# OHSRP Investigator Seminar Series

# Quality Management in Clinical Research

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# Disclosure

- The views and opinions expressed in this presentation represent those of the presenters and do not reflect the official views of the National Institutes of Health (NIH) or the Department of Health and Human Services (DHHS).

# Objectives

- Define components of quality management.
- Describe three examples of quality control activities that the team can perform involving the informed consent process.
- Determine two corrective and preventive actions if a research participant is found to be ineligible after enrolling.

# Defining Quality

- **Definition**: The degree to which a set of inherent properties of a product, system, or process fulfills requirements.
- From ICH Q9(R1) Quality Risk Management
- **ICH**: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

# More About Quality

- History of quality:
  - Manufacturing – creating a widget
  - Clinical research – human experience
- Organizational (Team/Institute) approach:
  - Plan Do Check Act (PDCA), Kaban, Sigma Six, others
  - What is the “low hanging fruit”? (easy things that can improve process)
  - SOPs
  - Checklists
  - Templates (i.e., progress notes, adverse event reporting, consents)

# Definitions – ICH E6(R2) Good Clinical Practice

## 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, tools, and procedures for data collection and processing, as well as the collection of information that is essential to decision making.

# Definitions – ICH E6(R2) Good Clinical Practice

**Section 1.46 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 good clinical practice (GCP) and the applicable regulatory requirement(s).

# Definitions – ICH E6(R2) Good Clinical Practice

**Section 1.47 Quality Control (QC)**

- The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled. Quality Assurance (QA).

# Definitions – ICH E6(R2) Good Clinical Practice

**Section 2.0 The Principles of ICH GCP**

- 2.13 Systems with procedures that assure the quality of every aspect of the trial should be implemented.
- Addendum: Aspects of the trial that are essential to ensure human subject protection and reliability of trial results should be the focus of such systems.

# Application of Definitions: Case Studies

# Case Study #1: The Big Snowstorm

- **Scenario:** A big snowstorm hits the NIH campus, and the participant is unable to travel to NIH for their scheduled research appointment. They were able to travel to NIH the following week for their appointment.  In the opinion of the investigator, there were no safety implications.
- **Issue identified**: Research appointment is outside the required timeframe.
- **What QM strategies could the team deploy to**
  - **Manage this in real-time?**
  - **Prevent this from reoccurring?**

# Is this a Protocol Deviation?

- **Protocol deviation** is any change, divergence, or departure from the IRB-approved research protocol.
  - **Minor Deviation:** Departure from the IRB-approved protocol that does not have the potential to negatively impact the rights, safety, or welfare of subjects or others, or the scientific integrity or validity of the study.

# Case Study #2: Consent Mix-up

- **Scenario**: Participant signed a consent for a different protocol than the one discussed during the consenting process. The coordinator noticed the error 3 months after the consent was signed. Research activities were performed during this three-month period.
- **Issue identified**: Research activities were performed without participant's consent.
- **What QM strategies could the team deploy to**
  - **Manage this in real-time?**
  - **Prevent this from reoccurring?**

# Is this a Protocol Deviation?

- **Protocol deviation** is any change, divergence, or departure from the IRB-approved research protocol.
  - **Major Deviation:** Departure from the IRB-approved protocol that have, or may have the potential to, negatively impact, the rights, welfare or safety of the subject, or to substantially negatively impact the scientific integrity or validity of the study.

# Case Study #3: Short Form Woes

- **Scenario**: Participant prefers their medical information in French. Protocol discussion between the participant, PI and interpreter took place, all essential elements of informed consent were discussed. The participant signed the French short form and the English long form.
- **Issue identified**: Participant should only sign the consent they can read. In this case, the French short form.
- **What QM strategies could the team deploy to**
  - **Manage this in real-time?**
  - **Prevent this from reoccurring?**

# Is this Non-Compliance?

- **Non-Compliance**: The failure of an investigator to follow the applicable laws, regulations, or institutional policies governing the protection of human subjects in research or the requirements or determinations of the Institutional Review Board (IRB), whether the failure is intentional or not.
  - **Continuing non-compliance:** A pattern of recurring non-compliance that either has resulted, or, if continued, may result in harm to subjects or otherwise materially compromise the rights, welfare and/or safety of subjects, affect the scientific integrity of the study or validity of the results.
  - **Serious non-compliance:** Non-compliance, whether intentional or not, that results in harm or otherwise materially compromises the rights, welfare and/or safety of the subject.

# Case Study #4: Multiple Sites = Multiple Problems

- **Scenario**: Multi-site study in which NIH is the coordinating site. Consent version error occurred at a participating site (pSite). The site reported the error 4 months after it occurred. The NIH PI reported the event as soon as they became aware of it.
- **Issue identified**: pSite did not inform the NIH site in a timely fashion. It is considered non-compliance because they did not use the current IRB-approved version of the consent.
- **What QM strategies could the team deploy to**
  - **Manage this in real-time?**
  - **Prevent this from reoccurring?**

# Reporting Non-Compliance, Major Deviations, and Minor Deviations: Policy 801

- Major deviations and any noncompliance issues are reported in PROTECT within 7 days via Reportable New Information (RNI) submission.
  - RNI submissions should not be a surprise to the PI.
  - Helpful to have a non-team member review the RNI prior to submission for completeness and clarity.
- Minor deviations must be reported in summary at the time of continuing review (CR).
  - Check with your institution's policy about how to track minor deviations.

# Completing a Reportable New Information (RNI) Submission

Describe corrective actions that have already been taken and any additional measures planned:

1. What have you done to correct the situation?
2. What will you do to prevent a future similar situation?

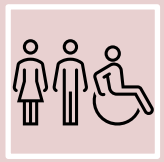
# CAPA: Corrective and Preventive Actions

- **Corrective action**: An action to eliminate the cause of a detected error (to fix it).
  - Examples: Fix error, documentation, notification to the Clinical Director, IRB, Sponsor, or DSMB
- **Preventive action**: An action to eliminate the cause of the detected error (so it won't happen again).
  - Examples: Creation or revision of SOPs, process changes, retraining.
- Informal or formal documentation
- Evaluation of preventative actions. This is ongoing. Reviewing the process to ensure the plan is working. If not, make modifications.

# Digging Deeper and Performing a Root Cause Analysis

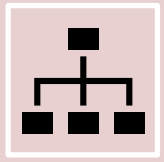
- Clearly define the problem.
- Gather and review related documentation.
- Identify contributing factors.
- Identify the root cause of the problem.
- Focus on the processes involved, **not** the people (or personalities) involved.
- Develop solutions to address the root cause. The solutions become preventive actions in the CAPA.
  - Examples: Writing down processes, group agreement to the new process, revising the process, developing manual of procedures (MOP), developing standard operating procedures (SOP) or polices

# Categories of Root Causes



**Human causes**: involve someone doing something wrong, not doing something that should be done, or doing something that doesn't need to be done

**Physical causes**: involve failure of materials such as broken or missing equipment



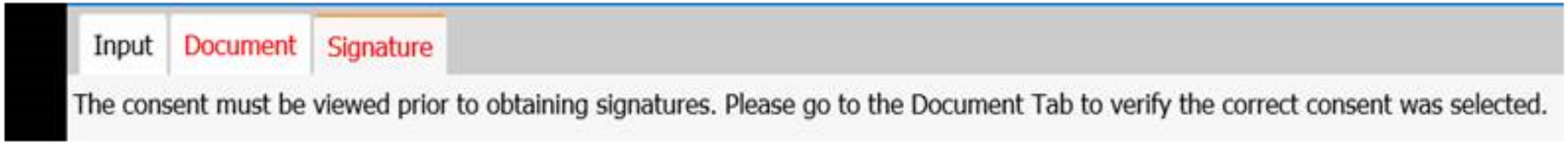
**Organizational causes**: processes, procedures, and policies that are contributing to the problem

# Example of the Organization Addressing the Issue

**From:** CC DCRI Notifications (DO NOT REPLY) <CCDCRINotificationsDONOTREPLY@cc.nih.gov>
**Sent:** Friday, January 19, 2024 1:34 PM
**Subject:** iMedConsent Electronic Signature System Update --- Friday, January 19, 2024 -- 1:34pm

***Effective immediately, the document tab must be viewed in iMedConsent prior to obtaining signatures on a consent.***

This change is to ensure the consent selected in iMed matches the consent that has already been reviewed with the patient prior to obtaining signatures. O
from red to black font and then the user can proceed with capturing signatures.




Questions can be directed to the HIMD iMedConsent™ Team, CC-HIMDiMedSupport@mail.nih.gov.

Thank you!

# Five “Why’s” of Root Cause Analysis

**Problem**: A research lab was not drawn.

**Why #1: Was the order entered into CRIS?**

**Why #2: Is the research lab listed in the protocol order set?**

**Why #3: Does phlebotomy stock the blood tube or does the team need to supply a special blood tube?**

**Why #4: Are there special requirement after the blood is drawn?**

**Why #5: Are the phone number to call for pick-up accurate and is someone available at the time of the blood draw?**

# Let's Go Back to Our Case Studies

- **Scenario**: Participant signed a consent for a different protocol than the one discussed during the consenting process.
- **How could QC have found these errors?** After the consent process but before the participant leaves is a QC action because you can immediately correct the mistake.
  - Double check that it is the correct consent (right protocol, right version)
  - Check that signatures are in the correct location
  - Did everyone sign and in the correct order (before research activities are performed)?
  - Is the date accurate (paper form)?
  - If iMed, was the consent uploaded into CRIS? If paper consent is needed, check within 24-48 hours that it was uploaded into CRIS.

# Corrective Actions: Fixing the Issue

- Notify PI and team of error and discuss what research activities were conducted and risk associated (minimal risk procedures versus more than minimal risk procedures).
- Consent the participant to the correct study.
- Notify the IRB (via RNI), Sponsor, and Clinical Director.

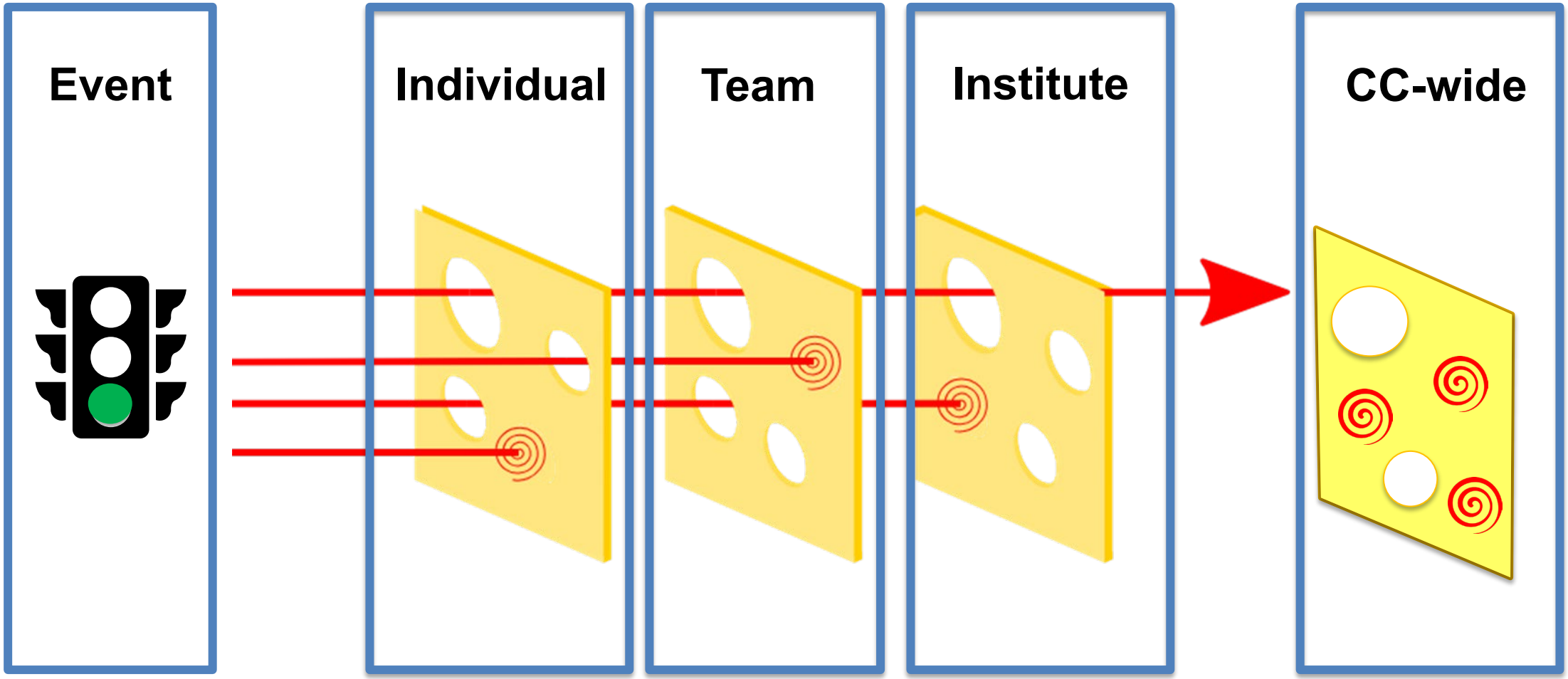
# Preventative Actions: Before the Next Participant

- iMed or paper consent:
  - Pre-populate documents (short form AND long form)
  - Confirm the participant's preferred language for medical information
  - Double check the version, title, and the IRB number list in the consent prior to the participant's arrival
- If you have a new AI, double check in PROTECT that they are approved to obtain consent.
- Check the delegation log to ensure they are allowed to obtain consent.
- Develop a personal accountability checklist.

# Quality Management Resources

- **QAPAC**: Quality Assurance Professionals Advisory Committee
  - NIH-wide intramural committee consisting of QC, QI, QA representatives from each Institute
  - A forum to discuss QA/QI issues, participate in working groups focused at addressing/resolving QA/QI, sharing best practices, and developing NIH guidelines (i.e., certifying paper records)
  - Chair: Sandy Martin
- **ORSC**: Office of Research Support and Compliance
  - Ensures the quality and integrity of clinical research and product manufacturing/compounding conducted at the NIH by providing regulatory and compliance support and guidance for all NIH Researchers in the areas of protocol navigation and coordination, quality assurance auditing and monitoring, support for FDA-regulated studies, and centralized facility oversight.
  - Director:  Gini Guptill, PhD

# Summary




https://commons.wikimedia.org/wiki/File:Swiss_cheese_model_textless.svg

# References


- International Council for Harmonisation
- ICH Q9(R1) Quality Risk Management
- ICH E6(R2) Good Clinical Practice
- NIH HRPP Policy 801: Reporting Research Events
- Institute for Healthcare Improvement (IHI): Patient Safety Essentials Toolkit
- FDA: Corrective and Preventive Actions (CAPA)

# Questions and Discussion