Issues that Matter
Notification and Escalation
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Issues that Matter may need to be escalated in that they require immediate decision and action by and/or notification of relevant stakeholders.

- **Clinical Development Enterprise**
  - Occurrences/Situations that require a simple correction, with no effect on clinical development activities, are managed through normal business processes and not via the issue management framework.

**Evaluate Issues and Filter through to “Issues that Matter”**

**Definition: Issues that Matter**

"Issues that Matter" are issues that materially impact any of the following:
- Patient safety, rights, and well-being
- Data Integrity and/or scientific rigor
- Compliance with regulatory requirements
- Trust in the clinical research enterprise

**Issues that Matter Notification and Escalation**

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Basic Principles

To ensure rapid escalation and notification takes place, the organization should:

» Prospectively define Issues that Matter (leveraging the organization’s risk management processes), and

» Ensure that an appropriately designed escalation pathway is in place.
Basic Principles

The nature, extent, and impact of the issue should drive the level to which escalation and/or notification occurs.

A clearly defined communication pathway and triggers should focus attention on issues that could undermine the goals of the organization.

Companies must consider defining and implementing appropriate documentation expectations to support the process.
Considerations

An Issue that Matters requires notification and escalation to the appropriate levels of management.

An Issue that Matters should be addressed with a sense of urgency based on its criticality.

Activities in this process may happen concurrently depending on the type of Issues that Matters and company escalation procedures.

A designated individual should take ownership of the issue that matters to ensure all aspects of notification and escalation activities are completed.

The escalation process is not meant to replace CAPA process activities. This information may feed directly into the CAPA process.
A decision tree model is a key tool that can enable proper notification and escalation pathways.

Example Diagram:
The Initial notification of an Issue that Matters should be in a timely manner to ensure immediate communication and awareness.

Notifications should be made to all persons that need awareness of the Issue that Matters. For example, a RACI tool would provide a communication guideline.

» If additional notification is required after the initial communication, recipients should be identified based on the nature, extent, and impact of the issue.

Notification should include the description and current status of the Issue that Matters.

Notifications should continue to ensure impacted parties are aware of the ongoing status. These should include a summary of activities, tentative timeline, and point of contact for questions.
1. An Issue that Matters should be escalated to appropriate management. This will ensure that the appropriate resources are assigned to address the issue in a timely manner.

2. When escalating, include the description of the Issue that Matters, its current status, and any known activities that require direct and/or Senior Management input.

3. After the initial escalation, if it is determined that additional escalation is required, recipients should be identified based on the nature, extent, and impact of the issue.
Escalation Decisions

1. Responses to an escalated Issue that Matters should be expected within an appropriate timeframe based on the severity of the problem. The person escalating the issue should communicate this expectation to the escalation recipient(s).

2. Consider the nature, extent, impact and prevention of any unintended consequences when making decisions and taking immediate actions.

3. Track all escalation decisions and immediate actions to completion and communicate status as appropriate.

4. Examples of decisions include:
   » How to contain
   » Decision to immediately stop enrolling patients
   » Conduct a “for cause” audit
   » Escalate to higher level of management based on the severity

Consider: Some of these decisions and actions may be an input into the CAPA process for documenting the immediate response.
Complete the Process

1. The Issue Owner should document the escalation activities and outcomes.

2. The Issue Owner should communicate next steps to management and notification recipients.
These are hypothetical, generalized examples.

The actions identified in these examples should not replace any company-specific procedures. Specific actions and order of actions may differ by company.
Issue:
Study XYZ had a site where 7 subjects violated Critical Inclusion Criterion A at 1 site. The study monitor discovered this during the first visit after the enrollment began, per the monitoring plan.

Background Information:
If more than 25 subjects violate 1 of 3 critical inclusion criteria for Study XYZ, their required exclusion from the per protocol analysis will result in a loss of statistical power.

Company ABC has set their Threshold for Action at 5 subjects violating at least 1 of the 3 criteria.

This is now an “Issues that Matter” based on this established threshold.
Scenario #1

Per Company ABC’s procedure for Issue Escalation, the Study Monitor **notifies** the Monitoring Manager. The Monitoring Manager **escalates** to the Study Program Manager.
Scenario #1

The Study Program Manager takes ownership of the Issue that Matters.

Based on Company ABC’s Issue Escalation SOP, the Study Program Manager escalates the Issue that Matters and calls an immediate meeting of all of the Escalation Recipients including:

- Direct management
- Clinical compliance management
- Study designated physician
- Safety management
Scenario #1

The following decisions are made during the escalation meeting:

Suspend enrollment at the site.

Safety will determine the potential impact to the subjects.

Compliance is assigned to investigate the cause of the non-compliance at the site and confirm that it is not a systemic issue.

Study Designated Physician will determine if continued participation of the affected subjects in the study is in the subjects' best interest.

Statistics will determine the impact to the study data from the site.

Clinical QA will determine if there is misconduct and if a directed audit is warranted.

Note: Some of these decisions will be inputs of the CAPA process.
Scenario #1

The escalation meeting also identifies additional areas that should be subject to notification:

Statistics, Data Management, and Regulatory representatives receive notification of the Issue that Matters by email.

Note: This notification is for awareness only, they do not have immediate actions and/or decisions to weigh in on at this time.
Scenario #1

The Study Program Manager documents all decisions and escalation activities.

The Study Program Manager communicates CAPA status at regular time points and any additional escalation activities or containment actions to management and notification recipients.
Scenario #2

Issue:
Study Monitor suspects fraud at an Investigator’s site.

Background Information:
Fraud was suspected at the ACME Investigator site for Study XYZ by the study monitor. The Study Monitor suspected that study records had been falsified. The falsification of study records impacts safety, quality, and regulatory aspects of the study.

This is identified as an Issue that Matters and will require notification and escalation.
Scenario #2

Study Monitor notifies their direct management of the Issue that Matters. The Monitoring Manager is the direct manager of the Study Monitor.

Per company SOP, the Monitoring Manager then escalates the Issue that Matters to Clinical Compliance management. Clinical Compliance management then takes ownership of the Issue that Matters.
Scenario #2

**Additionally, the Issue that Matters is escalated to:**

GCP QA Program Manager

GCP QA Director

Clinical Program Lead

Monitoring Management Lead
Scenario #2

The following decisions were made during the escalation meeting including the previously identified escalation recipients:

Senior Management will decide if the data from the site needs to be removed from the data set and if the site needs to be closed.

QA will conduct an audit to confirm suspected fraudulent activities.

A CAPA will be initiated to investigate the cause and breadth of the fraud and determine appropriate corrective actions.

Regulatory will decide if the FDA needs to be notified.

Statistics will determine the impact to the study data.
Scenario #2

Regulatory, Safety, Statistics and Data Management representatives will be notified of the Issue that Matters.

Additionally, Regulatory and Statistics will be notified of their assigned activities identified during the escalation meeting.
Scenario #2

Clinical Compliance management should document all decisions and escalation activities. Appropriate documentation should be included in the CAPA process activities.

Clinical Compliance management communicates CAPA status at regular time points and any additional escalation activities or containment actions to management and notification recipients.