UNIVERSITY OF MIAMI

Closing the Gaps: Turning Non-Compliance into Continuous Improvement

Di Ding, Ph.D., RAC, CIP
Sr. Manager, Human Subjects Research Office (HSRO)

Helen Miletic, MA, CHRC, RQAP-GCP
Director, Research Quality Assurance (RQA)

Ashley Kaufman, MA, CCRP
Sr. Quality Assurance Auditor, RQA

Introduction

Joint presentation by the HSRO and RQA:

Demonstrates how our offices compliment each other and communicate to ensure a unified commitment to quality and ultimately fostering a culture of continuous improvement across research and operational practices.

Learning Objectives

Fostering a culture of continuous improvement

Examine non-compliance trends at UM

Define elements of an effective CAPA Plan

Review reporting requirements

Importance of communication and collaboration

Human Subject Research Office (HSRO)

UNIVERSITY OF MIAMI

Navigating Non-Compliance: Reporting and Analysis

Definition of non-compliance and when to report it

In-depth review/analysis-report preparation

Frequent issues with RNI reports

Presented by:

Di Ding, Ph.D., RAC, CIP
Sr. Manager, Human Subjects Research Office (HSRO)

Definition of Non-Compliance

- Non-Compliance: Failure to follow the regulations, or the requirements or determinations of the IRB. – *UM HRP-SOP-001*
- * Continuing Non-Compliance: A pattern of non-compliance that suggests the likelihood that, without intervention, instances of non-compliance will recur, a repeated unwillingness to comply, or a persistent lack of knowledge of how to comply.
- * Serious Non-Compliance: Serious noncompliance can be defined as failure to comply with regulations, university policies, or the requirements/determinations of the IRB, when, in the judgment of the institution, such failure substantially increases risks to subject welfare/safety, subject rights, or data integrity. Serious noncompliance may also involve compromising the effectiveness of UM's human subject research protection program.

** Requirement of external report to the oversight agency*

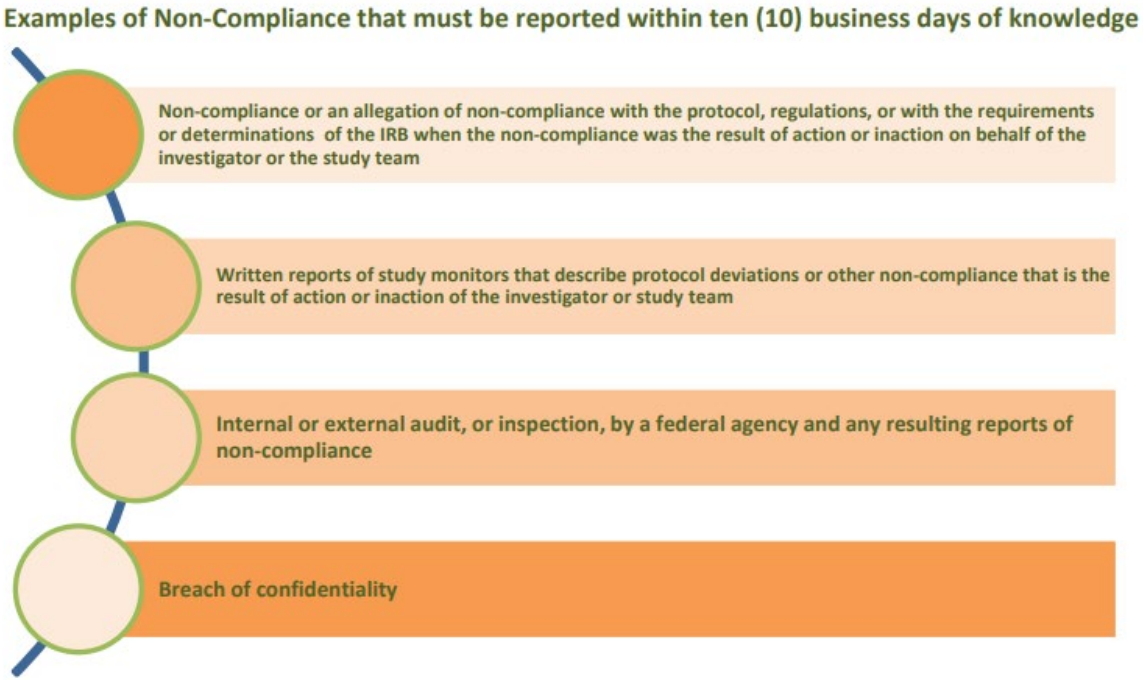
Reports of Non-Compliance

UNIVERSITY OF MIAMI

-Submit within 10 business days of knowledge

HRP-103 Investigator Manual

Investigators must submit reports of non-compliance that result from ***an action or inaction of an investigator or study team member***. If a research participant is frequently or continuously noncompliant with study requirements, you must address the non-compliance or consider withdrawing the participant. Please contact the HSRO for guidance "Study team member" includes departments that support the research, such as the laboratory, nursing, or Investigational Drug Services.



The University of Miami must inform Jackson Health Systems of noncompliance that occurs at a JHS facility. You must report the location of deviations and other non-compliance.

UM IRB does not define major or minor deviation. Please do not submit deviations through CR reports. According to the UM policy, all non-compliance should have been submitted within 10 working day timeframe already.

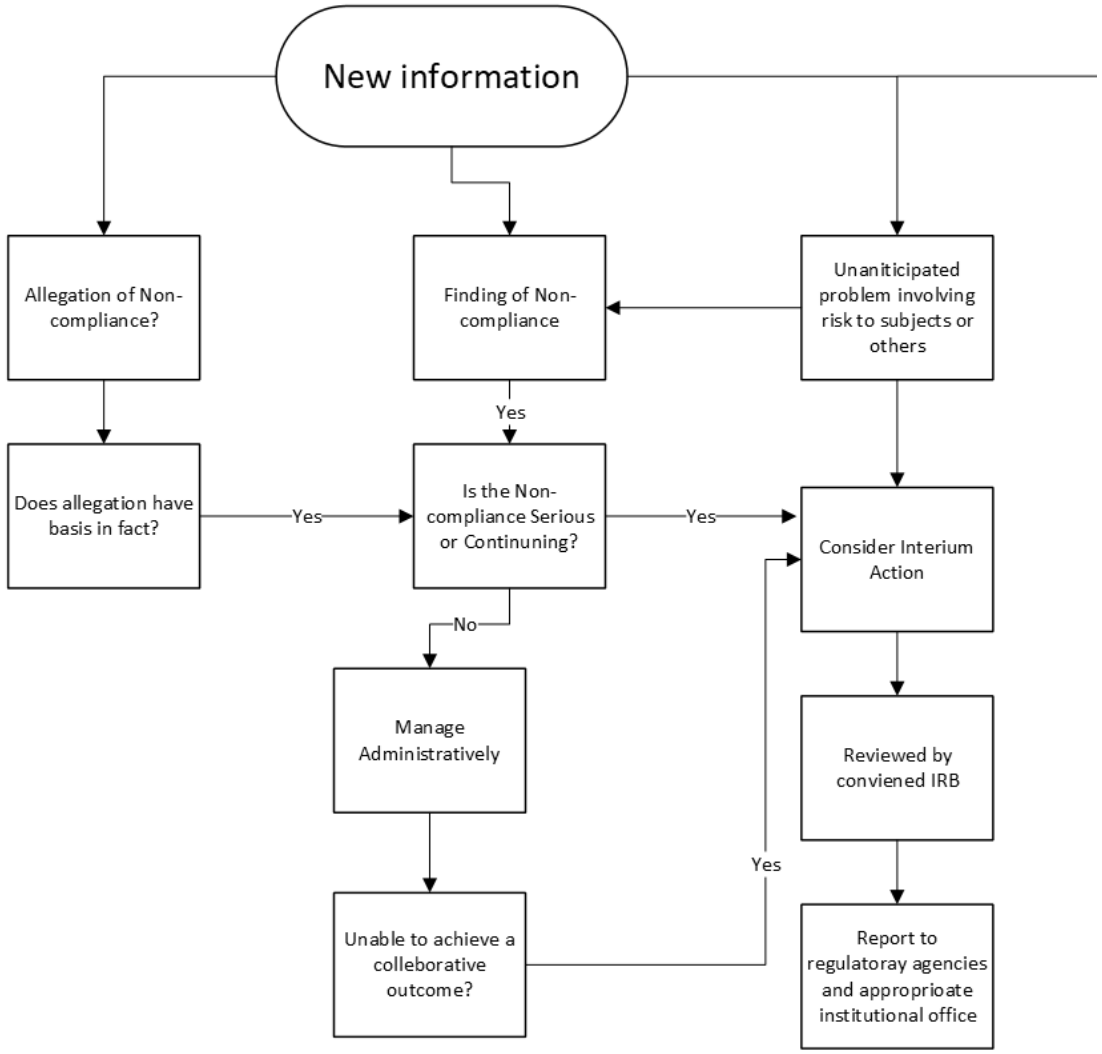
HRP-024-New Information

The IRB is required to prompt report to the appropriate institutional officials, and regulatory agencies of:

1. Any **unanticipated problems involving risks to human subjects or others**;
2. Any instance of **serious or continuing noncompliance** with these regulations or the requirements or determinations of the IRB; or
3. Any **suspension or termination** of IRB approval.

-45 CFR 46.103(b)(5), 38 CFR 16.103(b)(5) and 21 CFR 56.108(b).

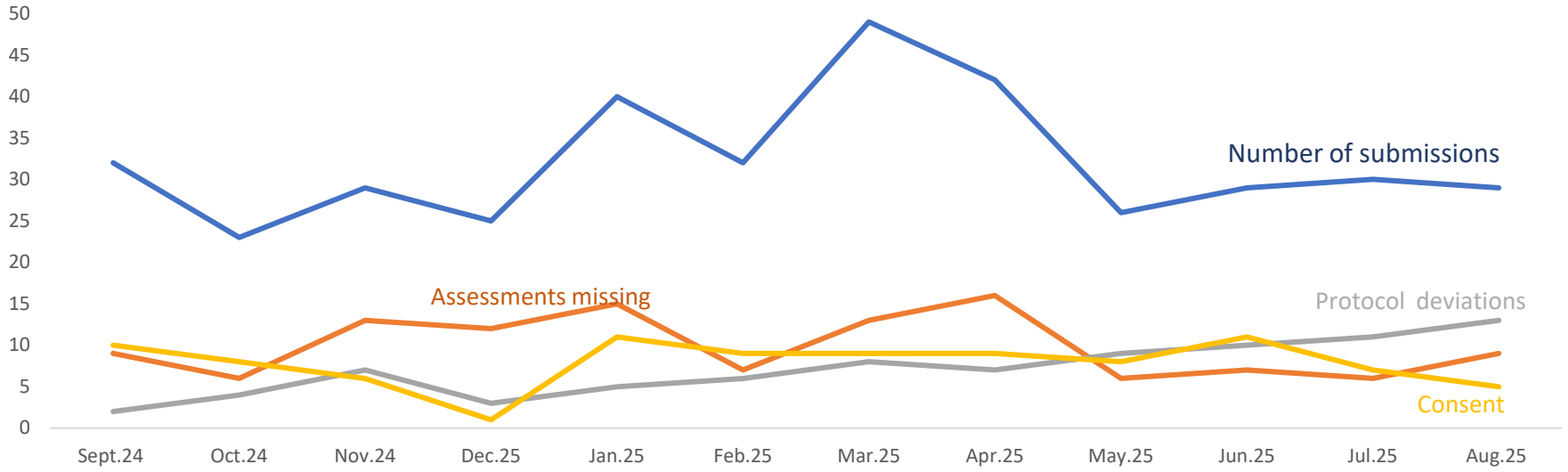
HRP-001 - SOP - Definitions



-Chart excerpt for non-compliance related process

Non-Compliance Submissions

	Sept.24	Oct.24	Nov.24	Dec.25	Jan.25	Feb.25	Mar.25	Apr.25	May.25	Jun.25	Jul.25	Aug.25
Numbers of submissions	32	23	29	25	40	32	49	42	26	29	30	29
Assessments missing	9	6	13	12	15	7	13	16	6	7	6	9
Consent	10	8	6	1	11	9	9	9	8	11	7	5
PHI related	3	1	2	2	2	0	2	0	2	1	1	1
Inadeqate record keeping	3	0	0	1	1	2	2	1	1	1	1	0
Protocol deviation (Procedure was done incorrectly)	2	4	7	3	5	6	8	7	9	10	11	13
Eligibility	0	2	1	3		3	1	4	0	1	2	0
Delegation/training	0	0	0	1	0	5	6	2	1	5	0	2



Recent Trends in RNI Reports

UNIVERSITY OF MIAMI

Increased amount of protocol deviation

Deficiencies in consent process

High level of missing protocol assessment

In Depth Review/Analysis - Report Preparation

UNIVERSITY OF MIAMI

Study-wide evaluation

Multiple Deviations

A. Were the deviations identified during the internal review?

Provide a complete list of the incidents identified in the same process.

Conduct root causes analysis for each deviation and provide a corresponding CAPA plan based on each identified root cause.

B. Were the deviations identified incidentally?

(Does the number of randomly identified deviations suggest the possibility of additional, undetected issues?)

Conduct internal monitoring or a comprehensive review of the remaining study documents to assess for further deviations.

Single Deviation

Is this a repeated issue?

When was the last report submitted regarding this deviation?

Was a CAPA implemented at that time?

*If the issue has recurred, a more robust CAPA and clear justification are required to prevent future occurrences.

Risk analysis

Is there a safety impact?

- ***Eligibility-Screening Error***
- ***Medical error (Procedure, Assessment, etc.)***
- ***Missing Assessments - Safety Monitoring***
- ***Other Errors Potentially Impacting Safety***

Frequent Issues with RNI reports

- **Parent study is missing - Add related study/studies**
- **Basic information:**

Ambiguous/unclear reports

Have your colleague review the report and ask clarifying questions before submission

Clear Title:

Provide a concise title summarizing the report content.

Clear Description:

When and how was the deviation(s) identified?
What is the deviation or non-compliance?

Lack of Responses (Clarification Requested / Action Required Stages)

Maintain active communication throughout the process:

1. If the report is in preparation or pending a response from the sponsor, leave a comment to inform the IRB.
2. If the submitter is leaving the department, the RNI should be transferred to the next team member.(This will be supported by a new function in the upcoming IBIS 10.5 system update.)

***Lack of response to the IRB's requirements meets the "Non-compliance" definition.**

- **Missing CAPA**

Research Quality Assurance (RQA)

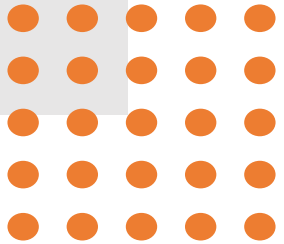
UNIVERSITY OF MIAMI

The Highlights:
Assistance with Corrective & Preventive Action (CAPA) Plan Development

Presented by:

Helen Miletic, MA, CHRC, RQAP-GCP
Director, Research Quality Assurance (RQA)

Ashley Kaufman, MA, CCRP
Sr. Quality Assurance Auditor, RQA



Assistance With CAPA Development

RQA can assist study teams with the following:

- IRB-requested CAPA Plan
- Team identified issue & wants to create a CAPA Plan
- CAPA Plan needed in response to:
  - internal audit (e.g. RQA)
  - external audit (e.g. FDA or Sponsor)

How Do We Begin?

UNIVERSITY OF MIAMI

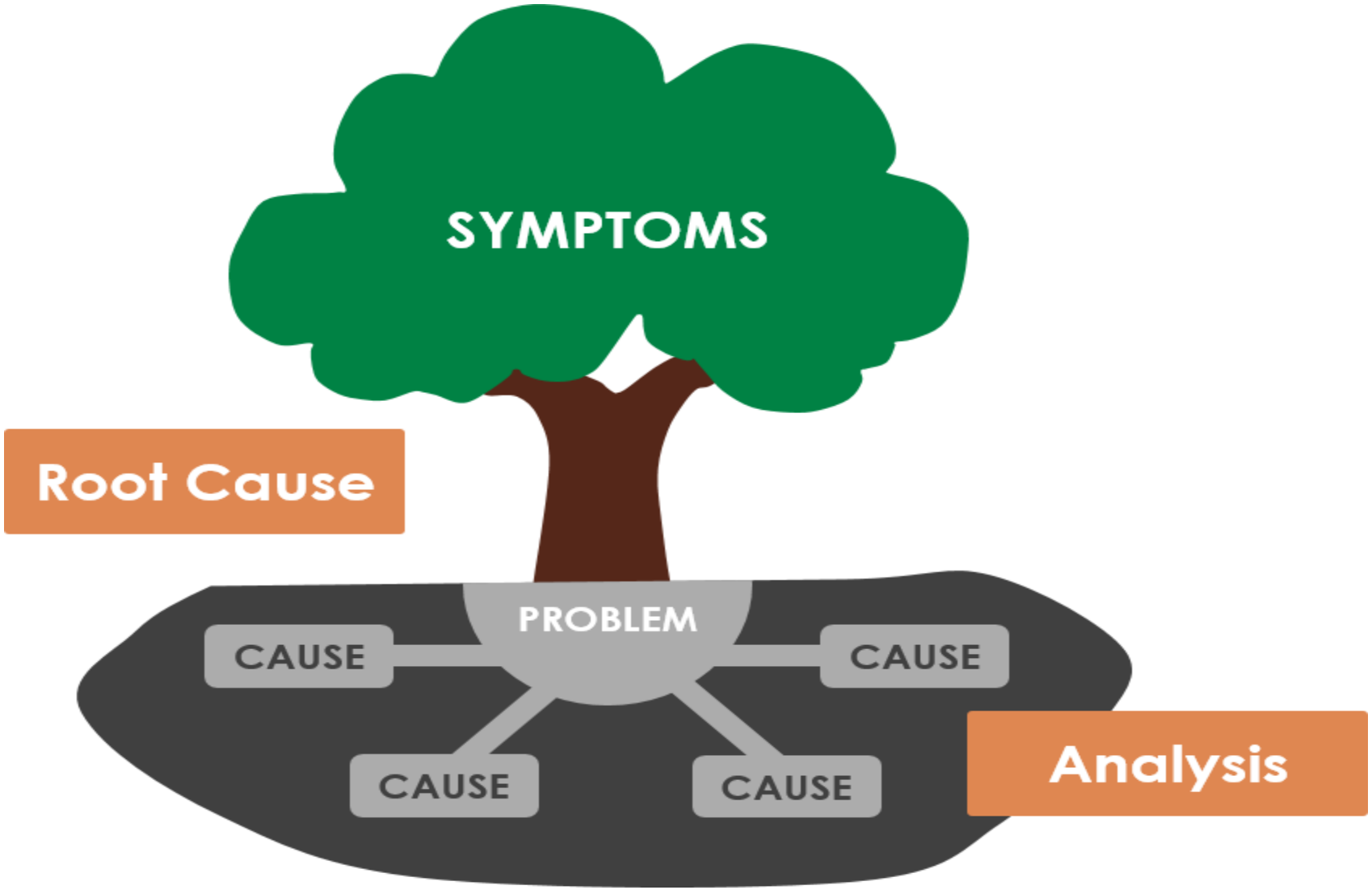
Define the Problem

Determine the Root Cause

UNIVERSITY OF MIAMI

The root cause is the true source of the problem

Root Cause Analysis…



Symptoms vs. Causes

UNIVERSITY OF MIAMI

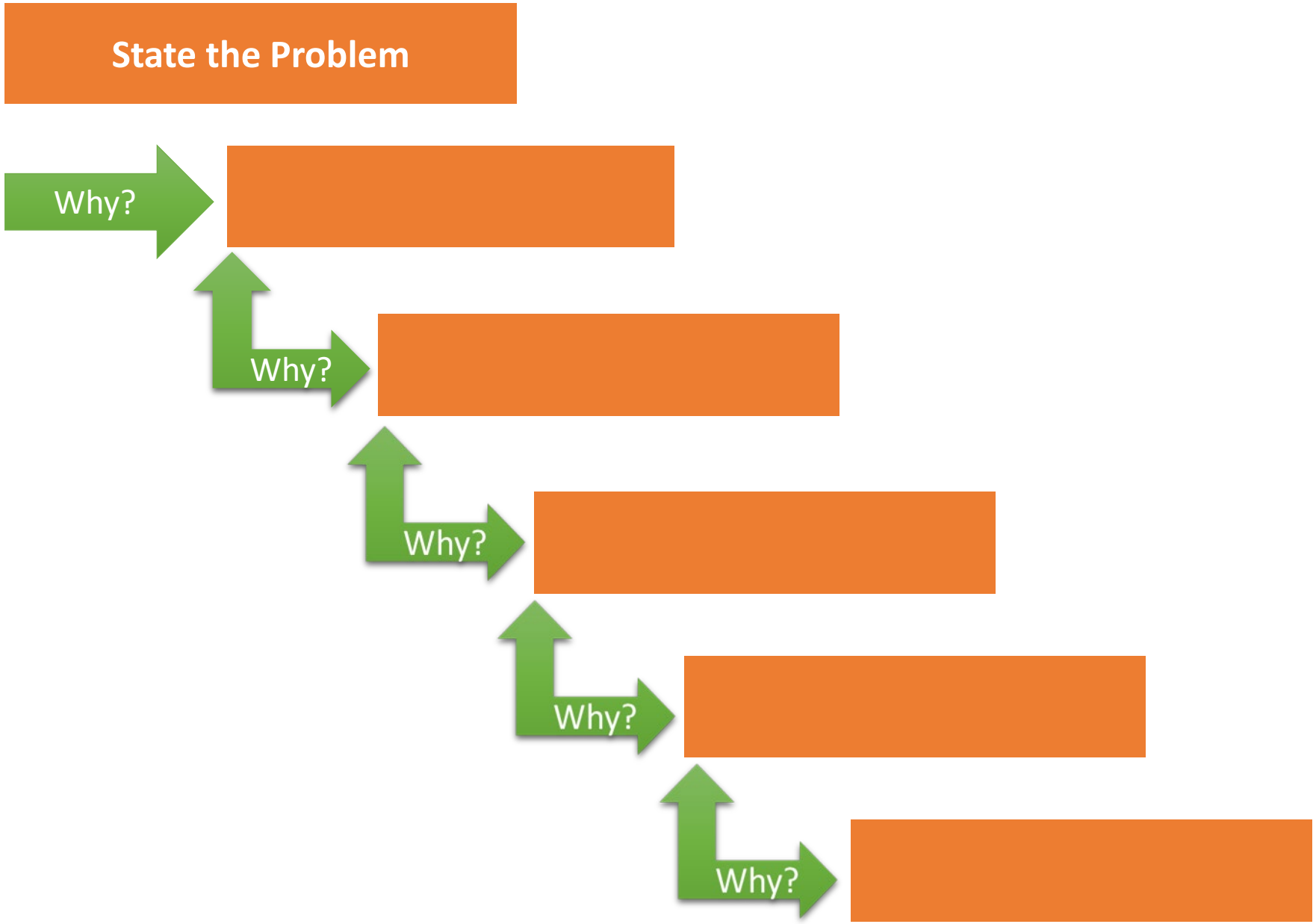
Symptoms
- Result or outcome of the problem
- What you see as a problem *(Obvious)*

Causes
- "The Roots" – system below the surface, bringing about the problem *(Not Obvious)*

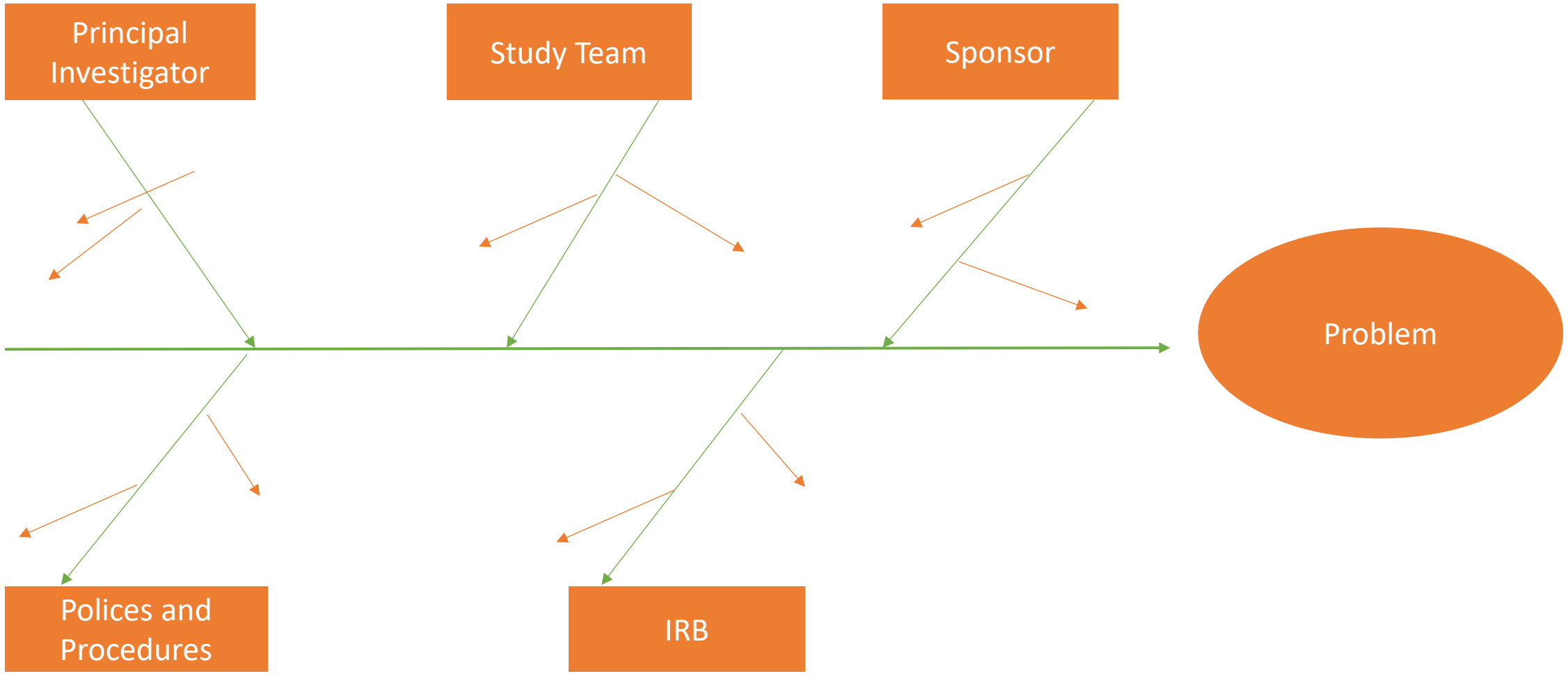
Solutions to Problems must address the **Root Causes**, **not** symptoms

“5 Whys” – Root Cause Analysis Tool

UNIVERSITY OF MIAMI



Fishbone Diagram – Root Cause Analysis Tool
- Brainstorming activity



CAPA Components: Key Distinctions

UNIVERSITY OF MIAMI

Corrective vs. Preventive Actions

A corrective action is a reaction to *a problem that has already occurred*

- Action taken to correct a problem:
  e.g. correcting a typo

Question: ***Is it always possible to correct a problem that has already occurred?***

Preventive Actions

Actions taken to prevent the issue from *occurring or recurring <u>in the future</u>*

Actions that prevent the Root Causes:

<u>Examples</u>:

- reminder systems
- checklists
- documentation prompts
- amending a study protocol to clarify procedures
- increased communication via team meetings
- training, etc.

Ensure Your CAPA Plan is…

UNIVERSITY OF MIAMI

- Feasible:
  - Can be done within proposed timelines
- Sustainable:
  - Practical, not burdensome
- Communicated to your team:
  - Team is trained on all new procedures/SOPs

Systemic Approach:
Apply your Preventive Actions across all studies

Is Your CAPA Plan Effective?

UNIVERSITY OF MIAMI

Ask yourself:

- Is the problem you were trying to prevent still occurring?

If "Yes" , your CAPA Plan did not address the Root Cause(s) of the problem.
To determine the true cause (source) of a problem, you must dig deeper.

Effective CAPA Plans prevent the root causes of a problem

Closing the Gaps: Addressing Non-Compliance

Issue: <u>The Research Team consented a subject with an outdated consent form</u>

- Background:
  - Issue discovered during a routine audit conducted by RQA
  - An Investigator-Initiated Study
  - The updated Investigator's Brochure contained new risk language for the Investigational Product used in the study
  - The ICF was updated with the risk language and provided to UM's IRB for approval
  - The approved ICF was made available in IBIS for the Research Team to use
  - The Sub-Investigator used an outdated ICF to consent a potential new subject

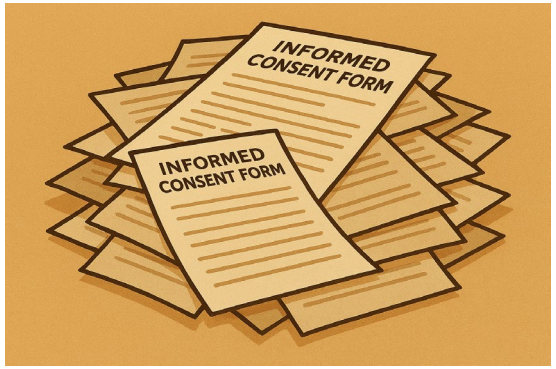
Why Did this Happen?

The Root Cause(s): Identifying the Gaps

Study Team
+
Auditor

<u>Dig For the Root Cause:</u>

- *Why* did the Sub-I use an outdated ICF?
  - Research Nurse prints copies of ICFs from IBIS and provides them to Sub-I to conduct consent (Sub-I: “I used whatever was given to me…”)



<u>Dig Deeper:</u>

- Neither the Sub-I nor RN were aware of the new ICF

Why?

<u>Keep Digging:</u>

- Neither the Sub-I nor RN attended PI oversight or weekly Team meetings where new ICF was discussed; neither reviewed meeting minutes uploaded by Study Manager in Box
- Neither acknowledged email reminder from PI and Regulatory staff that new ICF version was approved

Correct & Prevent the Gaps

Study Team + Auditor

Corrective Actions:

- Record and Report the Deviation
- Reconsent the Subject (was there anyone else impacted?)

Study Team + Auditor

Preventive Actions

- Cease & Desist printing ICFs months in advance
- Train team on the importance of using the most current version (compliance w/ regulations, GCP; compromising validity of the subject's consent; future deviations or findings)
- Creating an SOP for document control and consenting procedures
- Creating and utilizing an ICF Checklist
- If can't attend PI oversight or team meetings, review the meeting minutes; acknowledge communication among the team regarding study updates

Closing the Gaps: Example #2

Issue: Cortisol is not being collected from all subjects at study visits

- Background:
  - Issue discovered during a routine audit conducted by RQA
  - Cortisol is required at every study visit prior to treatment, per protocol
  - Cortisol appears on every lab order set (for phlebotomy to draw)
  - Cortisol is included in study visit checklists used by the research team
  - Auditor noticed a weird pattern: Subjects who have lab appointments scheduled between the hours of 7-9 am have Cortisol drawn, while those who have lab appointments scheduled in the afternoon do not
  - By the time the team discovers it wasn't drawn, it's too late…

Why isn't Cortisol being collected consistently?

The Root Cause(s): Identifying the Gaps

Study Team
+
Auditor

<u>Dig For the Root Cause:</u>

- *Why* isn't cortisol being drawn from <u>all</u> subjects?
  - "I don't know"
  - "Cortisol is in all the order sets, but phlebotomists aren't always drawing it"

<u>Dig Deeper:</u>

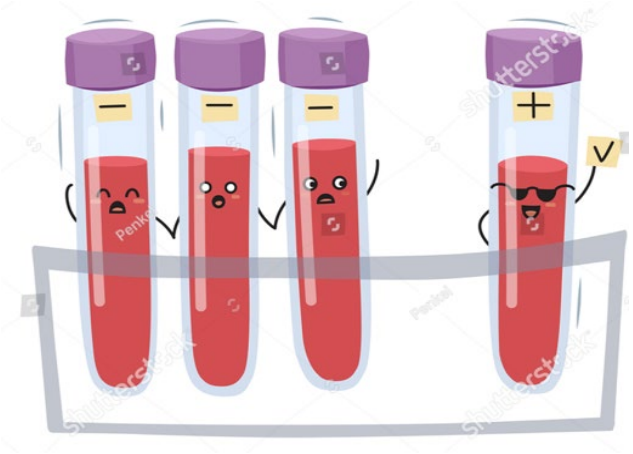
- *Is there a coincidence or reason why Cortisol is collected in the morning, but not in the afternoon?*

" Hmm…I didn't notice that"

<u>Keep Digging (aka Ask a Phlebotomist):</u>

"Cortisol is only drawn before 10 am for accurate test results…we already told "Carrie, the Coordinator" this many times"

*Carrie, the Coordinator left UM without conveying Phlebotomy's Cortisol instructions to her team

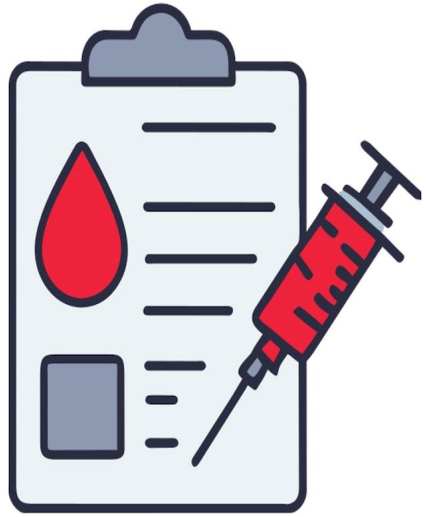


Correct & Prevent the Gaps

Study Team + Auditor

Corrective Actions:

- Record and Report the Deviation
- Update the order sets and study visit checklists (include note that Cortisol has to be drawn before 10 am)
- Assess impact on study integrity and subject safety



Study Team + Auditor

Preventive Actions

- Conduct training on cortisol collection (Discuss timing and importance of collecting the biomarker; review the updated order sets and study visit checklists; include instructions in the protocol and/or lab manual)
- Schedule subject lab visits prior to 10 am; send reminders
- Implement an internal Cortisol verification system (have team members check that all labs have been drawn prior to subject treatment)
- Communicate with your team all information that impacts the study and its subjects…**Don't be a Carrie**

Closing the Gaps