QUALITY ASSURANCE IN A GCP ENVIRONMENT AND THE RESOURCES AVAILABLE AT UPSTATE.

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AGENDA

- What is GCP?
- Quality Management
- Risk!
- CAPA
- Resources for research at Upstate
  - CAPA and Risk Management
  - Review of Monitor Reports
  - Audit Preparation
  - Audit Support
  - SOP Writing
  - Training

WHAT IS GCP?

- Most commonly the term GCP refers to the International Council for Harmonization (ICH) Ethical Guideline entitled Good Clinical Practice (ICH GCP E6) (R2)
- The FDA has several regulations and guidance documents that cover GCP.
  - 21 CFR 312 & 314 (Drug trials)
  - 21 CFR 312 & 601 (Biologics)
  - 21 CFR 812 & 814 (Devices)
- More recently the World Health Organization (WHO) put out a guidance entitled Good Clinical Laboratory Practice (GCLP)
- www.FDA.gov has many guidance documents that are also relevant.

WHAT IS GCP? FUN FACT-

1747- James Lind (Father of Clinical Trials)

Lind carried out clinical trials while at sea to try and address the problem of scurvy in sailors. He broke the effected sailors into 6 groups.

1- Cider
2- Elixi Vitriol
3- vinegar
4- seawater
5- nutmeg
6- oranges and lemons

In just 6 days the group receiving citrus fruit were fit to go back to work.

QUALITY MANAGEMENT

- Quality Systems (QS) / Quality Management Systems (QMS)
  - ISO defines it as the management system used to direct and control an organization with regard to quality.
  - FDA defines it as “the organizational structure, responsibility, procedures, processes, and resources for implementing quality management.”21 CFR 820.3
  - ICH E6R2 does not define.

QUALITY MANAGEMENT

"QUALITY IN CLINICAL TRIALS = THE ABSENCE OF ERRORS THAT MATTER"
ANN MEEKER-O'CONNELL IS VP, GLOBAL HEAD, QUALITY ASSURANCE AT IQVIA

- Quality systems attributes
  - Set the standards that you are working to meet
  - Define how you are going to meet them
  - Define the people, actions and documents necessary to carry out the work in a consistent manner
    - Provide documented evidence of what happened
    - May include manuals, handbooks, procedures, policies, records and templates
- Where can clinical QS Be applied?
  - Control of trial design
  - Personnel training and qualification
  - Acceptable Data management
    - Good Documentation Practices
    - Verification and or validation of processes

RISK MANAGEMENT

- Risk management is documenting…
  - What the risks are,
  - what can be done to reduce or eliminate the risks,
  - what are the planned risk management strategies and
  - how one knows that the controls are effective.

RISK MANAGEMENT

- A key aspect of risk management is having a process to correct problems if/when they occur and implement steps to prevent the problem from occurring…
- How is this done???

CAPA

- What is CAPA?
  - Corrective Action- action to eliminate the root cause of a **detected** nonconformity or other undesirable situation.
  - Preventive Action- action to eliminate the root cause of a **potential** nonconformity or other undesirable situation.
- When used properly with an effectiveness check the CAPA system will provide a means to prevent the mistake from reoccurring.

FDA WARNING LETTER EXAMPLE

- **2. Failure to maintain accurate, complete and current records evidencing informed consent and case history records. [21 CFR 812.140(a)(3)(i) and 21 CFR 812.140(a)(3)(ii)]**

- As a clinical investigator, you are responsible for properly obtaining and documenting informed consent. You are also responsible for maintaining accurate, complete, and current subject records including signed and dated consent forms, as well as, records of subject's case history and exposure to the device. Examples of your failure to fulfill these responsibilities include, but are not limited to the following:

- a. The informed consent document for Subject 103003 was dated and timed by one of your staff members and not the legally authorized representative (LAR). This subject was re-consented, but dated the consent October 22, 1913 and the form was not witnessed or signed by any other study personnel.

- b. There is no documentation that qualified study personnel determined that Subjects 103026 and103008 were eligible prior to randomization. Screening images for Subject 103026 showed a possible carotid dissection and occlusion prior to being randomized, and Subject 103008's images showed stenosis. Your actions placed these subjects at increased risk of serious complications and death from their existing cerebral vascular disease. Qualified study personnel should have documented and confirmed, under your supervision, that all subjects met the study inclusion/exclusion criteria in order to be safely enrolled in the study.

- Your response acknowledges the above deficiencies and includes updated standard operating procedures (SOPs) for obtaining informed consent. Additionally, you conducted re-education on the consent process and requirements but you did not include names of staff trained and when the training was performed. Also, you created an inclusion/exclusion form for study personnel to use when enrolling subjects. However, your response does not include the form nor does it include any related SOPs to provide instructions on this new process. In addition to this, your response does not include documentation to show that the Institutional Review Board was notified of these issues. Therefore, your response is inadequate due to lack of documentation and a preventative plan to prevent recurrence of the violations.

RESOURCE FOR UPSTATE RESEARCH

- Resources for research at Upstate
  - CAPA and Risk Management
    - Writing, reviewing, implementing CAPA's and Risk management.
  - Review of Monitor Reports
    - Second set of eyes for review of monitoring reports
  - Audit Preparation
    - Are documents and staff ready for an outside agency inspection?

RESOURCE FOR UPSTATE RESEARCH

- Audit Support
  - Help during and agency audit
  - Assistance with response to findings
- SOP Writing
  - Support in writing effective SOP's
  - Review of SOP's
- Training
  - Aid in setting up training, training logs and conducting relevant training.

QUESTIONS?

QAIP: QUALITY ASSESSMENT & IMPROVEMENT PROGRAM

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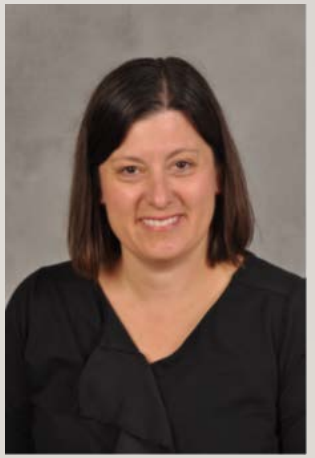

REMEMBER:

- We have a common goal
- We share the important responsibility of protecting human subjects in research

WHAT WILL BE COVERED TODAY:

- What is QAIP
- Before, during and after a site visit
- Common findings
- Becoming compliant
- Site initiation visits
- Contact info

WHAT IS QAIP?

- Internal post-IRB approval monitoring of human subject research
- Established in the Fall of 2005
- Reviews the conduct of the study in real time

EMAIL SUBJECT LINE:

- QAIP site visit request
- Hmm…What does this even mean?

LET'S MAKE A PLAN:

- Meet on day and time that's convenient
- If subjects have yet to be enrolled site visit will be postponed
- Ensure files are in order

PREPARING FOR THE SITE VISIT:

- Do study activities follow the protocol exactly?
- Using current consent/assent document(s) with IRB approval mark/exp date?
- Make sure that anyone participating in study activities and/or is obtaining consent is listed as a study team member and performing duties as designated on the current IRB application. Submit amendments to update team as necessary.
- Review and confirm documentation of subject eligibility.

PREPARING FOR THE SITE VISIT:

- Have all subjects received a copy of their signed ICF? Is there documentation that they received this copy?
- If you list an emergency telephone number, make sure there is someone available to answer it.
- Is all confidential information in a locked file cabinet or locked location and computers and electronic info password protected?
- Are specimens stored as approved in the protocol?

PREPARING FOR THE SITE VISIT:

- If the study is subject to the Privacy Rule…
- Have subjects been provided with the Upstate Notice of Privacy Practices at the time the consent/authorization form was signed?
- https://upstate.ellucid.com/documents/view/4288

WHAT IS SUBJECT TO THE PRIVACY RULE?

- PHI=Protected Health Information=Identifiable Information
- The HIPPA Privacy Rule defines PHI as individually identifiable health information that is transmitted or maintained in any form or medium (electronic, oral, or paper) by a covered entity or its business associates, excluding certain educational and employment records.

STEPS OF QAIP SITE VISIT:

- Thorough review of study in IRBNet
- Interview PI/Coordinator
- Review subject records
- Wrap-up summary

FOLLOWING THE QAIP SITE VISIT:

- Detailed report of findings is submitted to the Vice President for Research
- Report of findings is submitted to the IRB for review at next convened meeting.
- PI is encouraged to address any compliance issues via letter of response to the IRB

COMMON FINDINGS:

- Consent form issues
- Consent process issues
- Protocol issues
- Regulatory issues

CONSENT FORM ISSUES:

- Incorrect consent used
- Missing consent forms
- Missing pages
- Missing signature and/or dates
- Choice box not completed

TO BECOME COMPLIANT:

- Use correct version of IRB stamped consent
- Keep all original signed ICFs
- Ensure all pages of ICF present
- Make sure all signatures present
- All signatures must be dated
- Ensure choice boxes completed
- Maintain secondary documentation of consent (separate checklist)

CONSENT PROCESS ISSUES:

- Consent obtained by someone not approved as a study team member
- Subjects not provided with a copy of the signed consent form and the Upstate Notice of Privacy Practices (NOPP)
- No documentation that the subject received a copy of the signed consent form or Notice of Privacy Practices

TO BECOME COMPLIANT:

- Only IRB approved team members, delegated authority by the PI, are to obtain informed consent (consider maintaining a delegation of authority log)
- Provide a copy of the signed informed consent and the NOPP to each subject
- Document that a copy of consent and NOPP was provided to subject in study file

PROTOCOL ISSUES:

- Changes implemented on an approved study prior to IRB review and approval of changes
- Eligibility not documented and/or approved criteria not followed

TO BECOME COMPLIANT:

- Wait for IRB approval before initiating any changes to the protocol unless the change is necessary to eliminate apparent immediate hazards to the subject (in which case the IRB must then be notified at once).
- Have an eligibility checklist for each subject

REGULATORY ISSUES:

- Disorganized study/regulatory files
- Incomplete or late submissions of required documents to the IRB

TO BECOME COMPLIANT:

- Keep all IRB correspondence
- Keep all sponsor/FDA correspondence
- Organize all study and subject files in chronological order if possible
- Maintain a subject log and delegation of authority log
- Submissions to IRB in accordance with deadlines

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SITE INITIATION VISITS AVAILABLE AT STUDY START UP:

- Assistance with set-up/organization of study records and required documents
- Instruction concerning local IRB reporting requirements as it pertains to adverse events, amendments, continuing review, data safety and monitoring reports and protocol deviations
- Education about the informed consent process and documentation
- Clarification of confidentiality and HIPAA issues

SCHEDULE A SITE INITIATION VISIT IF YOU:

- Are a new investigator or coordinator
- Are an investigator with no study coordinator
- Have questions about IRB reporting requirements
- Are not assisted/monitored by other entities
- Would like assistance with study set up before enrollment begins

QAIP WEBSITE:

- https://www.upstateresearch.org/compliance/qaip/

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