



Audit Ready, All the time!

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Goals

- **Define Core Quality & Audit Concepts:** By the end of the session, participants will be able to distinguish between three main types of audits (Internal, External, Regulatory) and explain how Quality by Design (QbD) principles reduce compliance risk.
- **Analyze & Prevent Non-Conformances:** Participants will be able to identify the top three most common audit findings and evaluate their current operational processes against best practice to mitigate those risks.
- **Demonstrate In-Audit Execution:** Participants will be able to outline the step-by-step protocol for hosting an auditor, including proper communication etiquette, document handling, and real-time query management.
- **Develop a CAPA Remediation Plan:** Following an audit outcome scenario, participants will be able to perform a root cause analysis and construct an actionable Corrective and Preventive Action (CAPA) plan that satisfies regulatory standards.



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Quality

- Quality should be built into the scientific and operational design and conduct of clinical trials
 - Fit for purpose
 - Identified prospectively – critical quality factors
 - Factors to avoid, detect, address and prevent recurrence

ICH, E6(R3): https://database.ich.org/sites/default/files/ICH_E6%28R3%29_Step4_FinalGuideline_2025_0106.pdf

Quality Management

- Quality management includes the design and implementation of efficient clinical trial protocols
 - including tools and procedures for trial conduct (including for data collection and management), in order to ensure the protection of participants' rights, safety and well-being and the reliability of trial results.
- Data Integrity Data integrity includes the degree to which data fulfill key criteria of being attributable, legible, contemporaneous, original, accurate, complete, secure and reliable such that data are fit for purpose.

ICH, E6(R3): https://database.ich.org/sites/default/files/ICH_E6%28R3%29_Step4_FinalGuideline_2025_0106.pdf

Quality Assurance vs Quality Control

- Quality Assurance (QA):
 - All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded) and reported in compliance with GCP and the applicable regulatory requirement(s).
- Quality Control (QC):
 - The operational techniques and activities undertaken to verify that the requirements for quality of the trial-related activities have been fulfilled.

ICH, E6(R3): https://database.ich.org/sites/default/files/ICH_E6%28R3%29_Step4_FinalGuideline_2025_0106.pdf

Quality Assurance Examples

- Creation of standard operating procedures
- Review of documentation (e.g., of completed checklists) to confirm that an established quality process is being followed
- Review of training logs to ensure that sufficient and relevant training has been completed and documented.

Quality Control Examples

- Completing checklists to confirm the appropriateness of each subject's informed consent process
- Conducting systematic comparison of the electronic (or paper, if applicable) clinical data to the medical records
- Reviewing the contents of the Essential Documents Binder and documenting the results of the review.



Definitions

- **Monitoring:**
 - The act of overseeing the progress of a clinical trial and of ensuring that the clinical trial is conducted, recorded and reported in accordance with the protocol, SOPs, GCP and the applicable regulatory requirement(s).
 - Continuous oversight
 - Real-time
- **Audit:**
 - A systematic and independent examination of trial-related activities and records performed by the sponsor, service provider (including contract research organization (CRO)) or institution to determine whether the evaluated trial-related activities were conducted and the data were recorded, analyzed and accurately reported according to the protocol, applicable standard operating procedures (SOPs), Good Clinical Practice (GCP) and the applicable regulatory requirement(s).
 - View at a given moment
 - Process-Based
- **Inspection:**
 - The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records and any other resources that are deemed by the authority(ies) to be related to the clinical trial and that may be accessed at the investigator site, at the sponsor's and/or service provider's (including CRO's) facilities, or at other establishments deemed appropriate by the regulatory authority(ies).

ICH, E6(R3): https://database.ich.org/sites/default/files/ICH_E6%28R3%29_Step4_FinalGuideline_2025_0106.pdf



What Standards Does an Auditor Use?

Federal
Regulations

(21 CFR, HIPAA)

Guidance
Documents (ICH GCP
& FDA)

Institutional SOPs & Standards

Departmental SOPs

Protocol



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QUALITY BY DESIGN

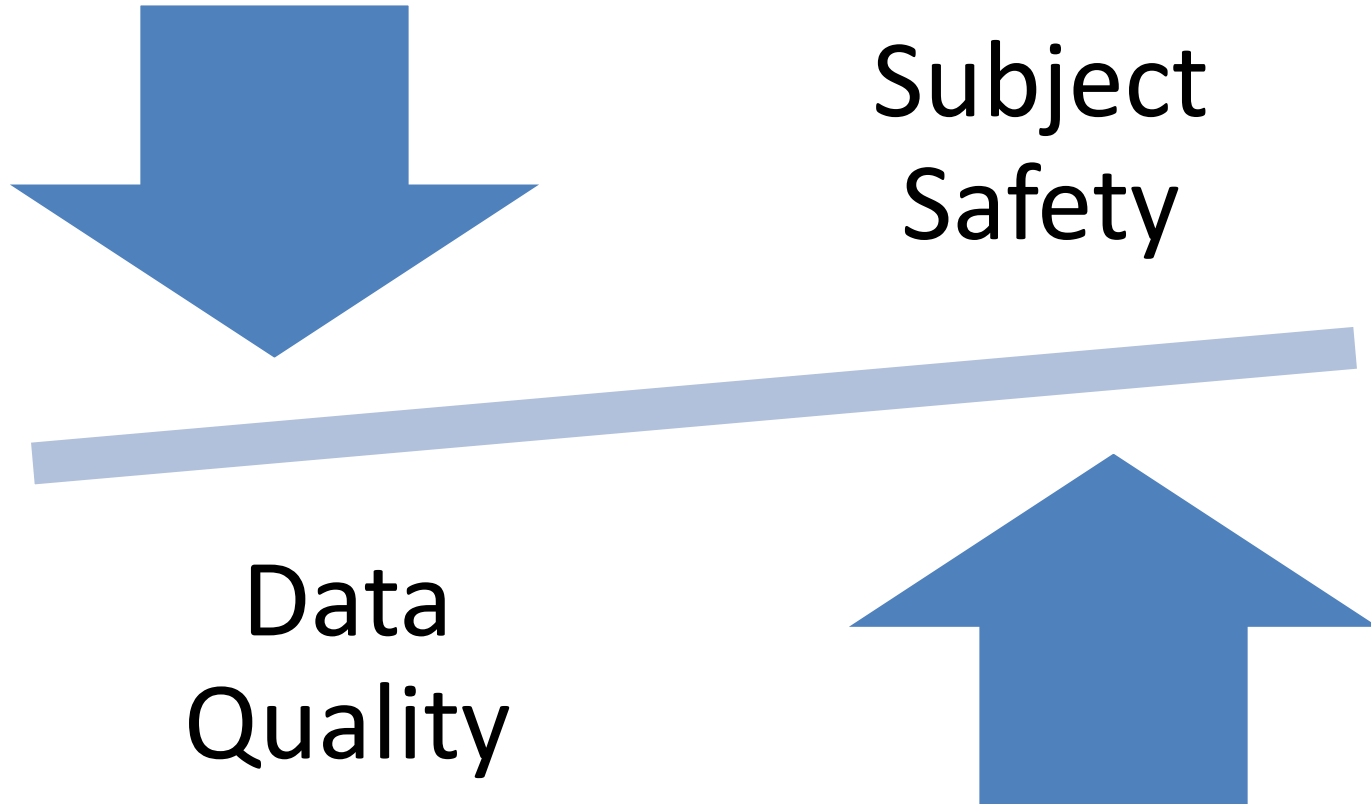


Rory Collins, MBBS, MSc, University of
Oxford

“Undue emphasis has been
placed on data accuracy when,
in fact, reliable results can be
obtained even from imperfect
data.”



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Quality by Design: QbD Defined

**“Quality” in clinical trials is defined as
the absence of errors that matter**

Prospectively examining
the objectives of a trial and
defining factors critical to
meeting these objectives

... focusing effort on
those “errors that
matter” for the success
of the clinical trial

... taking action to
prevent important risks to
these critical factors from
negatively impacting
outcomes

Understanding what
data and processes
underpin a successful
trial is essential to
subsequently identifying
and managing important
and likely risks to
**improve quality and
outcomes for clinical
trials**





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How QbD Improves Clinical Trials

**QbD helps
organizations
become**

***prospectively and fully
aware throughout the
trial lifecycle***

**of the important errors
that could jeopardize
the ability to ...**

Protect patients during the trial

Obtain reliable results and meaningful information
from the trial





QbD Implementation: Plan, Do, Check, Act

Build/plan quality into clinical trials from the beginning, focusing on what matters most

PLAN



Systematically drive
remediation and
learning

ACT



CHECK



DO



Implement study risk
management
strategies

Monitor leading indicators of
quality in the study



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Mitigate those risks that will likely lead to errors
that matter and determine how to rapidly
identify and react when there is an issue



What does QdD Look Like?

- Building a protocol that collects data that is relevant to the objectives of the study and no more
- As a study team identify risks to participants rights, safety and well-being and the reliability of the results
 - Risk identification
 - Evaluation of risk (Critical to Quality Factors)
 - Mitigation/control of risk
 - Risk review

Scenario: Phase III Oncology Trial (Investigational Oral Targeted Therapy)

Identification of Critical-to-Quality (CtQ) Factors

- Instead of tracking hundreds of low-impact parameters, the team identifies what directly affects **participant safety** and **primary endpoint reliability**:
- **CtQ Factor 1:** Correct patient selection based on genetic tumor biomarkers (minimizing risk to ineligible patients).
- **CtQ Factor 2:** Timely detection and reporting of Serious Adverse Events (SAEs)—specifically drug-induced liver injury (DILI).
- **CtQ Factor 3:** Precise measurement of primary progression-free survival (PFS) via centralized imaging.

Operational Risk	Likelihood / Impact	Risk Control Design (QbD Approach)
Incorrect Enrollment: Local labs misinterpret biomarker eligibility.	Medium / Critical	Built-in Control: Protocol requires central lab confirmation <i>before</i> randomization. The eCRF system blocks treatment assignment until central lab validation is uploaded.
Delayed Toxicity Management: Sites miss early signs of DILI in patient lab panels.	Medium / High	Built-in Control: Automated alert in the EDC system flags elevated ALT/AST levels instantly to both the site and the safety monitor.
Excessive Monitoring: CRA spending hours verifying minor administrative protocol deviations (e.g., late visit windows by 1 day).	High / Low	Risk-Proportionality: Eliminates 100% Source Data Verification (SDV) for non-CtQ variables. CRAs focus 80% of their time auditing consent forms, lab safety alerts, and imaging compliance.

Key take away

Under **ICH E6(R3)**, QbD transforms risk management from a passive compliance checklist into a **proactive design process**.

Quality is achieved by designing out unnecessary complexity, protecting CtQ factors, and focusing oversight where risks truly impact patient safety and data reliability.



Common Audit Findings



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Regulatory Binders



Common Audit Findings: Regulatory Binder

- Incomplete/Incorrect Delegation of Authority Log
 - Study personnel assigned inappropriate responsibilities/tasks
 - Dates of study involvement vs dates of protocol/study training
 - Missing study personnel or no end dates

Common Audit Findings: Regulatory Binder

- Lack of protocol or study device training documentation
- 1572 not being updated with addition of Sub-Investigators
- Missing monitoring reports or inaccurate monitoring visit logs
- Unresolved financial COI for Investigators

Study Drug/Device Documentation

- Usually maintained in a separate binder where investigational drug/device is stored;
- Will need 2 documents:
 - Documentation of temperature log for drug
 - Even if stored in room temperature!
 - What is your off-hours storage plan?
 - Accountability Documentation

Common Audit Findings: Regulatory Binder

- Lack of Standard Operating Procedures for protocol-specific procedures
 - Fills the gap between protocol & institutional policies
 - Most commonly needed in investigator or non-commercial sponsored studies

Common Audit Findings: Drug/Device Accountability

- If subject consistently not returning study drug during study visits, what about drug compliance?
- Temperature excursions—what is the follow-up?
- If subject admitted to hospital, no documentation re: study drug compliance



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Informed Consent Documentation



Common Pitfalls ICF Documentation

- ICF process not documented
- Not checking box for opt-in/opt out sections
- If English is not native language & documentation of clinical interpretation in EMR, why ok to consent participant with English ICF?
- No re-consent or poor documentation of re-consent
- No written explanation in ICF process note for different signature dates for virtual consent
- For inpatient studies, not reconsenting the subject if an LAR consented on behalf of the subject



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Source Documentation



Source Documentation vs Case Report Forms

- What is Source Documentation?
 - Where you “show your work”, original form of data
 - FDA refers to source as “case histories”
- Need to build a story with your source data
 - “If it wasn’t documented, it wasn’t done.”
- Good source data is key to protocol compliance.
 - Look at protocol schedule of events for hidden “easter eggs.”
- Electronic Medical Record is part of source
- Checklists are your friend!

Common Audit Findings: Source Documentation

- No signature/date lines to attribute who is completing source
 - Differentiation between PI & CRC
- “Too much” source
 - Don’t double document
- Formatting
 - Subject identifiers on each page

Common Audit Findings: Inclusion/Exclusion Documentation

- Each criterion should have supporting documentation, whether it be in EMR, lab values or a PI note.
 - Be careful of criteria that is somewhat nebulous!
 - Documentation of discussion for required methods to avoid pregnancy and fertility preservation as indicated
 - Specific documentation for failure of conventional treatment

Common Audit Findings: Laboratory Results Review

- For any protocol-required labs, an Investigator should sign off indicating his/her review.
- Additionally, any abnormal values should be labeled as “CS” (Clinically Significant) or NCS “Not Clinically Significant.”
- Any labs labeled “CS” would then become adverse events with documented clinical follow-up.
- Not obtaining local pregnancy testing result prior to study visit and dispensation of study drug.

Inclusion/Exclusion Documentation

III. Inclusion/Exclusion Criteria

Inclusion Criteria (From IRB-approved protocol)	Yes	No	Supporting Documentation*
1.	☐	☐	
2.	☐	☐	
3.	☐	☐	
Exclusion Criteria (From IRB-approved protocol)			
II.	☐	☐	
III.	☐	☐	
IV.	☐	☐	
V.	☐	☐	

IV. Statement of Eligibility

This subject is ☐ **eligible** / ☐ **ineligible** for participation in the study.

Signature:	Date:
Printed Name:	

Adverse Events



Common Pitfalls Adverse Event Reporting

- Not thoroughly capturing all baseline conditions-
REDUCES AE BURDEN
- AEs not properly documented in log with PI signature review.
 - Please do this in REAL-TIME.
- Please review the study protocol regarding sponsor reporting requirements!

How to document AE evaluation?

Adverse event	Start and stop dates	Serious	Severity (Oncology Studies, Use CTCAE 1-5 system)	Relationship to study agent	Anticipated	Action taken with the study agent	If Serious, date PI became aware	Was the SAE reported to the sponsor?	Was the SAE reported to the IRB?	PI initials and date	Comments /PI Initials at AE Closure
	Start: Stop:	☐ Yes ☐ No		☐ Not related ☐ Possibly related ☐ Related ☐ Unknown	☐ Yes ☐ No	☐ None ☐ Reduced ☐ Interrupted ☐ Discontinued ☐ Other:		☐ No ☐ Yes Date:	☐ No ☐ Yes Date:		

AE Documentation: Pro Tips

- An AE that worsens into an SAE is a separate event—i.e. the SAE will have a start date that is the stop date of the AE.
- PIs need to be aware of what they're signing off on the AE Log!! If the AE is thrombocytopenia, then the PI should be identifying the low platelet count on the lab sheet as “Clinically Significant.”

Difference between Recording & Reporting AEs

- All AEs should be recorded,
- But not all AEs are reported to IRB!
 - Which AEs should be reported?
 - How do you know if an AE is unexpected?

FDA Inspection Preparation

(Also called a BIMO Inspection—Bioresearch Monitoring)



FDA Audit-Bad News

- Inspectors don't have to give much heads-up
- Can choose to audit a study at any time—usually inspect studies that are completed, some many years after the fact.

Good News: FDA Inspection

- Relatively small number: FDA finalized 609 inspections of PIs in 2024 (domestic & international)
- What they're going to inspect isn't a surprise:

[FDA Inspection Playbook](#)

- Detailed instruction of process and objectives for Clinical Investigators
- Sponsor-investigators are subject to both CI and sponsor requirements

If the FDA comes knockin'....

- “Field investigator” from field office will call the PI
- Average advance notification is five days
 - Will honor inflexible commitments
- Who should you notify?
 - Sponsor; IRB; Institution compliance officer
- Prepare like a super-duper monitoring visit-remove all stickies!
- Mock Q&A with PI/CRC
- Review “one off” subject situations
- Decide who will be the institutional “debriefers” and how electronic medical records will be reviewed

During Inspection

DO:

Answer questions concisely.

Provide copies of documentation if requested.

Maintain a log of what is copied for Inspector.

DON'T:

Guess or volunteer information.

Be defensive.

Completion of Inspection...

- The FDA investigator will usually hold an exit interview with team. Will indicate next steps.

Potential Inspection Outcomes

- NAI: “No Action Indicated”-483 is not issued
 - Approximately 80% of the FY24 CI inspections
- VAI: “Voluntary Action Indicated”
 - Objectionable conditions or practices were found that represent departures from regs
 - Must be completed within 15 business days
- OAI: “Official Action Indicated”
 - Objectionable conditions or practices found represent SIGNIFICANT departures from regs & may require the imposition of administrative/regulatory sanctions

CAPA Introduction

What is a Corrective and Preventive Action (CAPA)?

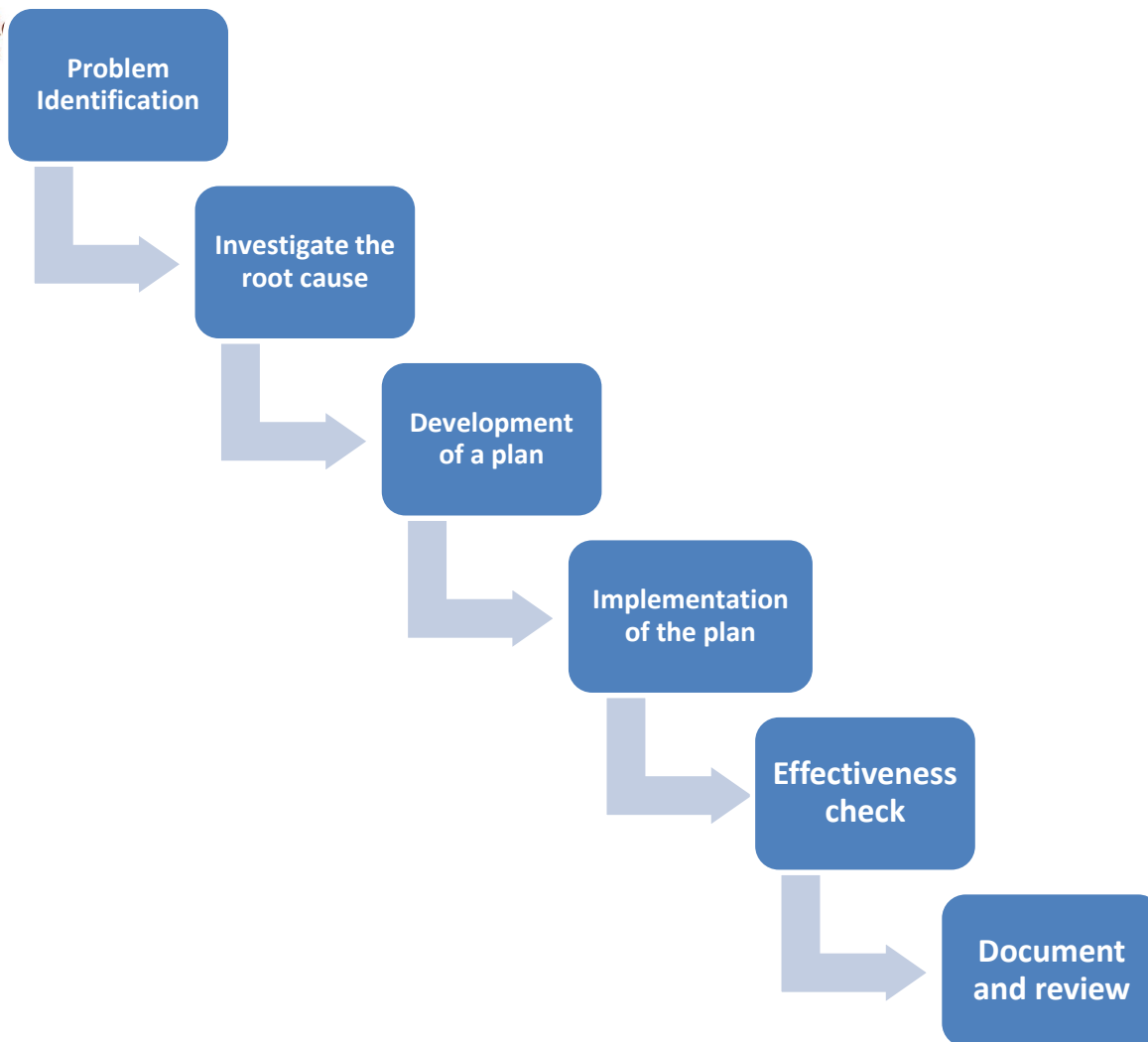
“A corrective and preventive action (CAPA) plan is a series of actions taken to resolve a compliance issue, and most importantly, to prevent further recurrence”

Corrective action

CAPA

Preventive action

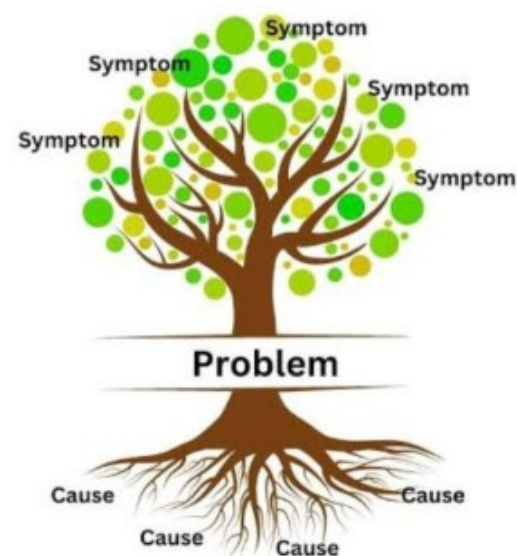
Stages of a CAPA



Components of a CAPA

1. Root Cause

- The root cause is the factor that contributed to the problem or deficiency and needs to be addressed to prevent this from happening again





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Components of a CAPA

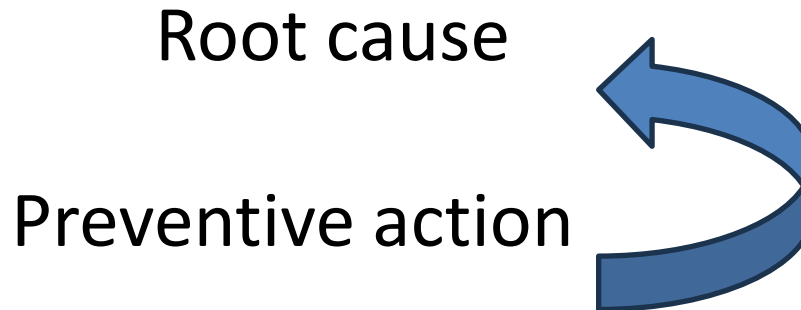
2. Corrective action

- Address immediate action needed to resolve or correct the problem identified
- Special attention should be given to participant safety issues.
 - Describe if participant was harmed or not harmed.
 - Actions taken to prevent or reduce harm
- Be specific and attach any documents necessary to substantiate the response.

Components of a CAPA

3. Preventive Action:

- Actions taken, after a root-cause analysis is performed, to prevent the specified deficiency identified from occurring again.
- The preventative action may also include plan to identify problems prior to them becoming a deficiency.





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Components of a CAPA

4. Evaluation (Effectiveness check)

- Describe plans to evaluate the implementation, completion, timeframe of the preventative actions.
- Critical to ensure that changes to prevent the identified deficiency have the desired effect.
- The evaluation should be specific – What, How, Who and When
- Regulatory authorities hold study team accountable – be realistic

Keep in mind!

- Trainings may not be a sufficient preventative action plan if it was already provided in the past.
- Evaluation plan should involve additional study team members, possibly the managers.
- At evaluation, if it is determined that the preventative action is not working as intended, a new plan should be developed.

Root Cause Analysis

Goals are to determine:

- What happened
- Why and how it happened
- Actions for preventing the deficiency from happening again

Each of the following causes should be explored:

- Human (e.g. staffing issues/ human error)
- Physical (e.g. there was construction or freezer malfunction)
- Organizational (e.g. no standards or onboarding)

5 Whys example

- Problem: The urine sample for the Urinalysis has been missed on the last three research participants at the screening visit.

Why?

- Why was the urine sample missed on the last three research participants at the screen?
 - *The research assistant forgot to collect it*

Why?

- Why did the research assistant forget to collect it?
 - *The research assistant did not know that it was needed*

Why?

- Why did the research assistant not know that it was needed?
 - *The Urine was not included on the study source flow sheet or CRF*

Why?

- Why was the urine not included in the study flow sheet or CRF?
 - *The CRC who developed the Flow Sheet / CRF left it off in error*

Why?

- Why did the CRC who developed the Flow Sheet / CRF leave it off
 - *There was no quality control mechanism to double check the flow sheet represented the protocol accurately*

Example

Problem: Concomitant medications were not captured in the EDC by the data coordinator (DC).

Root Cause

- Why – DC did not have the source to enter the data
- Why – When the CRC handed over the source documents to the DC, concomitant medication log was missed to be included
- Why – CRC did not check if the study binders had all documents
- Why – There was no checklist for hand off

Corrective Action

Concomitant medications log will be given to DC for completion of data entry.

Preventative Action

- A hand off checklist will be created to ensure all necessary source is handed to the DC
- If the DC notices there is no source to support data entry, they will consult with their manager to confirm if source is available or not.

Evaluation Plan

- Study team manager will quality check 20% of data entry every 3 months to evaluate accuracy and completion until there is less than 5% incomplete data entry rates
- After 3 such quality checks, CAPA effectiveness will be evaluated

Tips

- Pay close attention to the root cause analysis – it is the key to determining the appropriate corrective and preventative actions.
- Ensure the preventative actions and evaluation plan are tied to the root cause.
- Ensure the preventative actions and evaluation plans are realistically doable.



Subject Safety

Data Integrity

RECORD FINISH



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Discussion and Implementation



Questions?

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