Navigating Research Excellence: Applying GCP through Real-World Case Studies

June 11, 2024

Mary-Tara Roth, RN, MSN, MPH – BUMC/BMC

Alexandria Carey, MSN, MBA-HC, RN, CNE, CPEN, CEN – UF

Kimberly Luebbers, MSHS, RN, BSN, OCN® – UVM

Diana Lee-Chavarria, MA – MUSC

Session Objectives:

- Describe GCP and the importance of aligning study operations to practices that are worldwide accepted standards for excellence in research
- Provide specific examples of how study conduct is aligned with GCP requirements
- Discuss real-world cases to best understand how to effectively and correctly integrate GCP and best practice standards to the conduct of your research

Agenda:

- Introduction – Eagle view of GCP
- What is GCP and why is it important
- GCP Principles
- GCP in Action Jamboard activity
- GCP Main Elements
- Cases for discussion

GLOBAL HEALTH

How to Get TB Patients to Take Their Pills? Persistent Texting and a 'Winners Circle'

The drug regimens can be grueling, and patients often quit taking their medications. But turning it into a cellphone competition helps.

Health & Science

Go to bed! Brain researchers warn that lack of sleep is a public health crisis.

USA TODAY

Kids born right after a natural disaster more likely to have mental health issues, new research shows

YOUR MOVE

For a longer life, afternoon exercise may be best, a large study shows

The data collected from more than 90,000 people gives afternoon exercisers the edge for longevity, but morning exercise might burn more fat

Someday, an Arm Implant May Prevent H.I.V. Infection for a Year

In preliminary tests, a matchstick-size rod containing a new drug offered promise as a shield against the virus. But a large clinical trial must still be done.

CNN Health » Food | Fitness | Wellness | Parenting | Vital Signs

Yes, sitting too long can kill you, even if you exercise

By Susan Scutti, CNN

Updated 3:57 PM ET, Tue September 12, 2017

The New York Times

Deaths From Substance Abuse Rose Sharply Among Older Americans in 2020

In the pandemic's first year, death rates linked to alcohol and drugs climbed among seniors as lockdowns and isolation spread.

By Roni Caryn Rabin

PRINT EDITION
December 1, 2022

'A Rinsing of the Brain.' New Research Shows How Sleep Could Ward Off Alzheimer's Disease

An experimental COVID treatment could be a promising alternative to Paxlovid, study finds

THE WALL STREET JOURNAL.

Nicotine Addiction Is Quick in Youths, Research Finds

A young cigarette smoker can begin to feel powerful desires for nicotine within two days of first inhaling, new research suggests.

By Nicholas Bakalar

Medication Treatment for Addiction Is Shorter for Black and Hispanic Patients, Study Finds

The analysis of 15 years of prescription data showed that the racial disparities are widening.

By Emily Baumgaertner

Adolescents and young adults lost more than 1.25M years of life to drug overdose deaths in a 4-year period, study finds

The Washington Post
Democracy Dies in Darkness

Are Prebiotics Important for Gut Health?

And how do they differ from probiotics? Experts weigh in on how these trendy supplements may influence your well-being.

Health

Only 40 percent of U.S. adolescents are aerobically fit, ne research finds

The Boston Globe

Can psilocybin combat mental healt issues? How magic mushrooms shov promise in fighting addiction.

The New York Times — Health

WORLD | U.S. | N.Y. / REGION | BUSINESS | TECHNOLOGY | SCIENCE | HEALTH | SPORTS | OPINION | AR

Study of Breast Biopsies Finds Surgery Used Too Extensively

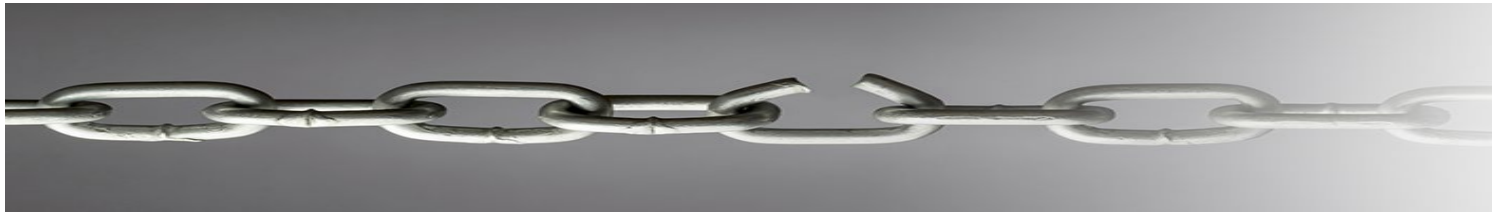
By DENISE GRADY
Published: February 18, 2011

Too many women with abnormal mammograms or other breast problems are undergoing surgical biopsies when they should be having needle biopsies, which are safer, less invasive and cheaper, new research shows.

RECOMMEND
TWITTER
LINKEDIN

Recent [mildly paraphrased] quote from an FDA scientist

"At the end of the day, all this stuff winds up being data…. Someone is going to look at all of the data, drop-out rates, compliance, etc. and determine: where is it hanging together and where is it not? Someone is going to deconstruct that sausage. If you're part of the chain of where this gets screwed up you're part of a $100 million dollar effort that is screwed up…. if that data can't be used."



Human Subjects Protection Lapses and GCP

"What we have witnessed – esoteric or complex standards have not been the issue, but rather the most basic elements of what it takes to properly conduct clinical studies…

- Enrollment of patients who did not meet the eligibility criteria for the study;
- Failure to report adverse events as required;
- Failure to ensure that a protocol was followed;
- Inadequate training for study staff;
- Investigators changing protocols without proper notice to the IRB and to FDA;
- Failure to incorporate agreed-upon protocol changes…"

Dr. Jane Henney, Commissioner, FDA, May 11, 2000

From which scenario would you prefer data was used to support medical care that you or your family members receive in future?

Scenario A	Scenario B
Data recorded on subjects meets ALCOA-C standard (incl. signed/dated source documentation)	Data recorded does not meet ALCOA-C standard; source docs do not show who collected the data and when
Delegation log shows which study staff were delegated to do what procedures; clear training SOPs were in place for the site; staff competency was assessed and documented as applicable to the task and role	No delegation logs; no detailed training records or training SOPs in place; no formal assessment of competency; staff just filled in where needed
Researchers and sponsor reported all outcomes of the investigational drug, both positive and negative	Researchers and sponsor selectively reported positive outcomes and minimized harmful side effects of the investigational drug
Full extent of data collection practices and sharing described to participants in the consent form and discussion	Data collection practices were not fully described in the consent form and discussion
Data collection has audit trail showing creation, modification, deletion of records, including who/when	Data collection utilizes is an excel spreadsheet and MS Word document; it's not clear if and why any data was changed
Protocol followed explicitly; modifications were IRB approved prior to implementation; Documentation shows protocol adherence	No documentation showing protocol adherence; changes made to research if team determined they did not result in risk to subjects (ex: timing of drug administration)

WHAT is Good Clinical Practice (GCP)?

- **An international ethical and scientific quality standard for:**
  - **Designing**
  - **Conducting**
  - **Recording**
  - **Reporting trials**

- Applies to **All Research** involving **Human Participants**

ICH harmonisation for better health

FDA U.S. FOOD & DRUG ADMINISTRATION

World Health Organization

WHY is GCP important?

Standard of Excellence

- Safety of Participants
- Quality of Data

RESEARCH PROFESSIONALS NETWORK

RESPONSIBILITY for GCP is shared by all parties involved in research, including:

- FDA/other regulators
- Sponsors
- Contract Research Organizations (CROs)
- IRBs
- Investigators
- Study staff

An additional point of interest:

Regulatory Gaps can be Informed by ICH GCP Guidance

Study Conduct Element	ICH GCP	FDA	OHRP
Protocol Compliance	4.5; 4.5.1; 4.5.2	21 CFR 312.60	
Investigator qualifications	4.1; 4.1.1; 4.1.2; 4.1.3	21 CFR 312.53	
Delegation of tasks	4.0; 4.1.5; 4.2.4; 4.2.5	FDA Guidance: Investigator Responsibilities…	
Study documentation	ICH GCP 4.9; 4.9.1; 8.0	21 CFR 312.62(b)	45 CFR 46.117 (Documentation of Informed Consent)

Anatomy of ICH GCP

- Intro
- Glossary
- Principles
- IRB
- Investigator
- Sponsor
- Protocol and Amendments
- Investigator's Brochure
- Essential Documents
- Investigator and Sponsor Responsibilities
- Trial Management, Data Handling, and Record Keeping
- Monitoring
- Audits
- Non-Compliance
- Clinical Trial Reports
- Progress Reports
- Safety Reporting
- Publication Policy

13 GCP Principles

Ethics

- … trials should be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with GCP and applicable regulatory requirements
- Before trial, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual subject and society. Anticipated benefits must justify risks.
- Rights, safety, and well-being of subjects prevail over interests of science and society

Protocol and Science

- Nonclinical and clinical information must be adequate to support the proposed trial
- Trials should be scientifically sound and described in a clear detailed protocol

13 GCP Principles

Responsibilities

- Trials should be conducted in compliance with the protocol that has received IRB (ethics committee) approval prior to initiation
- Medical care given to/decisions on behalf of subject made by qualified physician/dentist
- Each individual is qualified (education, training, experience) to perform his/her tasks

Informed Consent

- Freely given from every subject prior to participation

Data Quality and Integrity

- All trial data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification
- Confidentiality of records should be protected…

13 GCP Principles

Investigational Products

- Manufacture, handling, storage should conform to Good Manufacturing Practice (GMPs) and used per protocol

Quality Control/Quality Assurance

- Systems with procedures that assure the quality of every aspect of the trial should be implemented

GCP in *Action!*

Let's try to operationalize some of the GCP Principles. ***What do they really mean*** in the context of real research studies, i.e., YOUR research studies?

GCP in Action activity instructions

- We will use Google Jamboard
- There will be 4 GCP Principles, each on a separate Jamboard
- You are assigned to a Jamboard based on the first letter of your last name
- We will post the 4 Jamboard links in Chat; select the link corresponding to your last name
- For “your” assigned GCP Principle, provide examples of how you would operationalize, or what you have implemented, in your study.
- Try to come up with as many specific examples as possible in 4 min.
- We’ll briefly review all of them together and then plan to post images of the finished Jamboards along with the slides and videos on the RPN Workshop library

GCP in Action Jamboard activity example

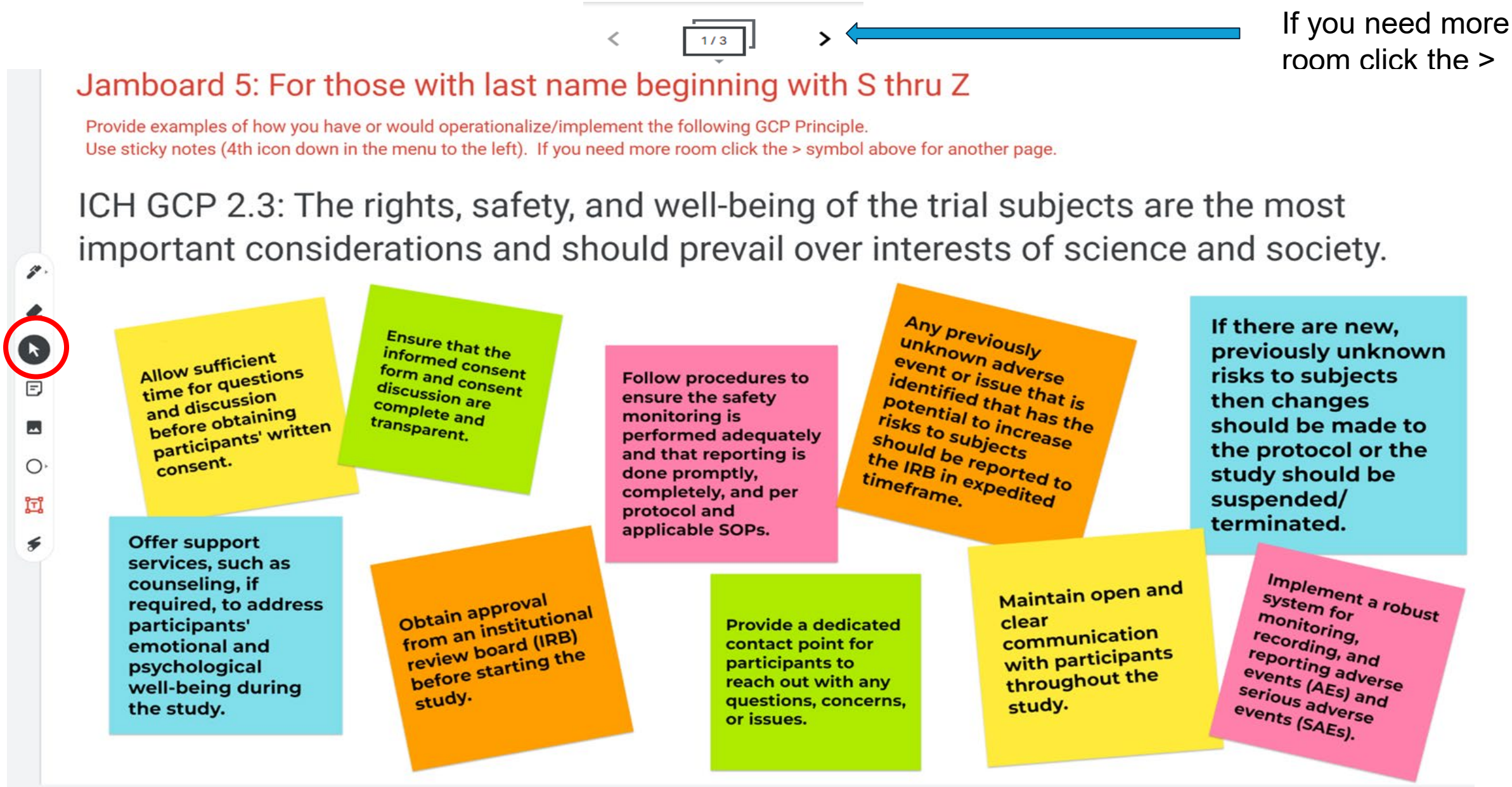
If you need more room click the >

Jamboard 5: For those with last name beginning with S thru Z

Provide examples of how you have or would operationalize/implement the following GCP Principle.
Use sticky notes (4th icon down in the menu to the left). If you need more room click the > symbol above for another page.

ICH GCP 2.3: The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

GCP in Action Jamboard activity example



Jamboard 1

RESEARCH PROFESSIONALS NETWORK

Jamboard 2

ICH GCP 2.9: Freely given informed consent should be obtained from every subject prior to clinical trial participation.

Additional comments from workshop chat:

- informed consent process checklist to ensure meeting all regulatory requirements

Jamboard 3

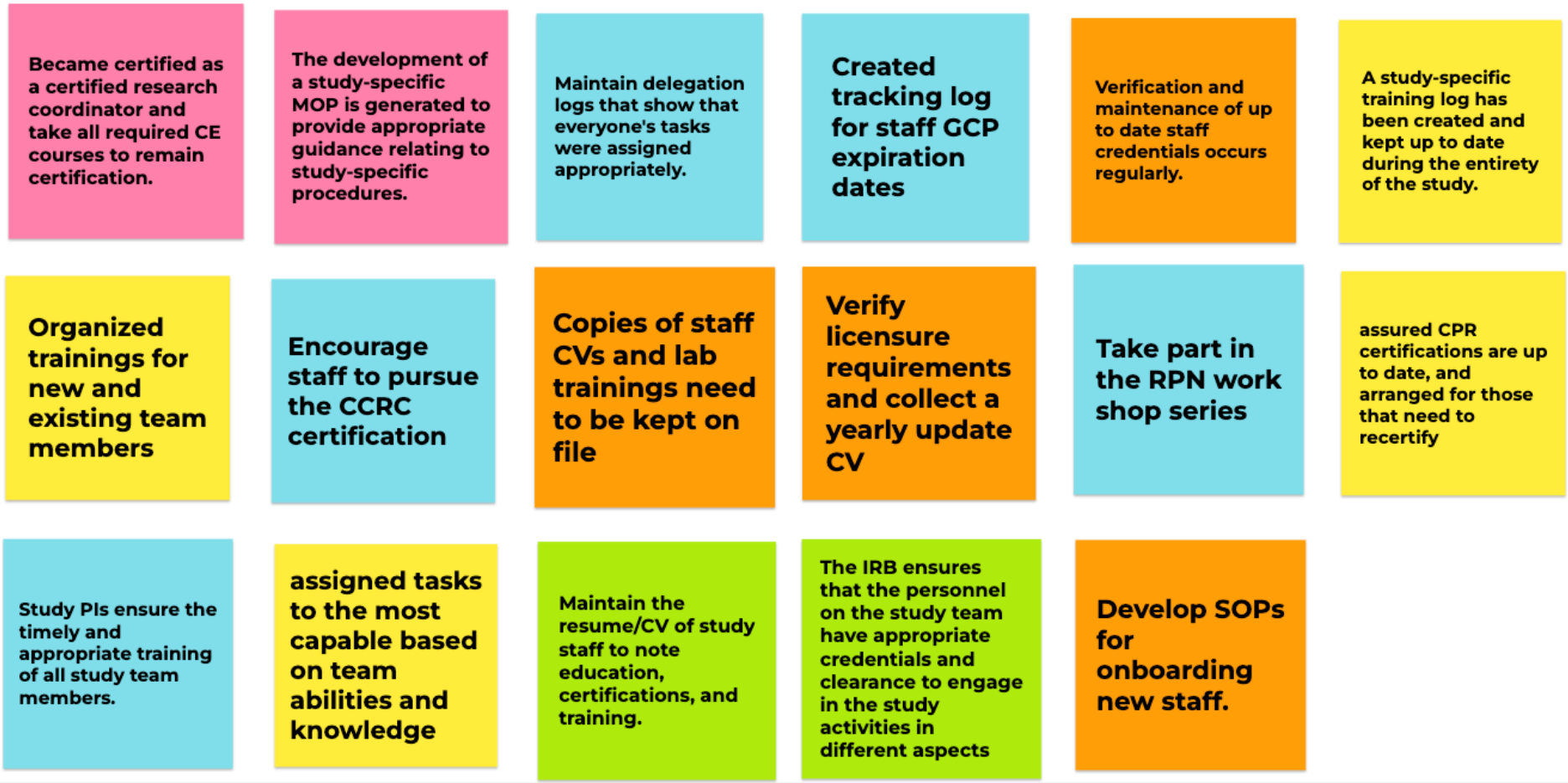
ICH GCP 2.6: A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB) approval.

Additional comments from workshop chat:

- If possible have informed consent completed before the morning of the screening visit.
- Document that all KP are trained in the protocol and updates to the protocol.
- Regular internal QA of study documentation (study subject binders)

Jamboard 4

ICH GCP 2.8: Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).



Additional comments from workshop chat:

- Keep up to date on your CITI trainings.

Main Themes of GCP

IRB oversight

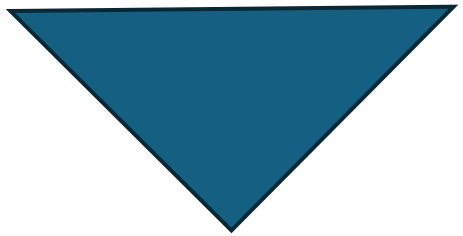
Follow the Protocol

Ensure proper qualifications/training/competency

Informed consent

Documentation to support quality of conduct of the study

Safety Monitoring and Reporting



Quality of Data

Rights, Welfare, Safety of Research Participants

IRB oversight

The IRB should:

- safeguard the rights, safety, and well-being of all study subjects.
  - Special attention should be paid to studies that may include vulnerable subjects
- review and document its views in writing
- consider the qualifications of the investigator
- conduct continuing review

Follow the Protocol

- Protocol adherence is the responsibility of all research team members
- Ensure staff are trained on the protocol and amendments to the protocol
- Ensure consistent communication of the protocol details among the research study team
- Conduct the study in compliance with the protocol approved by the IRB, Sponsor, and applicable regulatory authorities (FDA)
- Do not implement any deviation from, or changes of the protocol without Sponsor agreement and IRB approval (except to eliminate an immediate hazard(s) to participants)

Ensure proper PI and study team qualifications/training/competency

- The investigator(s) and study staff should be qualified by education, training, and experience to assume responsibility for the proper conduct of the study/role in study
- Must have an adequate number of qualified staff and adequate facilities to conduct the study properly and safely
- Ensure that the PI and all persons assisting with the study are adequately informed about the protocol, the investigational product(s), and their study-related duties and functions
    - The investigator is responsible for supervising any individual t o whom the investigator delegates study-related duties and functions

Informed Consent

- The investigator, or a person designated by the investigator, should fully inform the subject or LAR, of all pertinent aspects of the study
- No coercion or undue influence
- Participant should have time and opportunity to understand the study and ask questions to decide about participation
- The consent form should be signed and personally date by the participant or LAR and the person who conducted the discussion

Documentation

- Essential Documents: individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced

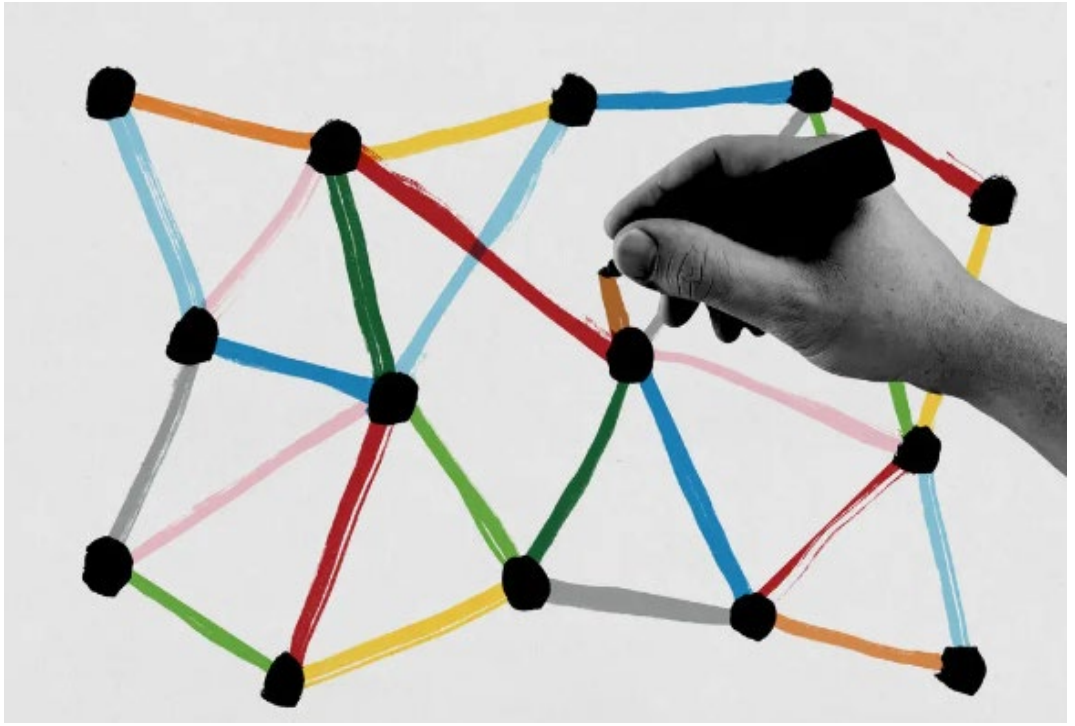
- The investigator should:
  - Maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects
  - Source data should be attributable, legible, contemporaneous, original, accurate, and complete
  - Ensure changes to source data are traceable, do not obscure original, and be explained if necessary
  - Ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports
  - Data on the CRF that are derived from source documents, should be consistent with the source documents

Safety Monitoring and Reporting

- Adverse events incl. lab abnormalities should be reported to the sponsor according to the reporting requirements specified in the protocol
- All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs identified as not needing immediate reporting
- The sponsor should promptly notify all concerned investigator(s)/institution(s) and the regulatory authority(ies) of findings that could affect adversely the safety of subjects, the conduct of the trial, or alter the IRB's approval to continue the study

Case Discussions

- It's one thing to read the ICH GCP guidance. It's another thing entirely to be able to relate formal GCP guidance to how it's specifically applied "on the ground" in research studies.
- We will present a few cases for group discussion, including some details of the case and prompts to get the conversation going. We will also affiliate the cases with the regulatory references.
- The cases can help to CONNECT the requirements of GCP with study conduct.
- Contribute to the conversation by unmuting and/or Zoom Chat.



RESEARCH PROFESSIONALS NETWORK

1) The case of “who done it”

The case

- During a QA review it was noted that the eligibility worksheets did not include the PI signature and date.
- Upon further review the QA reviewers noted initials were present on the eligibility worksheet, but the PI and research coordinator have the same initials.

The prompts

- What could the PI and research team have done to make it clearer who was documenting eligibility?
- What documents would capture information about this responsibility and cover attributability?
- What important information is missing on the eligibility worksheet?

Comments from Workshop Discussion

- *What could the PI and research team have done to make it clearer who was documenting eligibility?*
  - Use middle initials
  - Have separate signature lines on the CRFs
  - Line to print name
  - Specify that a signature from PI is required on the source

- *What documents would capture information about this responsibility and cover attributability?*
  - Delegation log
  - Our eligibility worksheets require the coordinator and investigator to write both their printed name and full signature

- *What important information is missing on the eligibility worksheet?*
  - The date it was assessed

Regulatory References for The case of “who done it”

- ICH GCP E6(R2) 4.9.0. The investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site’s trial subjects. **Source data should be attributable, legible, contemporaneous, original, accurate, and complete.** Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail).
- ICH GCP E6 (R2) 4.1.5 The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.

2) The case of the outdated consent form

The case

- Alcohol dosing and response study testing young adults and competence on mental acuity tests, judgment, and simulated driving
- An amendment was approved to increase the alcohol dosing
- On self-audit the study team found that they had not implemented the updated IRB approved consent form.
- 40 subjects consented on consent forms that described lesser alcohol dosing amounts.

The prompts

- What human protections issue do you see here?
- What should the study team do, if anything, to correct the problem?
- What could have prevented this problem from occurring in the first place?

Comments from Workshop Discussion

- *What could have prevented this problem from occurring in the first place?*
  - I try to not make up a bunch of consent forms in advance so the wrong versions aren't floating around
  - Only take the consent form from the IRB-approved source / only get blank consents from the "system of truth" IRB system / only consent on ICF pulled from IRB the DAY of consent. Always use the correct version
  - Make sure you are using the most recent stamped document / Always confirm you have the most recent IRB approved consent form prior to consenting each participant
  - A list of current consents and approval dates to refer to before consenting
  - Staff should be trained on where to retrieve the most up to date approved ICF and avoid accidentally using an old one / Informed Consent training
  - Any time a new protocol goes into effect, be sure to inform and discuss with all involved in the study
  - Habitual verification of the ICF version prior to printing/signing
  - A good ICF log (who signed what version) can be helpful
  - Make sure the eConsent is updated
  - Submit a major deviation to the IRB and provide a plan to fix the issue and how to avoid it in the future

- *What human protections issue do you see here?*
  - Major protocol deviations
  - Re-consent was likely required
  - There is a problem with safety
  - Increased risk to subject
  - This would not represent fully informed consent

- *What should the study team do, if anything, to correct the problem?*
  - Should have updated the consent forms and re-sent to all participants who signed the old form
  - Inform PI

Regulatory References for The case of the outdated consent form

- ICH GCP E6(R2) 4.8.10: Informed consent of trial subjects
- ICH GCP E6(R2) 4.8.10(c): Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following: …. the trial treatments ……
- OHRP 45 CFR 46.116(a)(4):

  The prospective subject or the legally authorized representative must be provided with the information that a reasonable person would want to have in order to make an informed decision about whether to participate, and an opportunity to discuss that information.

3) The case of the changing protocol

The case

- A study is testing a new drug infusion to decrease long-term effects of ischemic stroke.
- The protocol requires a particular neuro assessment score be obtained in-person by a certified investigator at study baseline assessment.
- After the first few participants, the study coordinator began to use the most recent neuro assessment score from the medical record (done per usual care) to complete the Case Report Form. This practice continued and new RAs were trained to this practice.

The prompts

- What do you think of this change in the protocol?
- What ramifications if any could it have… for subject safety? For data quality?
- What should be done here?

Comments from Workshop Discussion

- *What do you think of this change in the protocol?*
  - Protocol change would lead to inconsistent data
  - Staff cannot make changes!
  - Staff cannot administer an assessment required of the investigator
- *What ramifications if any could it have… for subject safety?…for data quality?*
  - Is a protocol deviation if not done by delegated staff, and potentially not usable data if protocol doesn't allow for pre-consent data
  - Subject safety is at risk! Increased risk given that they are relying on data not obtained at the time of the study visit for the particular safety check
  - QA checks were likely not performed by study team either
- *What should be done here?*
  - Report deviation
  - Staff should not be conducting the assessment since it is supposed to be a CERTIFIED investigator
  - Report to IRB, re-train staff

Regulatory References for The case of the changing protocol

- ICH GCP E6(R2) 4.5.1: The investigator should conduct the trial in compliance with the protocol which was given approval by the IRB
- ICH GCP E6(R2) 4.5.2: The investigator should not implement any deviation from, or changes of, the protocol without agreement by the sponsor and prior review and documented approval from the IRB of an amendment
- FDA 21 CFR 312.60: An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care…

4) The case of operationalizing screening and consent

The case

- The study is enrolling females age 16-45. Subjects will receive a new vaccination which is FDA-approved, but the new dosing schedule will be tested: 2 doses (experimental dosing) vs 3 doses (FDA-approved dosing).
  - Inclusion criteria: age 16-45; patient at SuperCity Hospital; Not yet received vaccine; afebrile 24 hours before injection
  - Exclusion criteria: pregnant/nursing, allergy to yeast, immunocompromised (treatment within the last 30 days); coagulation disorder

The prompts

- What are some considerations on
  1) consent and
  2) screening

  that the study team should take into account and develop processes for prior to enrolling?

Regulatory References for
The case of operationalizing screening and consent

- ICH GCP 1.61: Vulnerable subjects
- ICH GCP 4.8: Informed Consent of trial subjects (specifically, 4.8.12)
- ICH GCP E6(R2) 4.5.1: The investigator should conduct the trial in compliance with the protocol which was given approval by the IRB
- FDA 21 CFR 50.55: Requirements for permission by parents or guardians and for assent by children
- FDA 21 CFR 50.52: Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects
- FDA 21 CFR 312.60: An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan…
- OHRP 45 CFR 46.116: General requirements for informed consent
- OHRP 45 CFR 46.108: Requirements for permission by parents or guardians and for assent by children

Comments from Workshop Discussion

- *What are some considerations on 1) consent and 2) screening that the study team should take into account and develop processes for prior to enrolling?*
  - Minor consent and parent consent in addition to the adult
  - Legal representative / LAR consent option
  - Screenings: verification of age, patient status, vaccine status, temperature check, pregnancy check, allergy check
  - Precise screening to cover all possible exclusion/inclusion criteria
  - Sexual activity screening for likelihood of an early, unidentified pregnancy
  - 2 days of screening 24-hours apart
  - May need to ask subjective questions like “in the last 24 hours have you experienced chills, sweating, etc.?”
  - A good checklist with documentation of how the answers were determined
  - Develop an inclusion/exclusion document in accordance with the protocol
  - Check with sponsor to expand on what they mean regarding immunocompromised status (what sort of treatment?)
  - How to check for coagulation disorder? Verified by patient report vs. PCP or study MD with physical exam?
  - Since they are a patient in the hospital already, can we review the records for some of these answers?

5) The case of forgotten consent document

The case

- Minimal risk study involving brief 1x intervention, surveys, data collection in a two-hour study visit
- IRB approved consent form/HIPAA authorization including signature lines for the subject and investigator
- The investigator didn't have a consent form and so instead explained the purpose, study procedures, risks, etc. and provided time to consider.
- The participant says they don't need anything in writing and agrees to participate.

The prompts

- What are the major issues here?
- Is it ok to continue with research activities with this participant?

Comments from Workshop Discussion

- *What are the major issues here?*
  - Need an ICF
  - Investigator should have known better, this is a big training problem

- *Is it ok to continue with research activities with this participant?*
  - No
  - Not okay. Need documentation or it did not happen.
  - Absolutely not. That is a participant safety issue
  - Remind them that you need to follow policies even if the participant doesn't feel they need anything in writing.
  - Research activities should not proceed. If so this is a protocol violation

Regulatory References for The case of the forgotten consent document

- ICH GCP E6(R2) 4.8.8 Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.
- ICH GCP E6(R2) 4.5.2: The investigator should not implement any deviation from, or changes of, the protocol without agreement by the sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment
- ORHP 45 CFR 46.116 General Requirements for Informed Consent – specifically subsection B – basic elements of informed consent
- OHRP 45 CFR 46.117 Documentation of Informed Consent

6) The case of the operationalization of the safety monitoring plan

The case

- Study tests a new drug for treatment of COVID
- Hospitalized subjects receive investigational drug infusion daily for 5 days.
- Per the protocol subjects will be monitored for AEs throughout the hospital stay and then for 12 months after discharge.
- Any SAE (whether related or not or expected or not) should be reported to the Sponsor within 24 hours
- Other AEs should be reported via the data capture system within 60 days

The prompts

- How should AE monitoring procedures be operationalized for this study?
- What elements of study conduct relate to this case?
- What elements do you have to be sure to put in place to carry out this monitoring plan?

Comments from Workshop Discussion

- *How should AE monitoring procedures be operationalized for this study?*
  - Delegation log
  - Engagement of clinical team?
  - Making sure the participant is linked to the study in EPIC so the system pushes you a notification when they interact with the health care system

- *What elements do you have to be sure to put in place to carry out this monitoring plan?*
  - Review medical records and conduct check-ins on a regular basis
  - You should operationally define what “throughout the hospital stay” means – every few hours? Once per day? Etc.
  - Good procedures for following up with participants and documenting thoroughly
  - Thorough health history collected to differentiate pre-existing vs. AE
  - A heavily detailed MOP
  - Whoever is delegated in the log for reviewing AEs/SAEs should be approved in the IRB for that role
  - A procedure flowchart/checklist for what to do in each potential instance

Regulatory References for
The case of the operationalization of the safety monitoring plan

- ICH GCP E6(R2) 4.11: Safety Reporting
- ICH GCP E6(R2) 4.1: Investigator Qualifications and Agreements
    - 4.1.1 The investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial
- ICH GCP E6(R2) 2.8: Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).
- ICH GCP E6(R2) 4.9 Records and Reports
- FDA 21 CFR 312.64(b) Safety Reports
- FDA 21 CFR 312.53 Selecting Investigators and Monitors
- FDA 21 CFR 312.62(b) Investigator Recordkeeping and Record Retention

7) The case of a change in plans (Monitoring Plans)

The case

- Investigator Initiated Study, Local PI is the lead site, Investigator holds the IND,10 participating sites
- The investigator/sponsor's FDA approved Monitoring Plan is to monitor all sites every three months.
- Due to budget constraints, the investigator decides only to monitor one third of the sites annually and as an additional cost savings, plans to conduct some of the monitoring visits personally.

The prompts

- What issues do you see with this change in monitoring plan?
- What steps that need to be taken before implementing these changes?

Regulatory References for
The case of The case of a change in plans

- ICH GCP E6(R2) 5.18.3. Extent and Nature of Monitoring

  The sponsor should ensure that the trials are adequately monitored. The sponsor should determine the appropriate extent and nature of monitoring. The determination of the extent and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the trial…

- ICH GCP E6(R2) 5.18.7 Monitoring Plan

  The sponsor should develop a monitoring plan that is tailored to the specific human subject protection and data integrity risks of the trial. The plan should describe the monitoring strategy, the monitoring responsibilities of all the parties involved, the various monitoring methods to be used, and the rationale for their use…

8) The case of the memory regulatory file

The case

- PI obtained biological samples (blood, saliva, tissue) from participants undergoing surgery.
- On routine audit it was found there is no documentation of sample collection for research, such as date samples taken, from which participants, type of samples taken, etc.
- PI states this information “lives in their memory.”

The prompts

- What is/are the issue(s) here?
- What ramifications, if any, could these processes have on the study?
- How can this be corrected?

Regulatory References for The case of the memory regulatory file

- ICH GCP E6(R2) 4.9.1 Research Records and Reports: The investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary…
- ICH GCP E6(R2) 8.0: Essential Documents

  8.1 Essential documents are those documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced …

GCP – A Final Emphasis

- Compliance with this standard provides public assurance that…..
  - the rights, safety and well being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki,
  - and that the clinical trial data are credible.