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Singapore Clinical Research Professional (CRP) /Clinical Research Coordinator Society (CRCS) Forum

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TOPIC:

Issue Management / Quality Risk Management Implications with ICH GCP E6 (R2) and ISO 31000 and Implementation within Quality System

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About the Speaker

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Vice President
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- 35 years in pharma industry
- Most of career held management positions in clinical development and quality assurance in the research and development enterprise
- Breadth of drug development experience from cradle to grave.
- Past company affiliation: RWJPRD (Johnson & Johnson), Novartis, and Reata

I had the honor of being a presenter at the launch of the first Singapore CRP Forum in 2002, founded by Angie Sim who I had recently hired that year to establish a GCP function in Asia for J&J.
Thank you for inviting me again to present at this dynamic forum where key topics are presented and discussed with the intent of increasing knowledge and learnings.

Congratulations to the CRP Forum Committee on their 15 years of continuous dedication in bringing the community of clinical research professionals together in Singapore for the purpose of making a positive impact in the area of good clinical practice !!

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Quality Risk Management

Issue Management

RISK MANAGEMENT FRAMEWORK

ISO 31000 : 2009

- An internationally recognized standard
- Provides principles and guidelines for effective risk management
- Not specific to any industry or sector
- Able to be applied to any kind of risk
- Able to be applied to any kind of organization
- Intended to be tailored to meet the needs of the organization

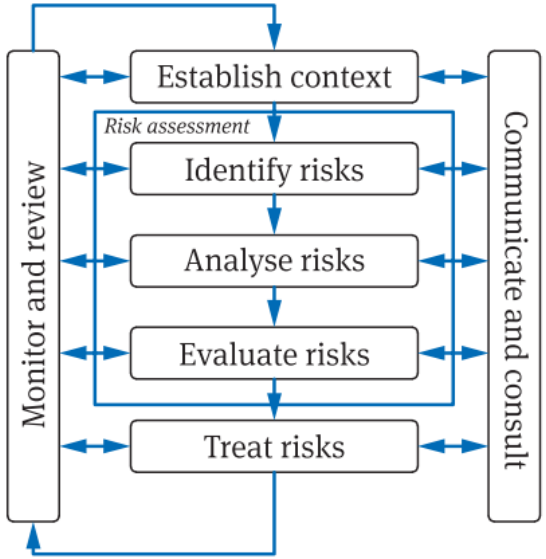

Figure 2 — The ISO 31000:2009 risk management process

ISO 31000: 2009 states that:

"The generic approach described in this standard provides the principles and guidelines for managing any form of risk in a systematic, transparent and credible manner and within any scope and context."

"Risk management can be applied to an entire organization, at its many areas and levels, at any time, as well as to specific functions, projects and activities."

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The ICH E6 Guideline was revised to:

Address changes in the scale, complexity, and cost of clinical trials since the previous version was adopted.

Encourage the implementation of improved and more efficient approaches to clinical trial design, conduct, oversight, recording, and reporting, while ensuring that human subject protection and data integrity are maintained.

↳ *This is supported by the fact that clinical researchers have access to new technology and risk management processes that may increase efficiency and focus on relevant clinical trial and essential documents.*

Help clinical researchers protect human subjects, maintain data quality and integrity, and properly document trial results.

Overview of ICH E6 (R2)

Sponsor Responsibilities

CRO Oversight

Quality Management

-Efficient Design

-Risk Management:

Identification

Evaluation,

Control,

Communication,

Review, and

Reporting

-Noncompliance (CAPA)

Monitoring

-Nature of monitoring (e.g. **risk based approach**, centralised)

-Centralised Monitoring

-Monitoring Plan

-Monitoring Report

Electronic Media

Computerized systems

-Validation- ensure accuracy, reliability and consistent intended performance, from design until decommissioning or transition to a new system.

-Records and Reports- source documents maintained, changes traceable

-Trial Data Systems- training needed and **ensure integrity of data**, especially with changes

Essential Documents

-Record of location

-Search and retrieval

Certified Copy

- A copy of the original record must be verified (i.e. by a dated signature or generation through a validated process)

Investigator Responsibilities

Delegation of Tasks

-Supervision of all personnel delegated study tasks

-Party should be qualified to fulfil the tasks

Source Documents and trial records

-Record of location

-Should be adequate and accurate

-Source data should be ALCOA + *Complete*

Essential Documents

-Record of location

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ICH E6 (R2): A focus on the Quality Management System

5.0 Quality Management

The sponsor should implement a system to manage quality throughout all stages of the trial process.

Sponsors should focus on trial activities essential to ensuring human subject protection and the reliability of trial results. Quality management includes the design of efficient clinical trial protocols and tools and procedures for data collection and processing, as well as the collection of information that is essential to decision making.

The methods used to assure and control the quality of the trial should be proportionate to the risks inherent in the trial and the importance of the information collected. The sponsor should ensure that all aspects of the trial are operationally feasible and should avoid unnecessary complexity, procedures, and data collection. Protocols, case report forms, and other operational documents should be clear, concise, and consistent.

The quality management system should use a **risk-based approach** ...

Quality Risk Management: ICH E6 (R2) Sections 5.0.1 to 5.0.7

Critical Process and Data Identification (during protocol development)

- Sponsor to identify those processes and data critical to assure human subject protection and the reliability of study results.

Risk Identification

- Critical study processes and data
- At the system level and clinical trial level

Risk Evaluation

(a) likelihood of errors
(b) the impact of such errors on human subject protection and data integrity.
(c) detectability

Risk Control

- Identify risks that should be reduced (through mitigating actions) and/or can be accepted.
- Risk mitigation activities may be incorporated in protocol design and implementation, monitoring plans
- Predefined quality tolerance limits should be established …and detection of deviations from the predefined quality tolerance limits should trigger an evaluation to determine if action is needed.

Risk Communication

- QRM activities should be documented and communicated

Risk Review

- The sponsor should periodically review risk control measures to ascertain whether the implemented quality management activities remain effective and relevant

Risk Reporting

- The sponsor should describe the quality management approach implemented in the trial and summarize important deviations from the predefined quality tolerance limits in the CSR

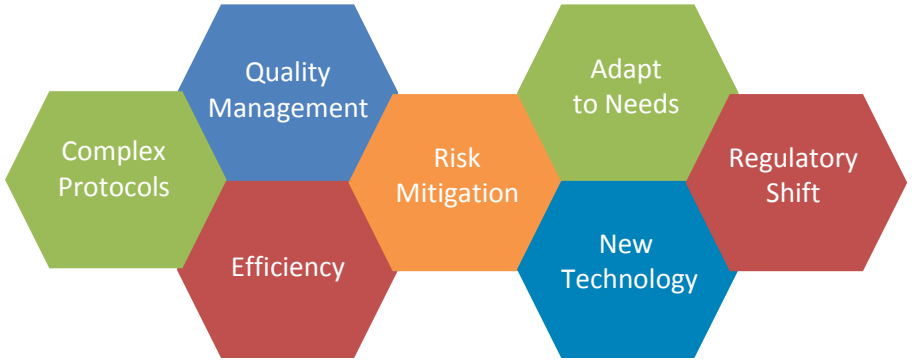
Proactively Determining Risk in a Clinical Development Setting

You can create a Quality Risk Management Plan for a specific clinical trial that:

- Includes the clinical and medical risks identified and
- Defines the actions that each function will take to proactively identify, assess, and manage risk throughout the life of a clinical trial

Ensures that cross-functional teams focus on the risks that are most important to subject safety, data quality and regulatory compliance

Creating a Monitoring Plan: A Risk Based Approach



ICH-GCP E6(R2) Section 5.18 Monitoring:

- ✓ The sponsor should develop a **systematic, prioritized, risk-based approach** to monitoring clinical trials
- ✓ The sponsor may choose **on-site monitoring, a combination of on-site and centralized monitoring**
- ✓ On-site monitoring is performed at the sites at which the clinical trial is being conducted. Centralized monitoring is a remote evaluation of accumulating data, performed 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 and help distinguish between reliable data and potentially unreliable data

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Changing the Culture

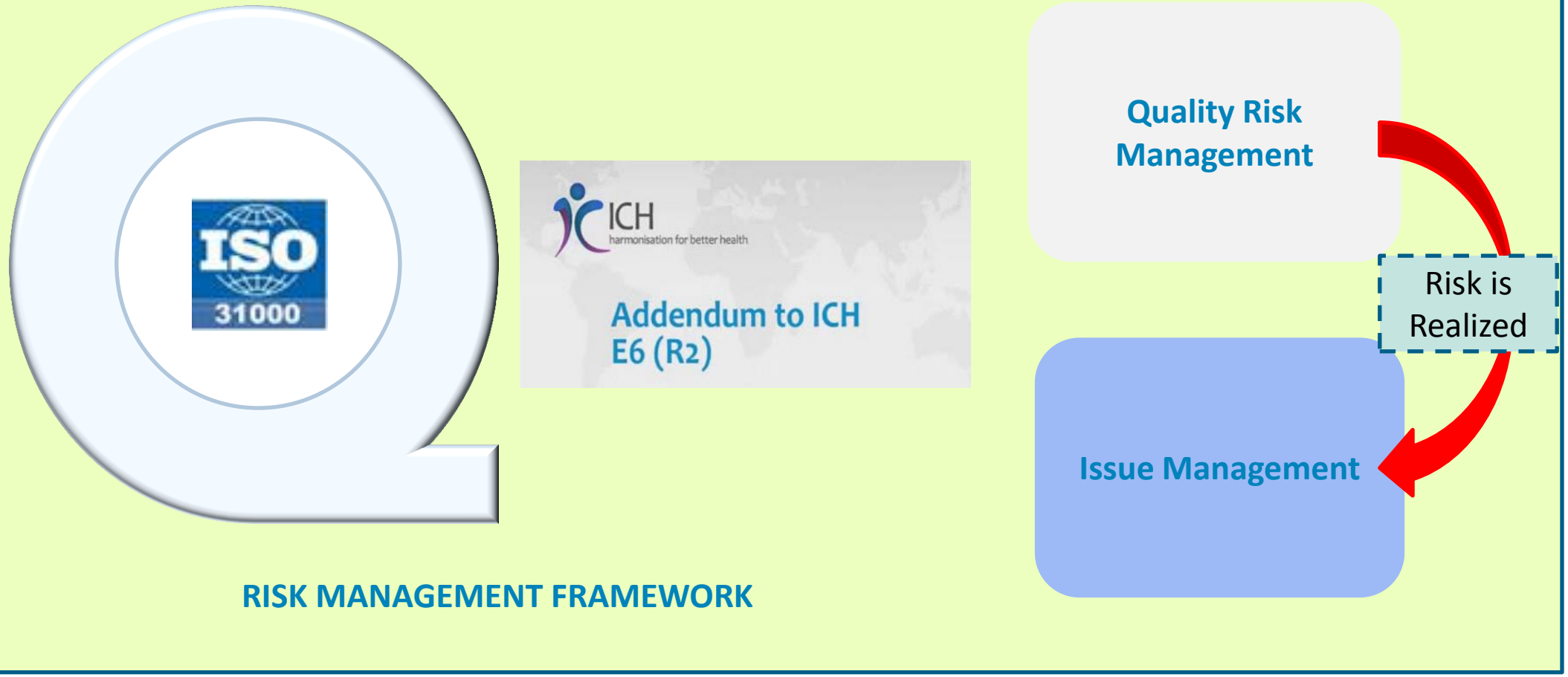
The key intent of the ICH E6 (R2) revision is to make Sponsors, Investigators and Coordinators think about specifics of the trial and how best to implement and manage what is important for the trial and should focus activities that may truly impact critical data or safety

Develop a scientific risk-proportionate approach/understanding and documentation commensurate with the level of risk

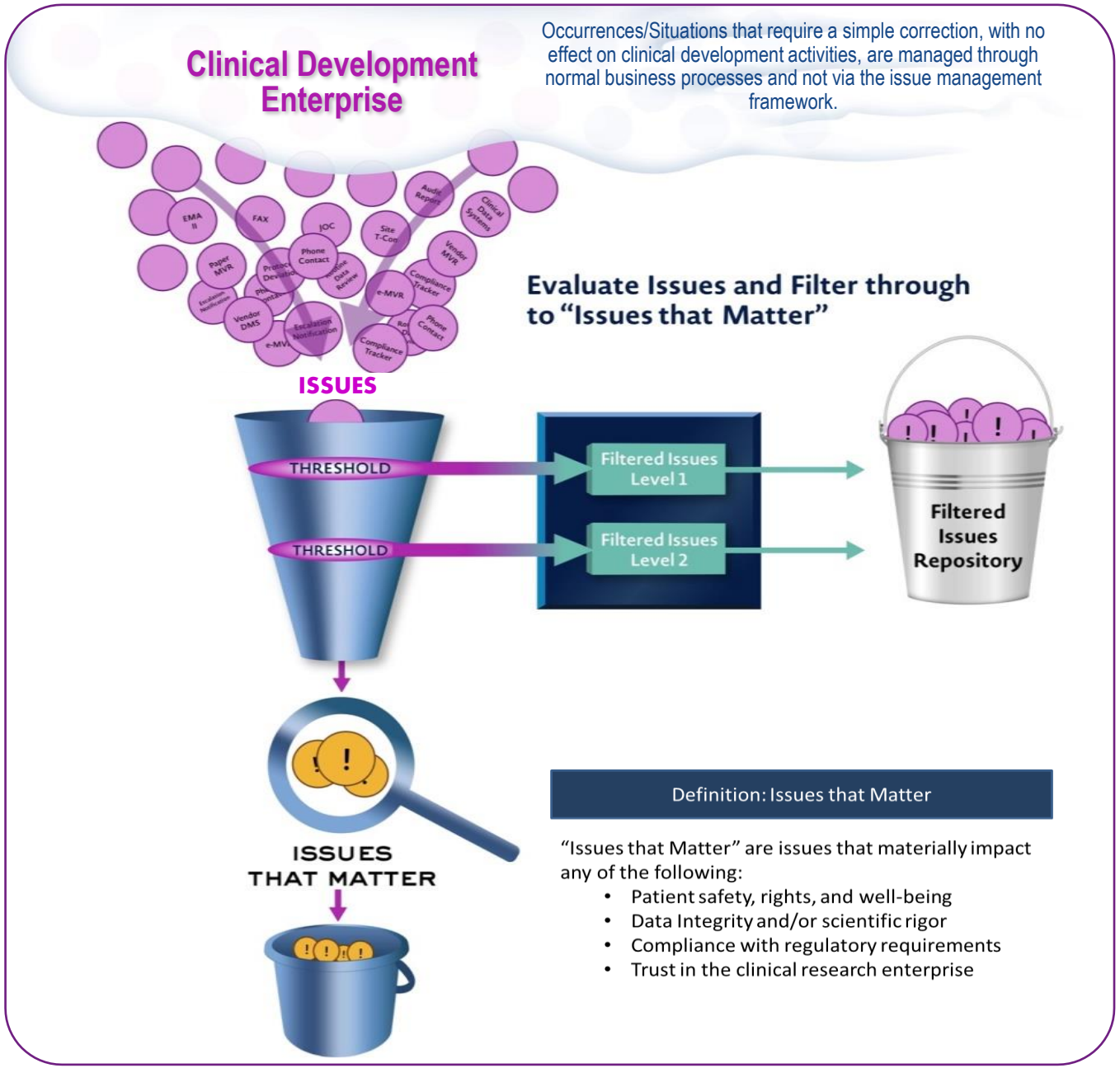
Create a culture that values and rewards critical thinking and open dialogue about quality, that goes beyond sole reliance on tools

> ***"The way that risks are identified, evaluated and mitigated commands a change in the mindset of those who have applied GCP for a very long time already."***

* Oct 20, 2015 by Artem Andrianov, PhD, Beat Widler, PhD, Maria Proupín-Pérez, PhD, *Applied Clinical Trials*



Issues that Matter "Triage" Framework



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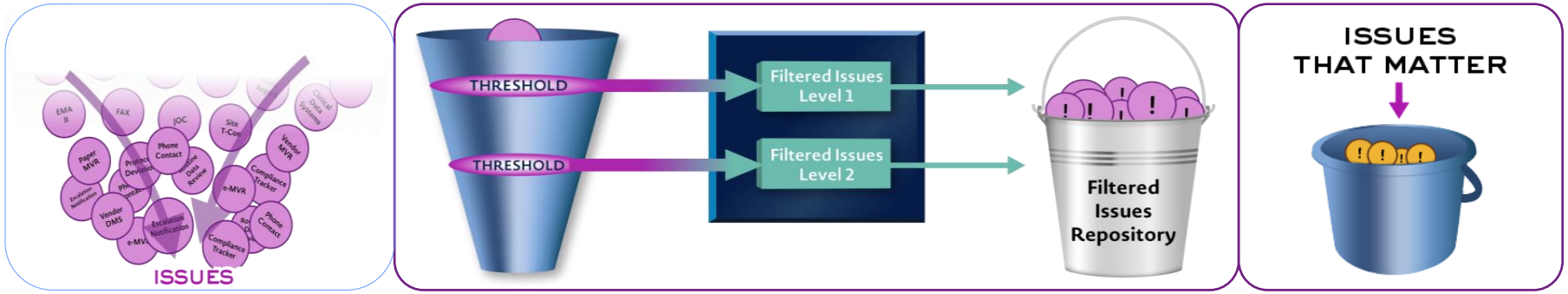

Examples of Sources of Issues:

- Study management and monitoring
- Data trending and analytics (including internal surveillance / metrics)
- Self-identified issues within the clinical development functions
- Issues reported by external parties
- Noncompliance to regulatory requirements throughout the clinical development enterprise
- Audit and inspection results

- Conceptual funnel is a mechanism for filtering issues based on the level of risk.
- Setting thresholds to allow focus on the "Issues that Matter"
- The number of and the definitions of the thresholds will generally be established during risk assessments.

- Issues not meeting definition of "Issues that Matter" are retained for trending and analytics
- In aggregate, filtered issues may uncover a potential risk requiring "Issues that Matter" triage.
- Trending and analytics will feed back into a risk assessment process.

- An issue(s) that materially impacts patient safety, rights, and well-being; data integrity and/or scientific rigor; compliance with regulatory requirements; or trust in the clinical research enterprise will move quickly through the funnel for appropriate escalation and CAPA process
- The preventive action will link back to risk assessment and evaluation of risk mitigation strategies.

The impact of issues is NOT Equal…"Actively Managing the Risk"

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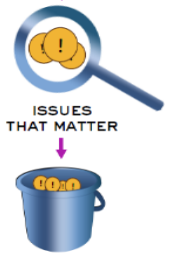
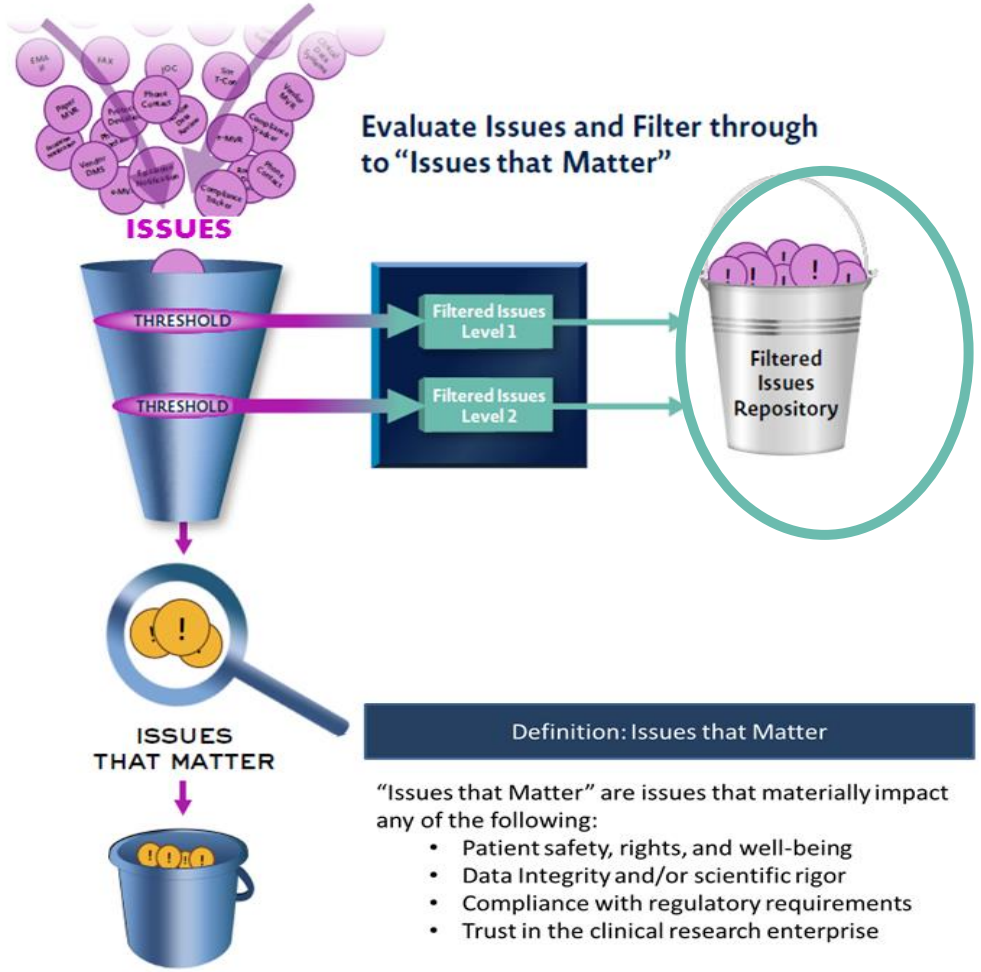
CAPA Process



- A holistic, systematic, and formal process for addressing **Issues that Matter**
- Enables a robust investigation to determine the **root cause(s)** and extent of the **impact** of the issue
- Provides for the development and implementation of a **comprehensive** action plan **(CAPA)**
- Features **robust effectiveness checks** to evaluate the corrections and preventive actions to ensure absence of future occurrences of the “Issues that Matter”

Trending and Analytics



Trending and Analytics - Activities focused on the use of data to aid in **identifying trends and patterns** that **provide insight and actionable recommendations** that lead to **reducing risk and preventing future occurrence** of issues. The output of trending and analytics may result in re-entry to the funnel.

Trending and analytics will feed back into a risk assessment process.

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Conclusion - Quality Risk Management within Clinical Development

- Effective management of risks calls for preemptive identification and mitigation of clinical study risks, thereby preventing occurrence of patient safety and data integrity concerns
- Resource prioritization occurs through reduction in efforts expended on low-value activities; targeting valuable resources to high risk areas
- Focus on key risk factors and critical data in order to mitigate trial errors
- Appropriate risk planning helps develop efficient monitoring approaches to rapidly detect and correct issues while a study is on-going
- Provides Knowledge Management for future applications / indications

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Conclusions – Issue Management

- Effective management of issues is a key driver for ensuring a state of control, continuous improvement, confidence in data and overall enhanced quality.
- The conceptual framework for Issue Management with the described elements will reduce or eliminate the constant rework that drains a company of resources (i.e., includes time, cost and people) and bring about increased collaboration within an organization across functions in the proactive mitigation of risks.
- Application of CAPA process and the utilization of trending and analytics as described in the Issue Management conceptual framework will bring about reduction of Issues That Matter over time.
- A robust Issue Management framework enables regulators to have greater confidence in the research and development enterprise allowing them to focus on the regulatory science.

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Thank you!


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