Beyond the Violation: Building Strong Corrective Action Plans in Clinical Research

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October 13, 2025

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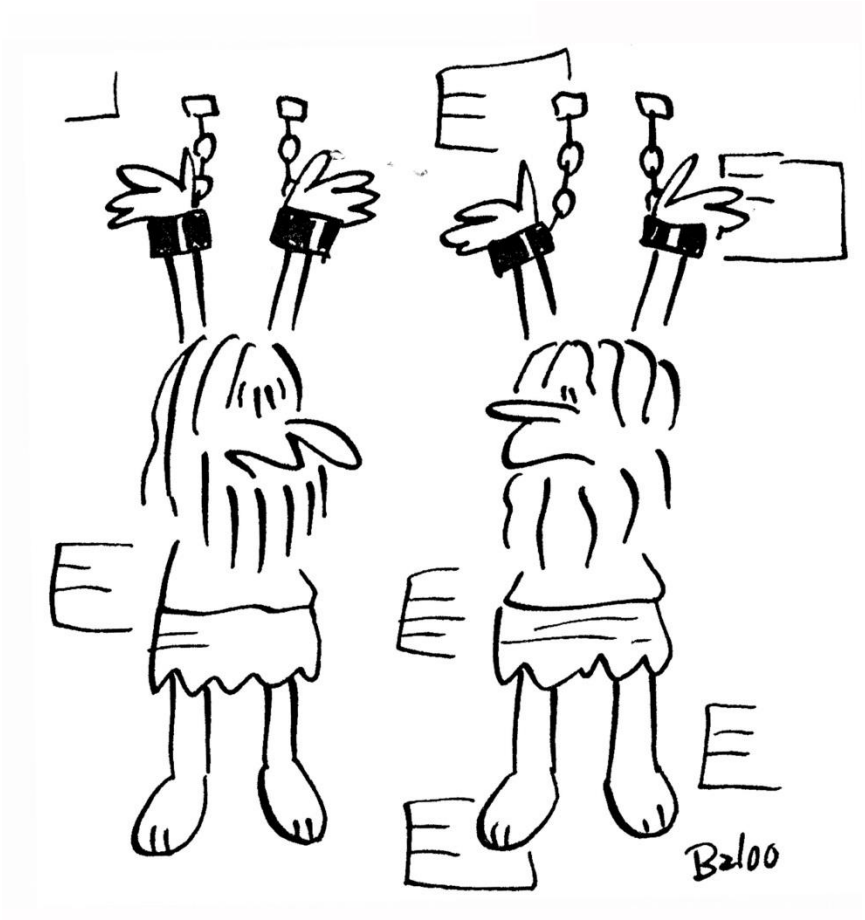


"I've been here so long I
don't remember what I did,
but it had something to
do with non-compliance."

What is Noncompliance?

- Compliance - "The state of according with rules or standards" (OED)
  - 45 CFR 46
  - 21 CFR 50, 56
  - ICH/GCP
  - HIPAA Privacy Rule
  - Accreditation standards
  - State law
  - Institution policy
  - …
- Noncompliance - "Failure or refusal to comply" (OED)

What is Noncompliance?

- "...investigators will conduct the research activity in accordance with the terms of the IRB approval until any proposed changes have been reviewed and approved by the IRB, except when necessary to eliminate apparent immediate hazards to the subject" (§_. 108(a)(3)(iii))

What is Noncompliance?

- "Any failure to follow 45 CFR part 46 (including any applicable subparts), the requirements or determinations of the IRB or the provisions of the IRB-approved research study."
  - "Guidance on Reporting Incidents to OHRP", K. Borror, July 2014

What is Noncompliance?

- "Any failure to follow 45 CFR part 46 (including any applicable subparts), the requirements or determinations of the IRB or the provisions of the IRB-approved research study."
  - "Guidance on Reporting Incidents to OHRP", K. Borror, July 2014
- "Any failure to follow federal regulations, HRPP policies, the requirements or determinations of the IRB or the provisions of the IRB approved research study" (UNMC HRPP Policy 8.4)

Noncompliance

- Do these events represent noncompliance?
  - Investigator fails to obtain informed consent
  - Pharmacy delivers wrong dose but error is caught by nurse before administration
  - Research team enrolls a subject despite not meeting one eligibility criterion
  - Mandatory monthly research and safety labs performed 2 days out of window
  - Subject is noncompliant with oral medication dosing
  - Subject misses scheduled clinic visit due to bad weather

Noncompliance

- "Any failure to follow federal regulations, HRPP policies, the requirements or determinations of the IRB or the provisions of the IRB approved research study" (HRPP Policy 8.4)

- All represent noncompliance
  - seriousness varies
  - nature of corrective action plan varies

Noncompliance

- Noncompliance is a statement of fact
  - failure to follow the protocol, the determinations of the IRB, organization policies, or regulations
  - intent doesn't matter
  - whether or not the investigator can control doesn't matter
- Noncompliance may be the result of action (or inaction)
  - by the PI or the research staff
  - by the subject
  - by the IRB or any other component of the HRPP

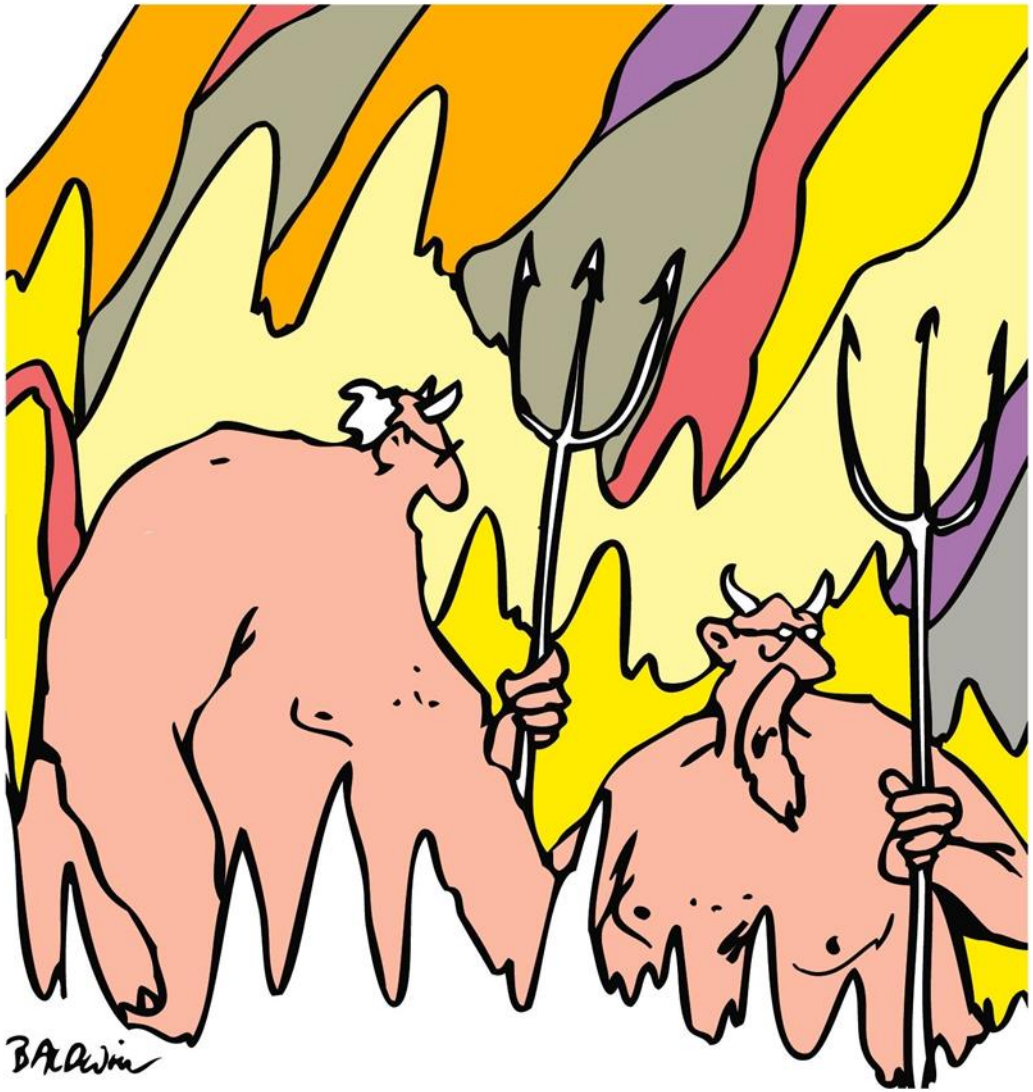
Regulatory requirements

- For each incident of noncompliance, the IRB must make a determination whether or not the event is serious and/or continuing
  - "Each IRB shall … follow written procedures for ensuring prompt reporting of … any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB"
    - to OHRP (45 CFR 46.108(a)(4))
    - to FDA (21 CFR 56.108(b)(1))
    - to Organizational officials

Noncompliance

UNMC HRPP policy 8.4

- Serious Noncompliance
  - "A violation of federal regulations, HRPP policies, determinations of the IRB, or the provisions of the approved protocol which
    - significantly increases the risk to subject; OR
    - otherwise compromises the rights and welfare of research subjects; OR
    - appreciably decreases the potential direct benefit to the subject; OR
    - compromises the scientific integrity of the research"



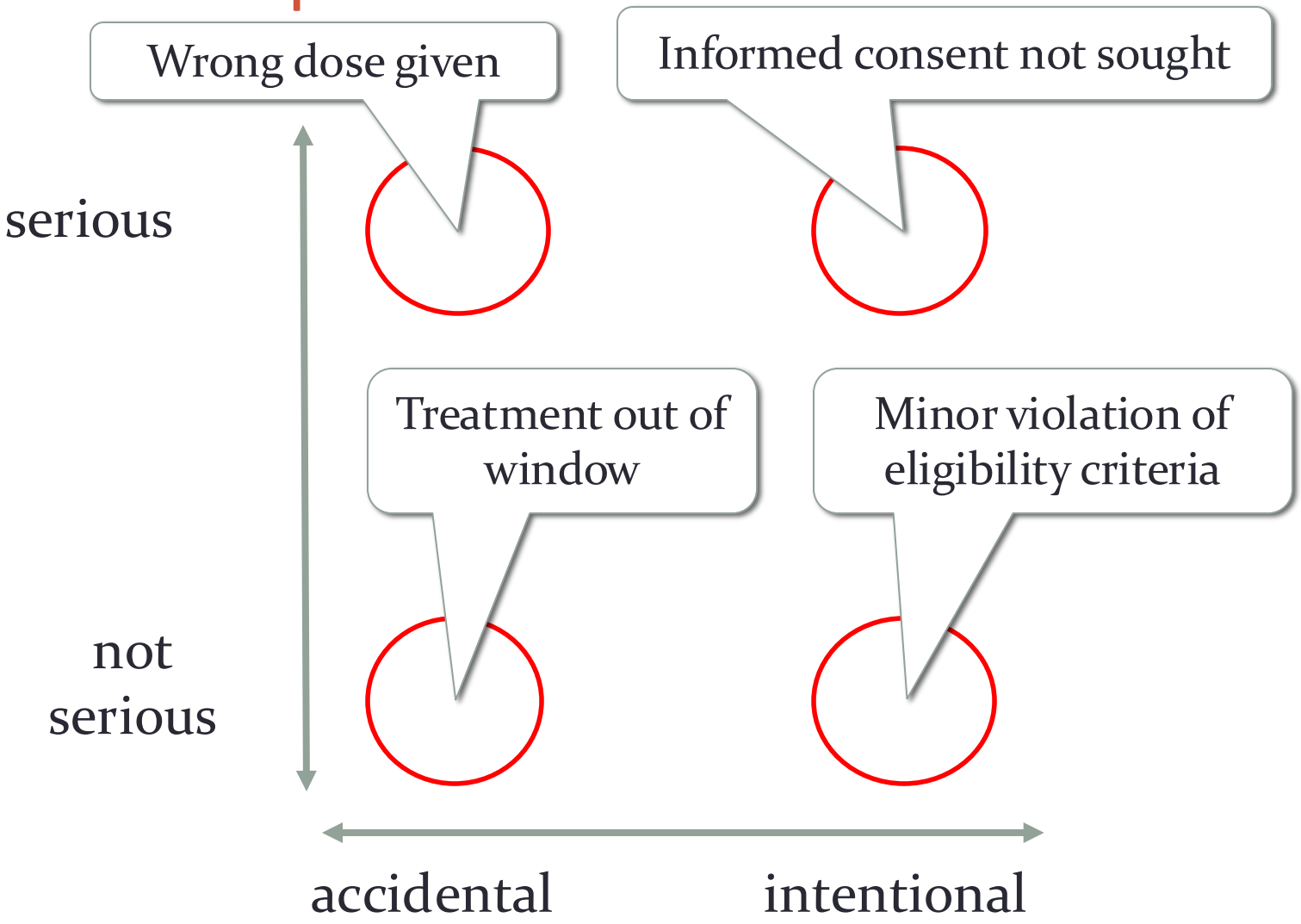
"You make 23,725 little mistakes,
they never let you forget it."

Noncompliance

UNMC HRPP policy 8.4

- Continuing Noncompliance
  - "Repeated incidents of the same or substantially similar noncompliance
    - after the investigator or staff has been notified that the action represents non-compliance or despite appropriate retraining and/or a specific corrective action plan; OR
    - of such a nature that the investigator should have reasonably been expected to know that such an action was noncompliance."

Noncompliance



Noncompliance

- Whether an incident of noncompliance is accidental or intentional does not *necessarily* make that incident more or less serious
  - however, it will affect the nature of the Corrective Action Plan

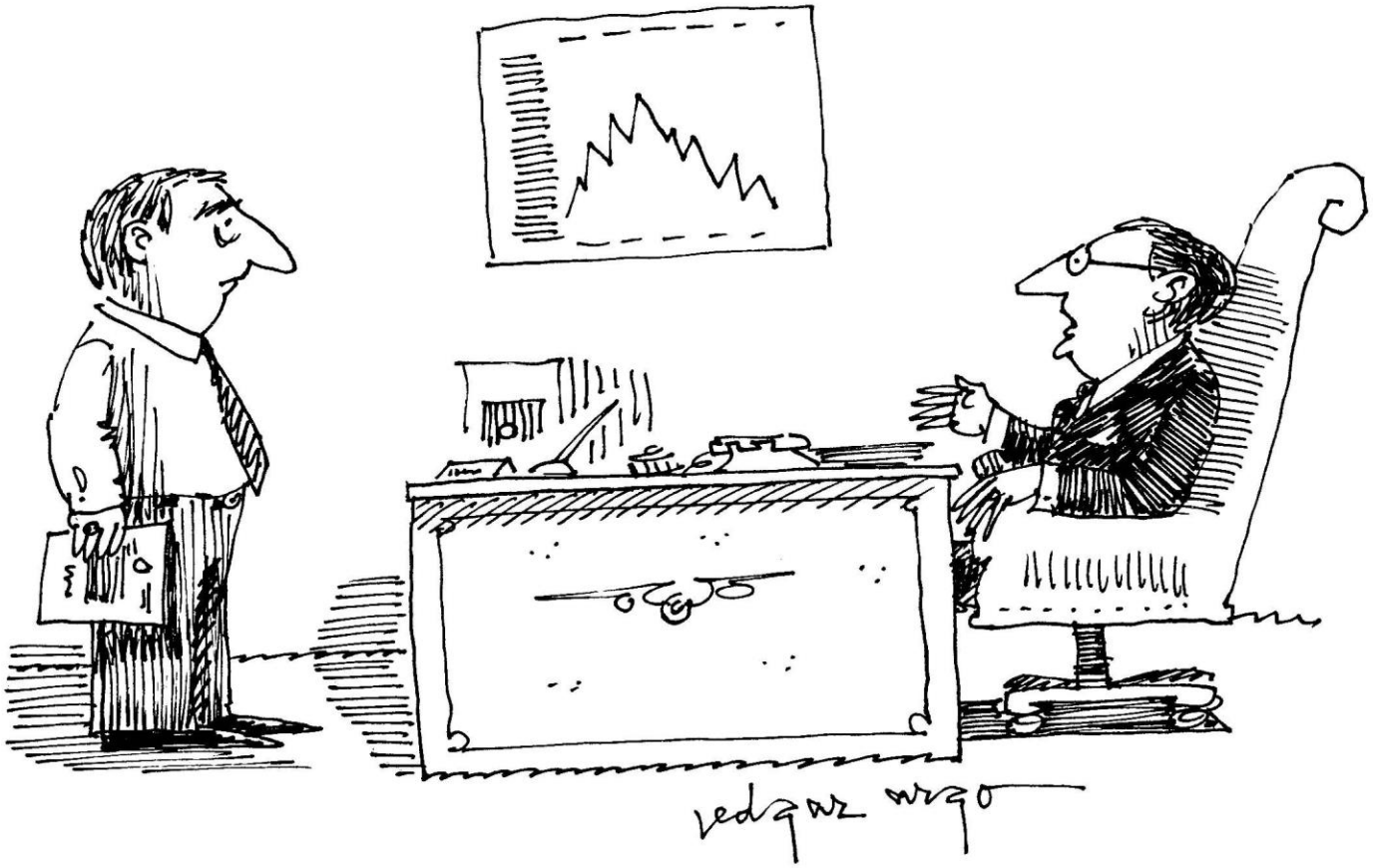
Reporting of noncompliance

- When to report (to the IRB)?
  - Regulations require "prompt reporting to the IRB [and] appropriate institutional officials … of unanticipated problems or any serious or continuing noncompliance" (§_. 46.108(a)(4))

  - "Reports of noncompliance made by the PI or study team must be made to the ORA within ten (10) business days of the study team becoming aware of the event, or five (5) business days when the possible noncompliance was associated with harm to subjects or others" (HRPP 8.4)

Deviation vs Violation (noncompliance)

- "…investigators will conduct the research activity in accordance with the terms of the IRB approval until any proposed changes have been reviewed and approved by the IRB, except when necessary to eliminate apparent immediate hazards to the subject" (§_. 108(a)(3)(iii))
- Single Subject **Protocol Deviation**
  - essentially, an expedited protocol change *for one single subject*
- **Protocol violation** (noncompliance) occurs when the research team (or the subject) does not follow the provisions of the IRB approved protocol or makes a change without IRB approval



"I DIDN'T SAY IT WAS YOUR FAULT, MILLMAN... I SAID I'M GOING TO BLAME IT ON YOU."

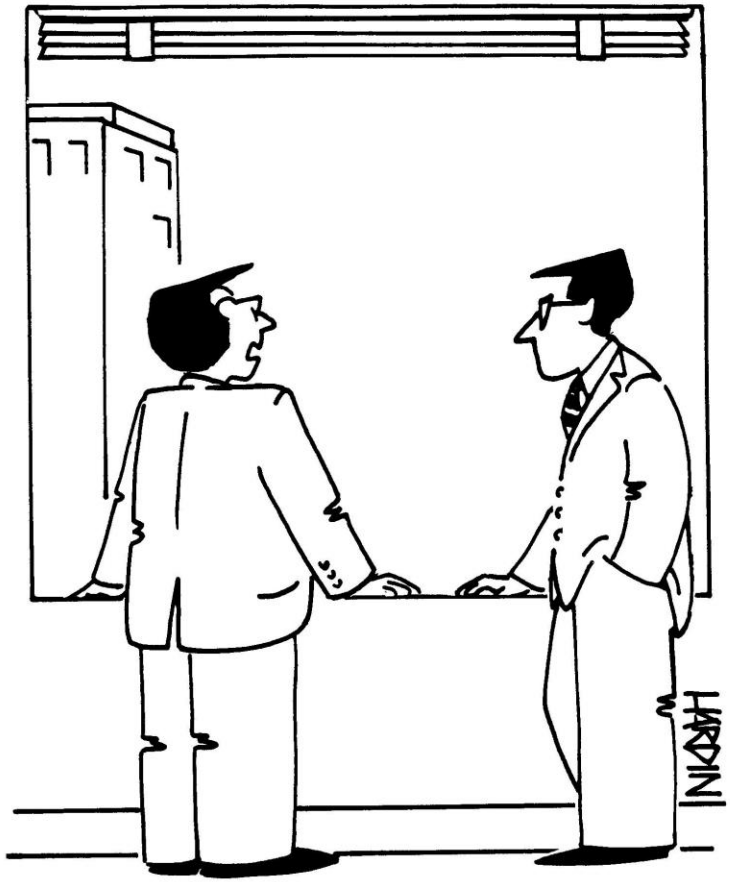
Case study

- Audit shows several patients did not get mandatory safety labs prior to receiving doses of chemotherapy
- Investigator's corrective action plan:
  - "We will re-educate coordinators on the importance of ordering safety labs"

  - Doesn't discover the cause(s) of the problem
  - Doesn't address the cause(s) of the problem
  - Doesn't prevent the problem from happening again

Analysis of incident

- Why did it happen?
- What needs to be done now to reduce risks to current subjects?
- What needs to be done now, and in the future, to keep it from happening again?



"The fault lies not in our stars, but in ourselves – If we move fast, though, we can pin it on Rendleman in Accounting."

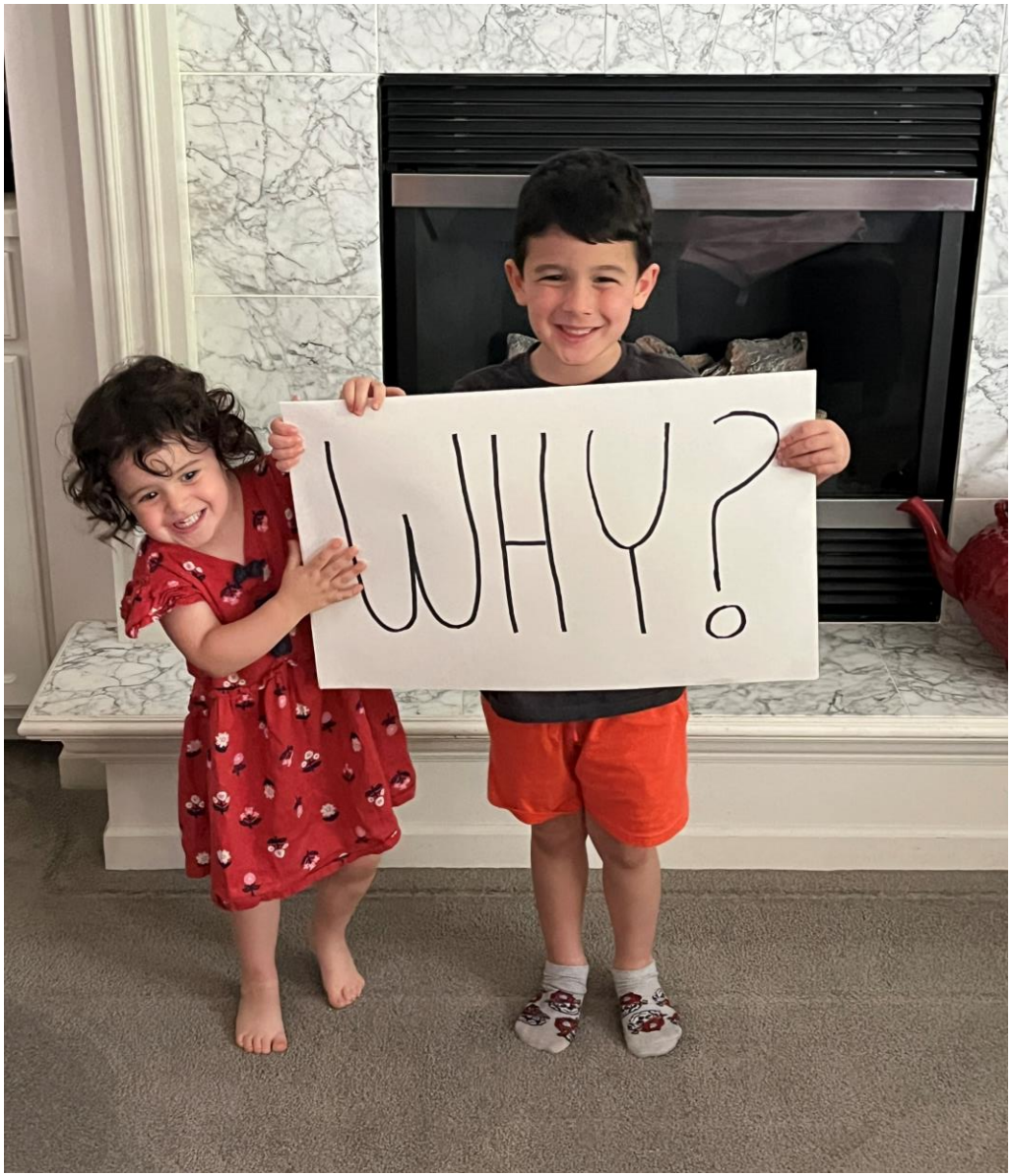
Analysis of incident

- Why did it happen?
  - Analysis needs to be performed primarily by the investigator
    - Investigator is familiar with the research, with the conditions surrounding the research, and with the event
  - Process-driven
    - Root cause analysis

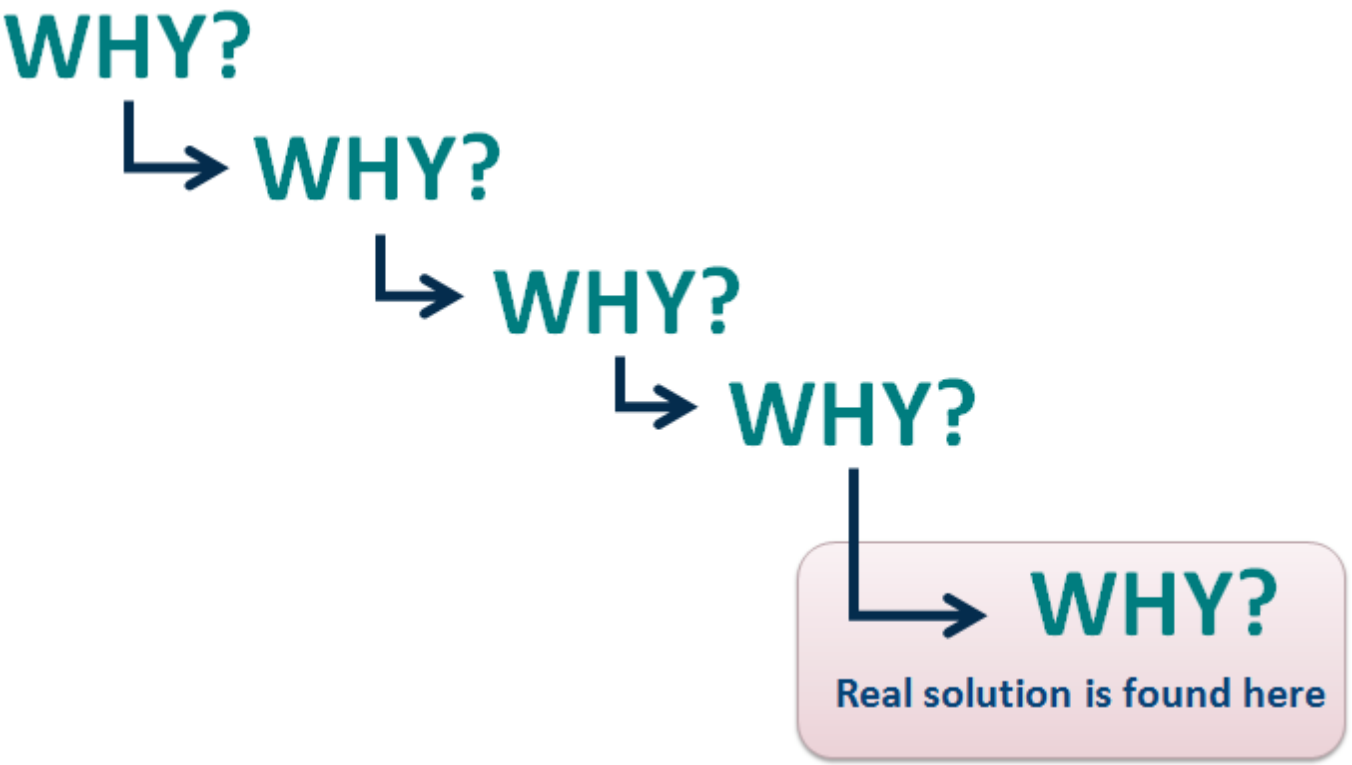
"To address this mistake we need to utilise our thorough system of root cause analysis. I will begin, if I may, by pointing out that it's not my fault"

Root cause analysis

- Root Cause refers to the fundamental reason behind a problem in a process. It is the underlying source that, when addressed, can prevent the recurrence of issues
- Root cause analysis is a systematic process used to identify and understand the core factors responsible for a problem
  - 5 Whys
  - Event / causal factor trees
  - Fishbone diagram


WHY?

Root cause analysis



Root cause analysis

- Safety labs not ordered
  - Why? → Research coordinator didn't add them to the routine order set
  - Why? → The coordinator wasn't informed that there were new required orders based on most recent protocol amendment
  - Why? → Protocol office submitted changes to the IRB and modified the "master protocol" but didn't realize coordinator didn't get a copy of the amendment and didn't tell them the protocol was updated
  - Why? → There was no SOP about communicating amendments to research coordinators

"I'm afraid I still have more questions than answers."

Root cause analysis

- But other events occurred …
  - PI did not communicate study progress report which alerted investigators to new toxicity (and generated change in protocol for new safety labs)
    - Why didn't they?

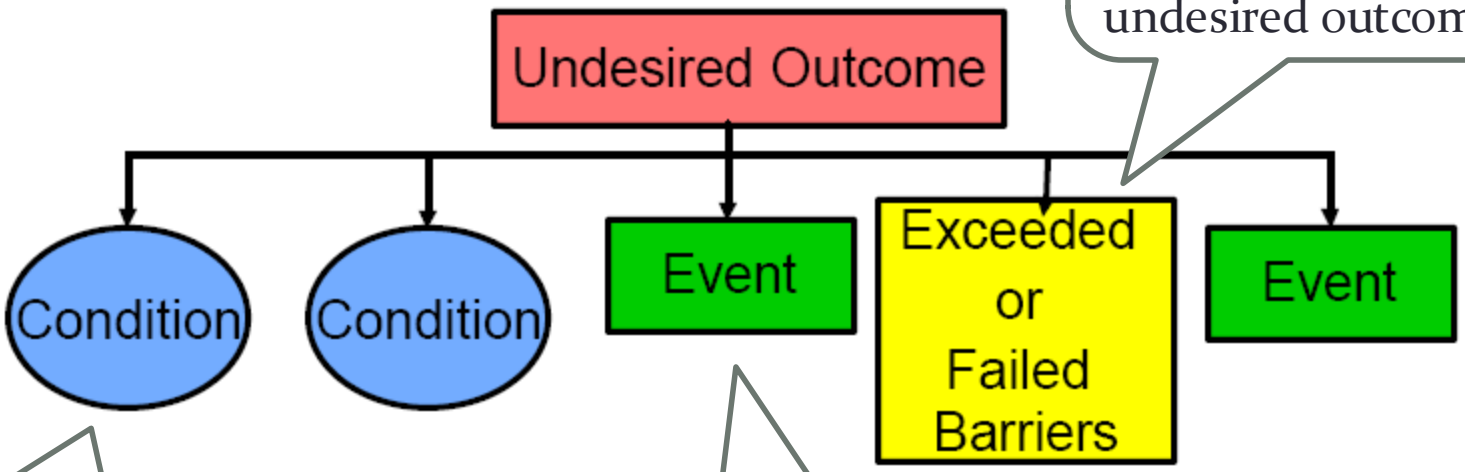
Root cause analysis

- But other events occurred …
- Other barriers failed …
  - Data managers should have collected lab results for CRFs in real time and noted absence of safety labs
    - Why didn't they?

Root cause analysis

- But other events occurred …
- Other barriers failed …
- Other predisposing conditions existed …
  - Research coordinator, managing multiple research studies, didn’t have time to regularly review "master protocols" for changes
    - Why didn't they?

Root cause analysis

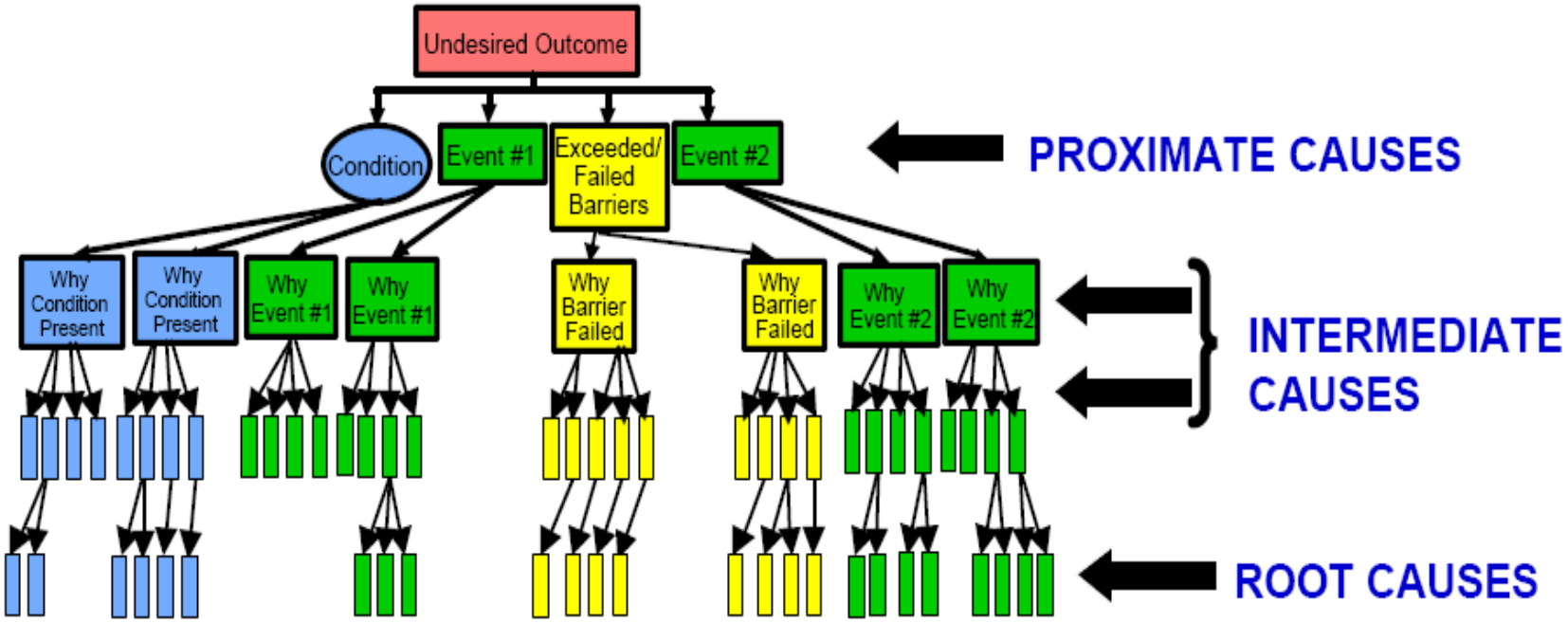


A physical device or an administrative control used to reduce risk of the undesired outcome

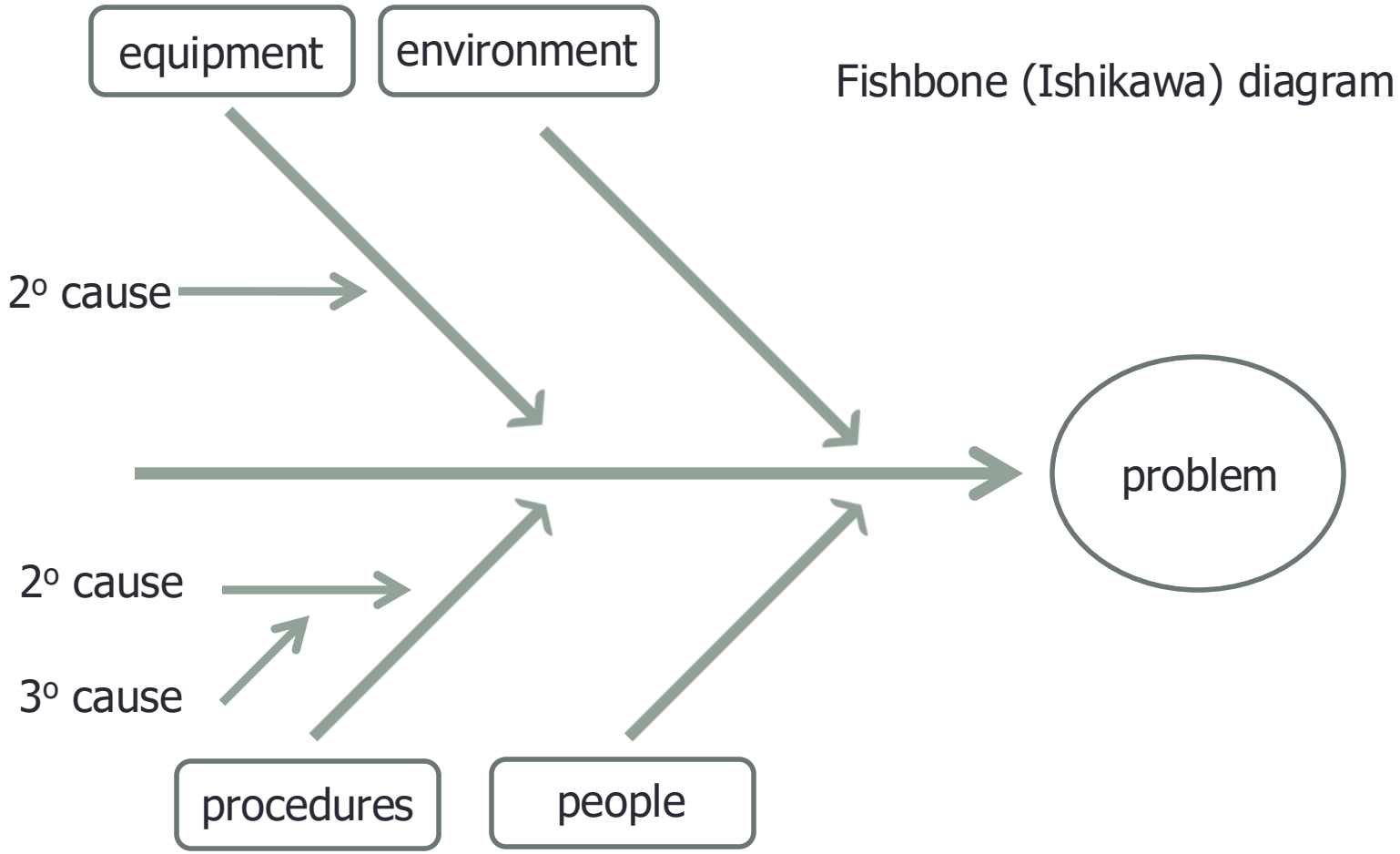
Any state or set of circumstances that may have contributed to the events leading up to the undesired outcome

A real-time occurrence describing one discrete action, typically an error, failure, or malfunction

Root cause analysis



Root cause analysis



"What do you mean 'it just happened'?
Didn't we discuss cause and effect?"

Analysis of incident

- Why did it happen?
  - Root cause analysis
- What needs to be done now to reduce risks to current subjects?
- What needs to be done now, and in the future, to keep it from happening again?

Analysis of incident

- Actions to reduce risk to current subjects
  - depends on the nature of the incident (and associated risks to subjects)
  - might include
    - protocol changes
      - additional monitoring for AEs
      - modification of subsequent dosing
    - immediate process changes
    - inform subject / re-consent
    - suspension / termination of research

Analysis of incident

- Why did it happen?
  - Root cause analysis
- What needs to be done now to reduce risks to current subjects?
  - Immediate actions
- What needs to be done now, and in the future, to keep it from happening again?
  - Corrective action plan

Corrective Action Plan

- A Corrective Action Plan (CAP) consists of
  - measures instituted to mitigate risk and protect the rights and welfare of subjects, AND
  - a clear and thoughtful plan to address underlying cause(s) of the noncompliance

Corrective Action Plan

- The Principal Investigator is responsible for developing a Corrective Action Plan aimed at the root-cause of the incident
  - "The investigator should develop … a procedure for the timely correction and documentation of problems …" (FDA guidance - "Investigator Responsibilities — Protecting the Rights, Safety, and Welfare of Study Subjects", October 2009)
- An effective CAP requires intimate knowledge of the specific processes and procedures around the research study

Corrective Action Plan

- The IRB (or the institution) may also need to develop a Corrective Action Plan to
  - address deficiencies in processes over which it has control
  - to assure compliance by the investigator and the research team

Corrective Action Plan

- For minor (non-serious) noncompliance, the immediate actions taken by the research team to minimize risk of harm (along with process changes as appropriate) may be an adequate "corrective action plan"
  - however, even for minor (non-serious NC) some degree of root-cause analysis by investigator is appropriate to determine whether process changes are needed to reduce risk of recurrence
- More serious noncompliance requires a more robust and formal plan

Corrective Action Plan

- CAPs should be SMART
  - Specific
  - Measurable
  - Achievable
  - Relevant
  - Time-bound

Corrective Action Plan

- CAPs should be SMART
  - Specific
    - "We'll make sure that research coordinators are informed of changes in protocol"
    - Is it unambiguous, clear and focused?
      - the CAP must
        - identify the root causes(s) and other relevant factors
        - describe all actions to be taken, how those actions will be implemented, and by whom
        - comply with regulations and policies

Corrective Action Plan

- CAPs should be SMART
  - Specific
  - Measurable
    - "… new process will fix the problem …"
    - Can the effectiveness of the plan be measured?
      - the CAP must
        - include a plan to assess effectiveness at intervals appropriate to risk, and a process to revise the plan as needed
        - define who will be responsible for assessing progress and effectiveness of the CAP

Corrective Action Plan

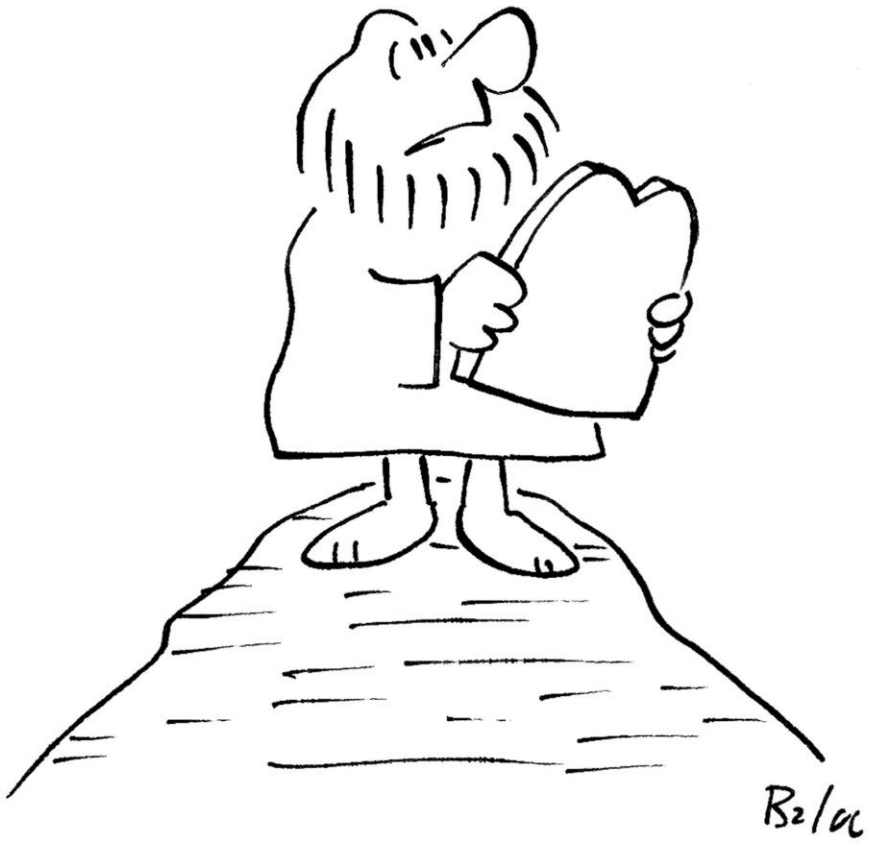
- CAPs should be SMART
  - Specific
  - Measurable
  - Achievable
    - "… hire three new coordinators"
    - Is the plan feasible and practical (realistic)?
      - the CAP must
        - address all implicated processes and causes
        - be able to be carried out, considering resources, knowledge and expertise (internal and external to the study team)

Corrective Action Plan

- CAPs should be SMART
  - Specific
  - Measurable
  - Achievable
  - Relevant
    - "… make the research team take CITI course again"
    - Does it actually address the root cause(s)?
      - the CAP must
        - address the full observation or root cause(s)
        - be appropriate for the level of risk

Corrective Action Plan

- CAPs should be SMART
  - Specific
  - Measurable
  - Achievable
  - Realistic
  - Time-bound
    - "We'll start after we hire the new coordinators …"
    - Can it be accomplished in an appropriate time frame?
      - the CAP must
        - be instituted in a timely manner
        - have a reasonable and achievable completion date



"How long do we have to get in compliance?"

Specific actions to reduce likelihood of future NC

- Protocol changes
- Process modification
- Investigator modification

Specific actions to reduce likelihood of future NC

- Protocol changes
  - If the problem was due to an unrealistic expectation in the protocol, revise the protocol
    - Vital signs every 5 minutes may not be necessary for patient safety, and is likely to be too burdensome to be achievable
    - Fifty-page questionnaire may be too burdensome, leading to subjects not completing

Specific actions to reduce likelihood of future NC

- Protocol changes
- Process modification
  - Provide education regarding current (adequate) processes
    - if the process is realistic and achievable, but not being followed because it is not understood by research team, then education is appropriate
    - however …
      - perhaps the initial process of education is defective and needs correction

Specific actions to reduce likelihood of future NC

- Protocol changes
- Process modification
  - Provide education regarding current (adequate) processes
  - Revise process so that it fits within the limitations of the system
    - Blood drawing for pharmacokinetics is being missed at the end of a long drug infusion because there is less nursing staff at the end of the day
      - you can't make the day longer – but you can start things earlier

Specific actions to reduce likelihood of future NC

- Protocol changes
- Process modification
  - Provide education regarding current (adequate) processes
  - Revise process so that it fits within the limitations of the system
  - Revise the process by providing more support (minimizing or removing limitations)
    - personnel
    - hardware

"Never attribute to malice what can just as easily be attributed to stupidity"

Malcolm Gordon
circa 1975

Specific actions to reduce likelihood of future NC

- Protocol changes
- Process modification
- Investigator modification
  - Education
    - General vs process-based
      - General education (ie, lectures on ethics or regulation) unlikely to solve problems, may be viewed as (or may be used primarily for) punishment
      - Process-based education (how to avoid problem in future by correcting the process) is more likely to be successful in the long run

Specific actions to reduce likelihood of future NC

- Protocol changes
- Process modification
- Investigator modification
  - Education
  - Restrictions
    - Different from punishment
    - Appropriate if noncompliance was due to manpower issues or time constraints

"I really can't explain it too much except to say that it's part of a court order."

Specific actions to reduce likelihood of future NC

- Protocol changes
- Process modification
- Investigator modification
  - Education
  - Restrictions
  - Punishment
    - "Let the punishment fit the crime"

Corrective action plans

- Ramnath (*IRB Eth Hum Res* 2016)
- 12,326 corrective action plans associated with 6500+ incident reports received by OHRP 2008-2014
  - re-review of protocol by an IRB
  - monitoring or auditing
  - requiring modifications to protocol or ICFs
  - requiring reconsent or notification of subjects
  - training of the PI on specific issues
  - suspension or termination of the research
  - disallowing or limiting the use of data
  - suspension or termination of the investigator

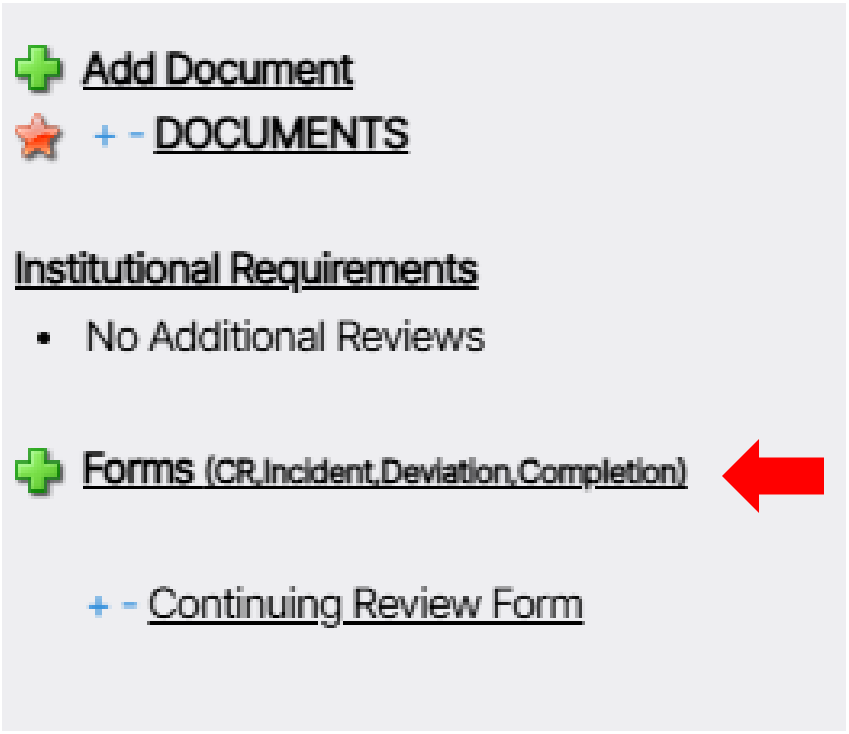
Corrective Action Plan

- Ramnath (*IRB Eth Hum Res* 2016)
  - 589 (5%) included some restriction on use of data

- SACHRP Recommendations 2021
  - Restriction of data use may be justified
    - (a) when informed consent was not obtained from subjects or research was not IRB approved, or
    - (b) when using or publishing the data would likely result in direct harm to subjects, or
    - (c) when noncompliance has impaired the data's integrity

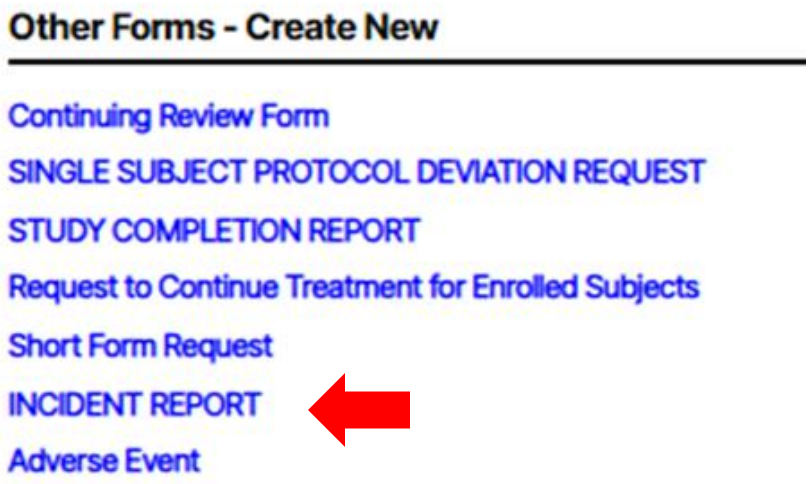
"If there's anything more we can do for you, don't hesitate to fill out the proper forms."

Reporting NC to the UNMC IRB



- Open the IRB-approved application in RSS
- Click on "Forms" in the gray area on the left of the screen (same area you choose for "Continuing Review")

Reporting NC to the UNMC IRB



- Open the IRB-approved application
- Click on "Forms" click on "Forms" in the gray area on the left of the screen (same area you choose for "Continuing Review")
- Click on "Incident Report"

Reporting NC to the UNMC IRB

- Open the IRB-approved application
- Click on "Forms" click on "Forms" in the gray area on the left of the screen (same area you choose for "Continuing Review")
- Click on "Incident Report"
- Open the "Incident Report" version you just created …

Reporting NC on CB studies

- NC must be reported to the reviewing IRB
- NC does **not** need to be reported to the UNMC IRB unless the reviewing IRB determines that the NC is serious or continuing, or represents an Unanticipated Problem (UP)
  - if the reviewing IRB makes that determination, you must upload a copy of their findings/notification to RSS
  - even if the reviewing IRB does not make that determination, we encourage you to upload the documentation from the CIRB

"I'm feeling a sense of conclusion here, so let's draw things to a close."

Summary

- Noncompliance (NC) is any failure to follow regulations, HRPP policies, the requirements or determinations of the IRB or the provisions of the IRB approved research study
- Noncompliance is a statement of fact, and doesn't imply intent (though intent may be a factor in determining response)
- IRBs must determine whether an incident of NC is serious, continuing, and/or an unanticipated problem
- Root cause analysis is a systematic process used to identify and understand the core factors responsible for a problem. RCA is a necessary component of the response to an incident of NC

Summary

- A CAP consists of measures instituted to mitigate risk and protect the rights and welfare of subjects, and a clear and thoughtful plan to address root cause(s) of the NC
- CAPs should be specific, measurable, achievable, relevant, and time-bound
- Specific actions described in the CAP depend on the nature and seriousness of the event, but may consist of protocol changes, process modification and/or investigator modification

"And that pretty much sums it up."