality Management

New section – Quality Management (5.1)

- Implement a system to manage quality using Risk Based approach
  - › includes efficient protocol design
  - › Data collection
  - › Information collection

- Risk on two levels:
  - › Systems
  - › Clinical Trial

Risk Identification >> **Risk Evaluation** >> **Risk Control** >> **Risk Communication** >> **Risk Review** >> **Risk Reporting**

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Sponsor – Quality Management

Risk Evaluation

- The likelihood of errors occurring, given existing risk controls.
- The impact of such errors on human subject protection and data integrity.
- The extent to which such errors would be detectable.

Risk Control

- Sponsor to identify the risks to be reduced
- Protocol should include activities to mitigate the risks & appropriate monitoring plans

Risk Communication >> Review >> Reported

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Sponsor - Monitoring

Another new section >>

Extent & Nature of Monitoring (5.19.3)

Sponsor to develop systemic, prioritized & risk-based approach to monitoring clinical trials.

- Combination of On-Site and Centralized monitoring
- The aim - to improve effectiveness and efficiency of monitoring

Centralized monitoring is a remote evaluation of ongoing and/or cumulative data collected from trial sites, in a timely manner.

Centralized monitoring processes provide additional monitoring capabilities that can complement and reduce the extent and/or frequency of on-site monitoring.

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Sponsor - Monitoring

Centralized monitoring would allow reduced On-site visits by using methods as:

- Routine review of submitted data.
- Identification of missing data, inconsistent data, data outliers or unexpected lack of variability and protocol deviations that may be indicative of systematic or significant errors in data collection and reporting at a site or across sites, or may be indicative of potential data manipulation or data integrity problems.
- Using statistical analyses to identify data trends such as the range and consistency of data within and across sites.
- Analyzing site characteristics and performance metrics.
- Selection of sites and/or processes for targeted on-site monitoring.

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Sponsor - Monitoring

Monitoring Plan

The sponsor should develop a Monitoring Plan for the specific study taking into consideration the identified risks. The plan will describe the following:

- Monitoring strategy
- Monitoring responsibilities of all parties
- Monitoring methods & rational

The plan to emphasize the monitoring of critical data & processes.

Especially to those aspects that are not routine clinical practice & require additional training

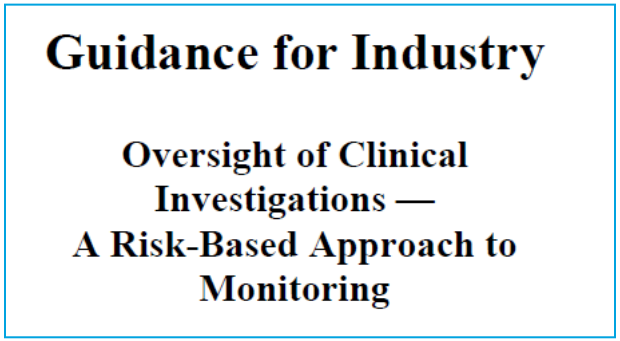
RBM

Industry Definition

Risk-based Monitoring *is the concept of monitoring trials electronically from a central location and sending monitors to sites only when necessary rather than every four to six weeks.*

(CenterWatch, 2012).

Regulatory Guidance



U.S. Department of Health and Human Services
Food and Drug Administration
August 2013
Procedural

FDA

- Recommends a quality risk management approach
- Flexibility to choose optimal combination of monitoring strategies
- Critical study parameters
- Appropriate use of centralized monitoring and technological advances

EMA

- Risk-based approach to quality management
- Systematic, prioritized risk-based approach
- "Targeted use of resources"

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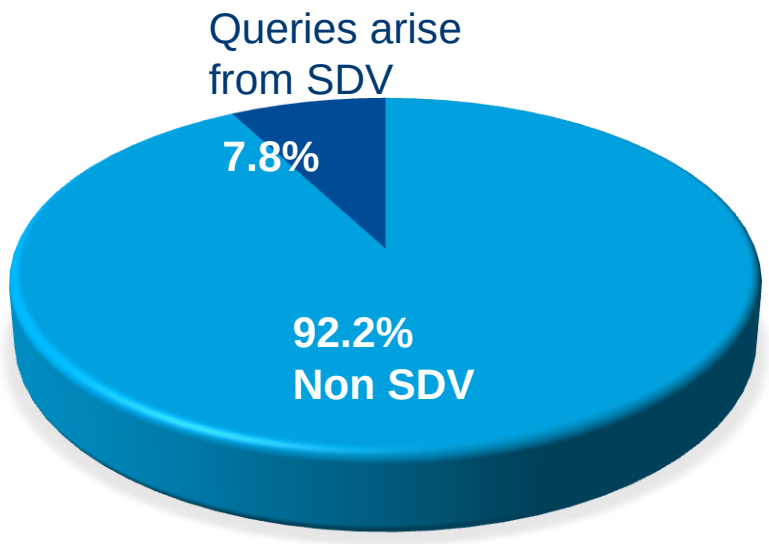
What is the Rate of SDV Generated Queries?

9 studies of 6 companies were analyzed:



7.8% queries generated following On-site SDV.

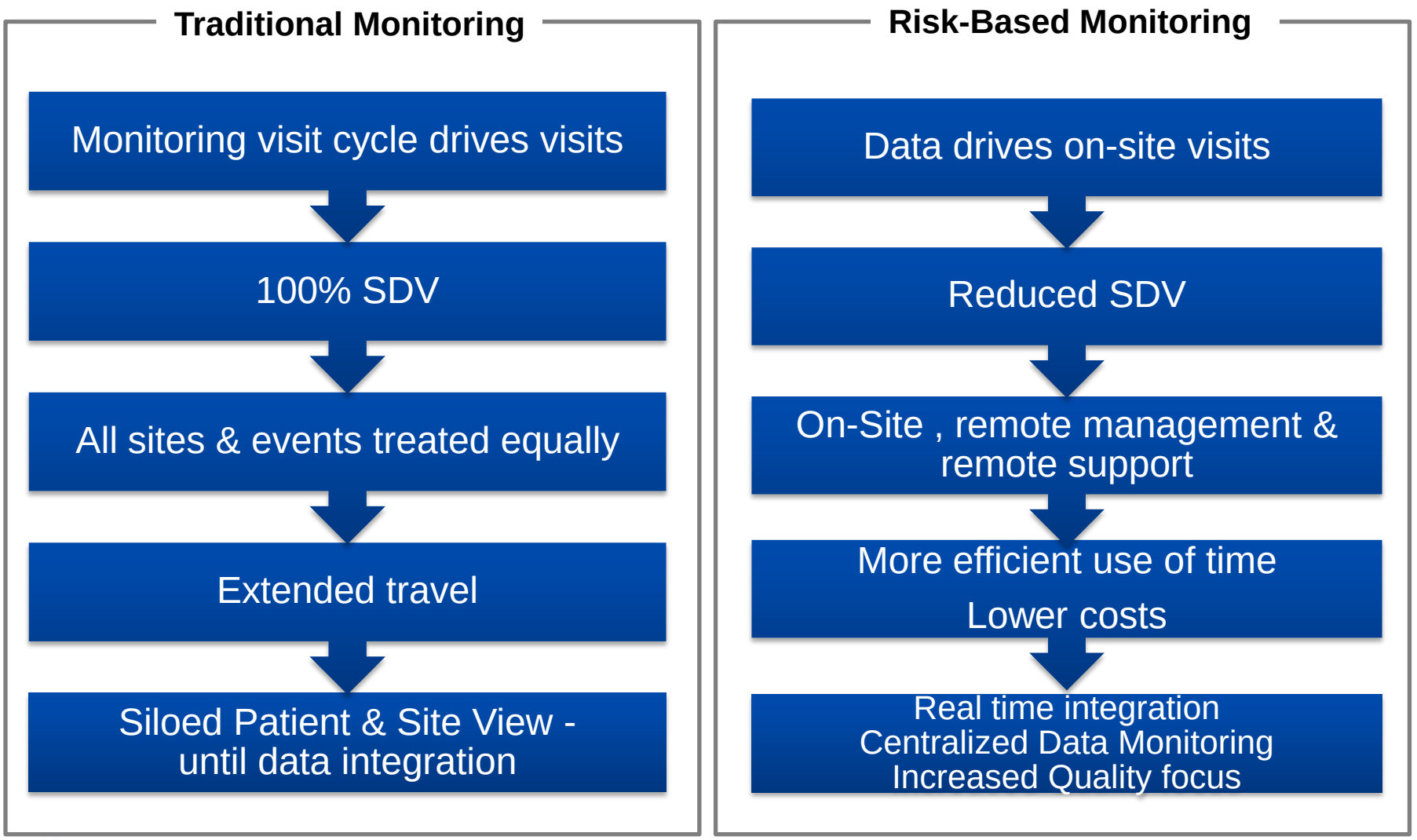
The overwhelming majority come from central data review.

(Applied Clinical Trials, Jul 11, 2013, By Lisa Henderson)

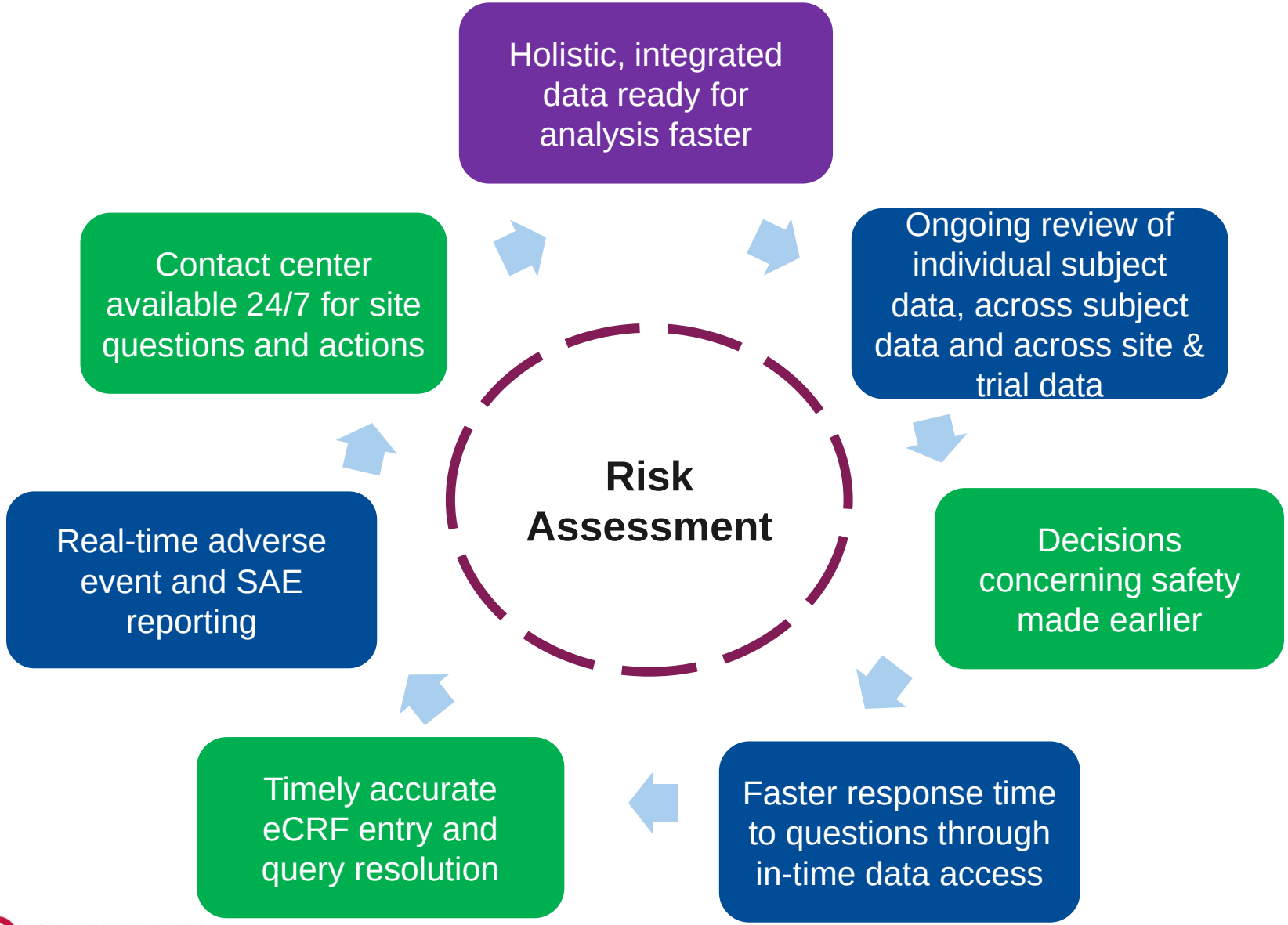
RBM – Different Names

- Just-in-Time (JIT)
- Fit for Purpose Monitoring (FFPM)
- DTE (Data-driven Trial Execution)
- Centralized Monitoring
- Focused Monitoring

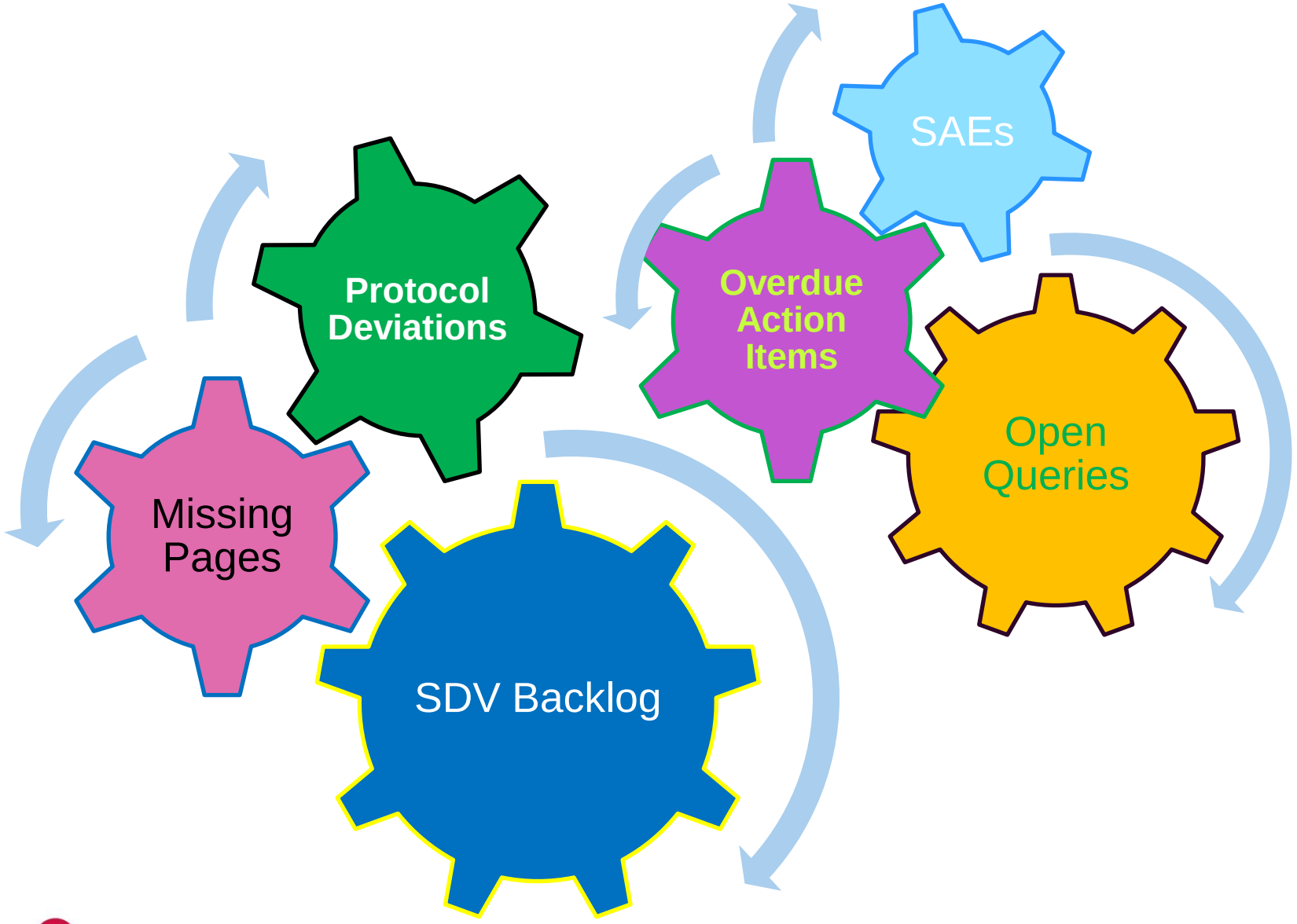
Traditional Vs Risk-Based Monitoring



Centralized Data Analysis



Example of Triggers for On-Site Visits



What is expected from Site staff?

- Timely eCRF data entry and real-time query resolution
- Site-driven quality control
- Site staff availability to Site Monitor is key for all visit types
- Communication & cooperation with site monitor

Monitor's Responsibilities

Reporting

- Monitor is responsible to complete a report following site visit, remote or any communication with site.

- Monitoring results will be provided to sponsor in timely manner for review and follow-up.

- Monitoring results should provide sufficient details to allow verification of compliance with Monitoring Plan.

Thank You

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