

Audit Trends: Issues, Findings and Remedies

Panel Members:

- Tom Asplan, RQAP-GCP
- Jean Gibson, RN, CIP
- Carla Hanekamp, RN
- Dawn Lowe-Gooden, MS, CQA
- Melissa Schneider

- Moderator:** Elva Turner, BSEd, CCRC, CCRA



Objectives

- Provide general overview of findings discovered during ORCRA quality reviews
- Discuss recommendations for corrective and preventive actions
- Provide tips for compliance and reporting



Definitions

- Non-conformance:
 - Verifiable qualitative or quantitative observation, information, record or statement of failure to comply with IRB-approved protocols, the ICH E6 GCP guidance, federal and state regulations, AAHRPP standards, CCHMC research policies and procedures relating to research involving human participants identified or occurring three or more times out of a total of 3-12 examples during the QR or one observation that is determined to be severe non-compliance.

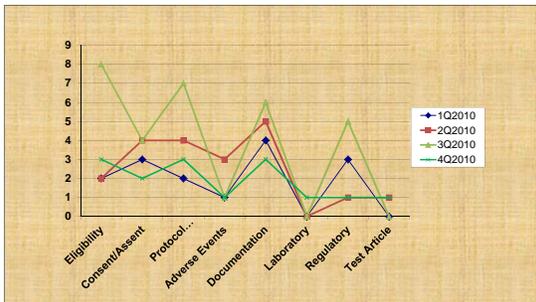


Definitions

- **Audit:**
 - A systematic and independent examination of trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data recorded, analyzed, and accurately reported according to the protocol, sponsor's SOPs, GCPs and the applicable regulatory requirement. Definition from ICH E6



2010 Audit Trends



Eligibility Quality Review Checklist

- Participants met initial inclusion/exclusion criteria for the IRB approved protocol in effect at the time of enrollment
- Inclusion/exclusion criteria were verified by the PI or designee



Issues and Findings: Eligibility

QR Checklist question: Participants met initial inclusion/exclusion criteria for the IRB approved protocol in effect at the time of enrollment.

Findings:
There was no data available to confirm that 17 of 17 participants reviewed met criteria listed in the protocol

The inclusion criteria as listed in the protocol could not be verified for 2 participants.

Eligibility was unclear or could not be verified for 5 subjects for 2 different eligibility criteria as listed in the protocol




Issues and Findings: Eligibility

QR Checklist question: Participants met initial inclusion/exclusion criteria for the IRB approved protocol in effect at the time of enrollment.

Findings:
For 6 of 6 subjects protocol required inclusion/exclusion criteria could not be confirmed on the following:

- Inclusion criteria: "Children will also be enrolled only through pilot study". There is no documentation that any of the study participants were in the pilot study.
- Exclusion criteria: "Predicted survival of 12 months or less as determined by the participant's treating physician or Principal Investigator". There is no supporting documentation that this was met.

Based on documentation available in all subject files, it could not be verified that they were eligible to be enrolled into the study. For example, it could not be determined that the subjects were not taking any of the 15 excluded drugs as detailed in the protocol




Issues and Findings: Eligibility

QR Checklist question: Inclusion/exclusion criteria were verified by the PI or designee

Findings:
Documentation could not be located to verify that all eligibility criteria were confirmed by the PI or designees prior to study procedures taking place for 11 of 11 subjects reviewed

There was no determination of eligibility by the PI or designee

There is no documentation that exclusion criteria were verified by the study staff for 4 of 4 subjects reviewed prior to any study procedures being performed.




Remedies and Tips: Eligibility

- Possible Corrective Actions:
 - Notes to file for the affected participants
 - General note to file for all participants
 - Determine eligibility now with proper documentation
- Possible Preventive Actions
 - Retraining of the study staff on the protocol-required eligibility
 - Create a source document that captures all eligibility criteria for use during screening include signature(s) of PI or designee



Example:
Note to file Template

Note to File 

Date
PIE Patient Number
Investigator
Study Title
Notes to File Regarding

REASON FOR DELEGATION DETERMINATION

COMMENTS

PREPARED BY

Signature _____ Date _____



Remedies and Tips: Eligibility

- Tips for Compliance
 - Ensure delegation determination of eligibility is on the DOA log
 - Obtain medical records/supporting documentation for eligibility determination



IRB Reporting Per R-18

Investigators must report the following events to the IRB Office **within 7 days** after an investigator's knowledge of the problem adverse events that:

- Are unexpected **and** related or possibly related to participation in the research
- Information that indicates a change to the risks or potential benefits of the research.
- Breaches of confidentiality
- Changes in labeling or withdrawal from marketing for safety reasons of a drug, device or biologic used in a research protocol
- Changes to the protocol made without prior IRB review to eliminate apparent immediate hazard to a research participant




IRB Reporting Policy per R-18

- Protocol violations
- Incarceration of a participant in a protocol not approved to enroll prisoners
- Complaints of a participant when indicative of unexpected risks or cannot be resolved by the investigator
- Other unanticipated problems posing risk to human subjects or others comparable to the events listed above




IRB Reporting Per Policy R-18

- For studies involving **investigational devices**, investigators must report the following events to the IRB Office **within 5 days** after investigator's knowledge of the problem:
 - Any unanticipated adverse device effects
 - Any deviations from the investigational plan to protect the life of a subject in an emergency
 - Any use of the device without obtaining informed consent




Quality Review Checklist: Informed Consent

- The informed consent document was signed and dated appropriately by the participant, or their legally authorized representative, and the person who obtained consent.
- The proper version of the Informed Consent was used.



Issues and Findings: Informed Consent

QR Checklist question: The informed consent document was signed and dated appropriately by the participant, or their legally authorized representative, and the person who obtained consent.

Findings:

- The subject signed a faxed consent dated different than the person obtaining consent.
- Consent forms for 4 of 4 enrolled subjects were not signed by 2 parents, as required by the IRB initial approval letter. Instead, the forms were signed by only 1 parent.
- The signature page of the consent form for subject 1 appeared to have been generated separately from the other pages of the consent. Page 5 was printed in color and had fold lines while the other pages were black and white with no creases.



Issues and Findings: Informed Consent

QR Checklist question: The proper version of the Informed Consent was used.

Findings:

- Participants did not sign the most currently approved version of the consent form in the following instances.
 - On 7/7/04, Subject A signed Phase 1 consent version 12/15/03, CCHMC IRB approved on 2/11/04. The participant should have signed Phase 1 consent version 3/10/04, IRB approved on 3/10/04.
 - On 9/22/08, 10/24/08 and 2/9/09, respectively, Subjects A, B, and C signed Phase 2 consent version 9/12/07, CCHMC IRB stamped on 9/12/07. The participants should have signed Phase 2 consent version 7/24/08, IRB approved on 8/18/08.



Remedies and Tips: Informed Consent

- Possible Corrective Actions:
 - Notes to file for the affected participants
 - General note to file for all participants
 - Consent participants now (or at the next scheduled visit) before additional study procedures
- Possible Preventive Actions
 - Retraining of the study staff



Remedies and Tips: Informed Consent

- Tips for Compliance
 - Review the IRB approval letters to check for reconsenting and parent signature requirements.
 - When get new consent throw away the old ones
 - Put new one in front of binder
 - Can print directly from ePAS



IRB Reporting: Informed Consent

Problems involving informed consent, such as not using the correct version should be reported to the IRB as unanticipated problems.

These types of events would fall under the category "other" on the unanticipated problem report, and should include an explanation of the corrective actions that have been put in place to prevent recurrence.



Quality Review Checklist: Protocol Adherence

- Study visits and procedures were conducted at protocol defined intervals
- Protocol deviations have been documented and reported to the IRB according to CCHMC policy.
- Study procedures were performed by study personnel delegated to conduct the task.




Issues and Findings: Protocol Adherence

QR Checklist Question: Study visits and procedures were conducted at the protocol defined intervals.

Findings:

- For all 3 subjects, it could not be verified that the protocol required blood sample was obtained.
- The protocol states that the PI will monitor the study for adverse events by querying the subjects' parents at each visit. There was no documentation that this occurred.
- The CCHMC protocol addendum indicates that a history of kidney disease information was to be collected at the 3 month visit. There is no evidence in the subject files that this information was collected for 4 of 6 subjects. All subjects were enrolled in the study after the addendum was approved
- A pregnancy test was not obtained for 3 of 12 subjects.




Issues and Findings: Protocol Adherence

QR Checklist Question: Study visits and procedures were conducted at the protocol defined intervals.

Findings:

- The protocol indicated that "patients will be continued on study drug in a continuation protocol since such medication is required..." There was no IRB approved continuation protocol. However all 5 participants reviewed were administered 3 months additional study drug after completion of the study.
- Study procedures were completed, but not per the protocol requirements in the following instances:
 - The protocol required that visit 2 take place approximately 14-17 days after the telephone visit. For participant A, the study visit took place 20 days after.
 - For participant B, visits 1 and 2 were not completed within 30± 3 days as required by the protocol. Instead the visit occurred within 24 days




Issues and Findings: Protocol Adherence

QR Checklist question: Protocol deviations have been documented and reported to the IRB according to CCHMC policy.

Findings:

- Two of 4 subjects missed visit #3, however no protocol deviation was written.

- Documentation could not be located to confirm monitoring of the study progress was performed by XX, MD as required by the study protocol. No deviation was documented and reported to the IRB.

- Procedures were not consistently performed as required by the protocol. The protocol indicated, procedure X is to be performed before procedure Y. In 7 of 11 subjects, procedures were performed out of sequence.



Issues and Findings: Protocol Adherence

QR Checklist Question: Study procedures were performed by study personnel delegated to conduct the procedure.

Findings:

- It was unclear if the coordinator completing the eligibility document was authorized to do so.



Remedies and Tips: Protocol Adherence

- Possible Corrective Actions:
 - Notes to file for the affected participants
 - General note to file for all participants
- Possible Preventive Actions
 - Retrain staff on protocol-required procedures
 - Revise protocol or clarify how protocol is written
 - Add visit windows (+/- 'X' days) to the protocol if possible
 - Study Calendar for all protocol required interventions
 - Review protocol prior to protocol interventions



Remedies and Tips: Protocol Adherence

• Tips for Compliance

- Review/revise the DOA log for staff responsibilities of protocol procedures
- Maintain a list of deviations as they occur for reporting purposes. Review in a timely manner at each study visit
- Know protocol and how to carry out procedures
- Create checklists/tools to help you to remember to do proper procedure
- Review protocol before actually conducting study view
- Have a system for subjects who drop out/withdrawals, missed visits, etc.



IRB Reporting: Protocol Adherence

Protocol violations should be reported to the IRB promptly via an unanticipated problem report, and should include an explanation of the corrective actions that have been put in place to prevent recurrence.

Protocol deviation – An accidental or unintentional change to the IRB approved protocol.

Protocol violations – A protocol deviation, meaning an accidental or unintentional change to the IRB approved protocol, which caused harm to participants or others or indicates that participants or others are at increased risk.



Quality Review Checklist: Adverse Events

- All AEs, SAEs, and UPs were **documented** per CCHMC policy procedure.
- All AEs, SAEs, and UPs were **reported** per CCHMC policy and procedure



Issues and Findings: Adverse Events

QR Checklist Question: All AEs, SAEs, and UPs were **documented** per CCHMC policy and procedure.

Findings:

- For all subjects reviewed and for all adverse events, there is no documentation that the PI or designee determined the causality or relationship to the study drug
- According to the protocol, "the PI will monitor the study for adverse events by querying the subjects' parents at each visit". There is no indication that this occurred for all subjects and there was no AE log documenting any adverse events.
- The dates indicated on the Unanticipated Problem Report detailing maternal death were unclear. The UP date of occurrence (4/10/07), the date study staff knowledge of the event as indicated on the UP report (7/19/07) and the date of the PI signature on the report (4/12/07) did not represent a linear timeline of events. The PI signature is dated prior to the study staff knowledge.




Issues and Findings: Adverse Events

QR Checklist Question: All AE's, SAE's, and UP's were **reported** per CCHMC policy and procedure

Findings:

- Unanticipated problems were not found to be reported to the IRB per CCHMC policy and procedure in the following instances
 - Subject X did not meet the eligibility criterion excluding obese patients (body mass index more than 95th percentile for age). Reporting to the IRB had not taken place
 - Subjects X and Y did not receive treatment measures consistent with the protocol in which they were randomized as detailed in section A of the protocol. Reporting of the occurrence to the IRB at the time of 2010 continuing review was not completed
 - Documentation could not be located to confirm whether follow-up occurred for adverse events experienced by subject X. A note to file was written to acknowledge and explain the missing documentation but there was no indication these adverse events were reported to the study sponsor or IRB at the time of continuing review.




Remedies and Tips: Adverse Events

- Possible Corrective Actions:
 - Notes to file for the affected participants
 - General note to file for all participants
- Possible Preventive Actions
 - Retrain staff on IRB Policy R-18 for reporting
 - Maintain a list of deviations as they occur for reporting purposes. Review in a timely manner at each study visit
 - Be sure all AEs are documented AND assessed appropriately




Remedies and Tips: Adverse Events

- Tips for Compliance
 - Create AE log to document as they occur for reporting purposes. This log is based on protocol requirements.
 - Consider, when writing the protocol, how to determine when to capture AE's and what constitutes an AE for the study



IRB Reporting: Adverse Events

These types of adverse events would fall under the category "other" on the unanticipated problem report, and should be reported promptly (within 7 days) to the IRB including an explanation of the corrective actions that have been put in place to prevent recurrence.



Audience Participation Question:

Events that occur as a natural disease progression are not considered to be AEs?

- A. Yes
- B. No
- C. It Depends



Audience Participation Question:

Events that occur as a natural disease progression are not considered to be AEs?

C. It Depends



Audience Participation Question:

Events that occur as a natural disease progression are not considered to be AEs?

C. It Depends

- It depends on what is written in the protocol
- It depends whether the disease has changed in severity from baseline



Quality Review Checklist: Documentation

- The study files (research record, CRFs and/or medical record) were organized, in good condition, complete, legible, and recorded in black or blue ink.
- Protocol specific source documents were complete
- CRF and source document entry errors or illegible entries were corrected by drawing a single line through the error, writing the correct information next to it without obscuring the original error, and initialing and dating the correction.



Issues and Findings: Documentation

QR Checklist Question: The study files (research record, CRFs and/or medical record) were organized, in good condition, complete, legible, and recorded in black or blue ink.

Findings:

- All source documents were missing initials/dates of the person obtaining information for 6 of 12 subjects
- The screening CRFs, source documents, consent forms, and sample collection forms were incomplete or insufficient based on the following
 - Subject 1: The consent form had blank spaces and the PI did not date; The screening CRF has blank spaces in the consent section; the disease activity source document did not indicate who completed the form
 - Subject 2: The PI did not sign/date the consent form ; Whiteout used on the sample collection form. Blank spaces on the demographic form, blank spaces on the physical exam form




Issues and Findings: Documentation

QR Checklist Question: The study files (research record, CRFs and/or medical record) were organized, in good condition, complete, legible, and recorded in black or blue ink.

Findings:

- The screening subject Qualification Checklist source document was not found to be completed in it's entirety in the following instances.
 - Subject 1: Inclusion criteria #4 and #5 were not marked as yes or no;
 - Subject 2: Inclusion criteria #4 was not marked yes or no
 - Subject 3: 0 of 6 criteria were not marked yes or no
- Source documents did not consistently contain the initials of the person completing the forms and the date in which the data was collected. It could not be determined who completed or when the documents were completed
- The data trail was incomplete for the Screening Control Qualification checklist for 8 of 8 subjects

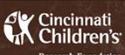



Issues and Findings: Documentation

QR Checklist Question: Protocol specific source documents were complete

Findings:

- Study documentation was not consistently completed per the regulations, guidelines, and standards as follows:
 - The physician order form and data charts for 8 of 8 subjects were difficult to interpret. Data cells were often incomplete and/or did not include the data requested by the column header and did not consistently include the initials and date of person who obtained the data.
 - The data charts (pages 5-7) did not consistently contain the information requested by the column headers for subjects 1, 2, and 3
 - The rating scale was not completed in it's entirety for 6 of 6 subjects reviewed. It was unclear if missing responses affected the overall scoring of the assessment.
 - The physician order forms were not completed, initialed, or dated by staff performing study procedures in the following instance. It could not be determined when or if the plasma, serum, and urine samples were obtained or the identity of the person completing the tasks for subjects 1, 2, 3 and 4.

Issues and Findings: Documentation

QR Checklist Question: CRF and source document entry error or illegible entries were corrected by drawing a single line through the error, writing the correct information next to it without obscuring the original error, and initialing and dating the correction

Findings:

- Five of 5 subject screening forms contained scratch-outs, scribbles, or whiteout
- The consent form page for subject 1 contained the partially blacked out signature and date of another parent/guardian and investigator. It is noted the consent document contains the original signatures of the parent of participant 1 and the investigator associated with the study.
- Correction tape was found on the study screening form, page 2 of 2 for subject 1



Remedies and Tips: Documentation

- Possible Corrective Actions:
 - Notes to file for the affected participants
 - General note to file for all participants
 - If documentation exists find it and put it in
- Possible Preventive Actions
 - Retraining of the study staff
 - Review source/CRF daily or for each visit for corrections for data errors by staff
 - Add lines for staff to initial and date for all documents



Remedies and Tips: Documentation

- Tips for Compliance
 - Create worksheet that only have spaces for the information needed, if necessary.
 - Make the worksheets documents user friendly
 - Make sure source/CRFs have the appropriate initials and dates
- Apply the ALCOA* acronym for proper documentation.
 - Attributable
 - Legible
 - Contemporaneous
 - Original
 - Accurate



Audience Participation Question:

When is it acceptable to use a signature stamp to sign study documents?

- A. On GCRC Physician Order Forms
- B. On Notes to File
- C. On consent forms
- D. Signatures can not be substituted for handwritten signatures



Audience Participation Answer:

When is it acceptable to use a signature stamp to sign study documents?

D. Signatures can not be substituted for handwritten signatures



IRB Reporting

- Documentation errors are usually not reported to the IRB
- Documentation errors may be reportable due to special circumstances (protocol adherence and safety measures: Dose changed from 0.1mg to 1.0 mg; consents not signed for all participants)



Quality Review Checklist: Regulatory

- A current copy (signed and dated) of the curriculum vitae and a current copy of the medical licensure/credentials for each investigator and all personnel listed on the Delegation of Authority Log were present
- Roles of study personnel were clearly defined and documented on the Delegation of Authority log. A signature log existed.
- Documentation of appropriate training for all researchers was documented (CITI, HIPAA, Protocol)




Issues and Findings: Regulatory

QR Checklist Question: A current copy (signed and dated) of the curriculum vitae and a current copy of the medical licensure/credentials for each investigator and all personnel listed on the Delegation of Authority Log were present

Findings:

- CVs were missing for 4 of 4 researchers listed on the 1572 and/or the DOA log
- CVs may be present but they are not signed and dated annually




Issues and Findings: Regulatory

QR Checklist Question: Roles of study personnel were clearly defined and documented on the Delegation of Authority log. A signature log existed and was either incorporated into the DOA log or was maintained as a separate document.

Findings:

- Upon initial review of the study documents, the Delegation of Authority Log was not found to be completed in it's entirety. A revised Delegation of Authority log was completed by the study staff prior to the finalization of the quality review report, but the following information could not be verified for 2 individuals.
 - Dr. A - missing current CV, medical license and CITI training
 - Dr. B. - missing medical license and CITI training




Issues and Findings: Regulatory

QR Checklist Question: Documentation of appropriate training for all researchers was documented (CITI, HIPAA, Protocol)

Findings:

- CITI training needs to be updated from basic CITI training to the Greater Cincinnati Academic and Regional Health Centers for Dr. A.
- Sponsor-required training did not exist for members of the study staff.



Remedies: Regulatory

- Possible Corrective Actions:
 - Provide training now and document that training
- Possible Preventive Actions
 - Train/retrain staff on the regulatory SOP of what needs to be in the binder
 - Research study staff should check expirations on their own CITI training and credentials



Remedies: Regulatory

- Tips for Compliance
 - Review SOP for regulatory binder
 - After using the regulatory binder checklist to assemble your regulatory binder have someone else review it with the checklist



IRB Reporting

These types of events should be reported to the IRB at the time of continuing review.



Quality Review Checklist: Test Article

- The investigational drug or device was properly stored in accordance with CCHMC research policies and procedures
- All participant inventory and product accountability forms were complete



Issues and Findings: Test Article

QR Checklist Question: The investigational drug or device was properly stored in accordance with CCHMC research policies and procedures.

Findings:

- The investigational drug was not dispensed per CCHMC policy in the following instance. Investigational Pharmacy records indicate that subject 1 was dispensed the drug from the Oak campus Apothecary at visit 5 instead of from the Oak campus Investigational Pharmacy. Additionally, it could not be determined whether the drug was paid for by the subject or the study budget.



Issues and Findings: Test Article

QR Checklist Question: All participant inventory and product accountability forms were complete.

Findings:

- Documentation could not be located to confirm specific study drug administration time points for subject 1. The study drug administration stop date of 0.9 mg/day dose and the start date of 1.2 mg/day dose of the study drug or placebo could not be determined. It is noted that the participant take-home diary was not fully completed by the family and the study site source documentation did not elaborate on the missing data. It is also noted that the completed pharmacy order forms for the 1.2 mg/day dose could not be located.
- Study drug was not found to be dispensed as required by the protocol in the following instance. The protocol study schema indicated the study drug was only dispensed at visit 4. However, the Investigational Pharmacy records shows the 7 tablets were dispensed at visits 4 and 5.



Remedies: Test Article

- Possible Corrective Actions:
 - Notes to file for the affected participants
 - General note to file for all participants
- Possible Preventive Actions
 - Retrain staff on test article use, handling and dispensing
 - Review accountability logs on an "as used" basis for accuracy and/or compliance.



Remedies: Test Article

- Tips for Compliance
 - Consider having an accountability checklist at the site where the drug/device is given to/return from the subject.
 - If the subject is not compliant, document reeducation of the subject.
 - The study staff and the investigational pharmacy work as a team to capture the information.
 - Ensure that the proper documents are forwarded to the investigational pharmacy.



IRB Reporting

These deviations should be reported to the IRB in summary form at the time of continuing review.



QUESTIONS