FDA Audit Readiness Workshop

When the FDA Calls: Introduction to Audit Readiness

Training Workshop
September 22, 2019

Speakers

Andrea Buchmeier, MHA, CCRC, LSSGB
Associate Regional Vice President of Cancer Services
Sarah Cannon

Leslie Byatt, CPHL, CCRC
Program Grant Administrator
New Mexico Cancer Care Alliances

Katie Goodman, RN, CCRC
Clinical Research Director
Florida Cancer Specialists

Aisha Johnson, MD, MPH, MBA
Medical Officer
FDA

Introduction

Andrea Buchmeier, MHA, CCRC, LSSGB
Sarah Cannon

Acknowledgements

- James Reeves, MD, Florida Cancer Specialists and Research Institute
- Susan Modugno, BSN, OCN, CCRC, from Sarah Cannon Research Institute
- Max Ning, MD, Food and Drug Administration

Workshop Objectives

- Review pre-meeting survey findings
- FDA perspective
- Site perspective and considerations
- Rolling up our sleeves: review case study and recommended best practices
Workshop Toolkit

- **Objective:**
  - Provide tools and resources to assist oncology research programs with ensuring FDA audit readiness

- **Content covered:**
  - Triggers of an audit
  - Questions to ask FDA
  - Pre-audit, during-audit, exit interview, and post-audit considerations

- **Features:**
  - Checklists, templates and forms
  - Helpful references

- **Toolkit next steps**
  - Share your resources to contribute to the toolkit!
  - Revisions and make public – posted online (RCF website), feature in webinar

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Disclaimer

- The workshop and toolkit were developed from personal experiences with FDA audit readiness.
- The views expressed in this presentation are those of the speaker and not necessarily those of the institution to which they are affiliated.
- The tips, guidance on best practices, and resources, are provided as examples only for consideration.

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**FDA Perspective on Clinical Investigator Inspections**

Aisha Johnson, MD, MPH, MBA
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Compliance
Office of Scientific Investigations
Division of Clinical Compliance Evaluation
Good Clinical Practice Assessment Branch

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Outline

- Introduction to Clinical Inspections
- PDFUA/BsUFA Inspections Process
- Inspections Metrics
- Consequences of Noncompliance
- Inspection Metrics
- Clinical Site Inspection Preparation

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Regulation of Clinical Investigations

  - Section 505(i) provides FDA the statutory authority for oversight of clinical investigations to establish the safety and effectiveness of new drugs
- Code of Federal Regulations (CFR) 21 Subpart D, Part 54, Part 56
  - Delineates the responsibilities of Sponsors and Investigators in conduct of clinical investigations
  - Financial disclosure, IRB
- Guidances
  - Non-binding advisory for Sponsors and Investigators to comply with the regulations

General Responsibilities of Investigators (§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; and for the control of drugs under investigation. An investigator shall, in accordance with the provisions of part 50 of this chapter, obtain the informed consent of each human subject to whom the drug is administered, except as provided in §§50.23 or 50.24 of this chapter. Additional specific responsibilities of clinical investigators are set forth in this part and in parts 50 and 56 of this chapter.

General Responsibilities of Investigators

§ 312.60 - General responsibilities of investigators
§ 312.61 - Control of the investigational drug
§ 312.62 - Investigator recordkeeping and record retention
§ 312.64 - Investigator reports
§ 312.66 - Assurance of IRB review
§ 312.68 - Inspection of investigator's records and reports
§ 312.69 - Handling of controlled substances
§ 312.70 - Disqualification of a clinical investigator

Goal of Bioresearch Monitoring of Clinical Trials

- To protect the rights, safety, and welfare of subjects involved in FDA-regulated clinical trials;
- To verify the accuracy and reliability of clinical trial data submitted to FDA in support of research or marketing applications;
- To assess compliance with FDA's regulations governing the conduct of clinical trials.

Good Clinical Practice (GCP)
An international ethical and scientific quality standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate and rights, integrity, and confidentiality of trial subjects are protected.

International Conference on Harmonization (for Registration of Pharmaceuticals for Human Use) (ICH) E6(R2) 2018

Types of Inspections

- PDUFA/BsUFA-related inspections: New drug applications
- For-cause inspections: GCP complaints
- Surveillance inspections: Compliance enforcement
Outline of Process for PDUFA/BsUFA-Related Inspections

Office of New Drugs
Inspections Requested

Inspector Report Received, First Regulatory Classification Assigned (OSI)

Inspections Assigned to and Conducted by Field Inspectors (ORA)

Site Selected for Inspection (OND, OSI)

Inspection Report Reviewed, Final Regulatory Classification Assigned (OSI)

Inspections Requested

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Outline of Process for PDUFA/BsUFA-Related Inspections

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Office of New Drugs

Site Selection Criteria

- Importance of the study
- Relevance to labeling
- Outliers (Number of Subjects/Protocol Violations/Deaths/SAEs)
- Statistical Impact of Data
- Findings of Previous Inspection(s)
- Domestic versus international
- Concern for Scientific Misconduct
- Specific Study Factors (variable)

Clinical Inspections Activities

- Compare data submitted to the Agency with source data (e.g., electronic/paper clinical records)
- Identify any instances where the data may not be identical
- Determine whether data was obtained according to the protocol
- Determine if the rights, welfare and safety of subjects involved were protected
- Ensure the conduct of clinical trials is in compliance with FDA's regulations

Documents Field Inspectors Have at Inspection

- Study protocol(s) and amendment(s)
- Investigator’s brochure
- Sample consent form(s)
- Annotated case report for
- Data line listings for each study patient enrolled at the site
- Manual(s) related to key study conduct (e.g., submission of scans and/or tumor tissue) if applicable
- Others (e.g., Adjudication Committee Charters)

Key Inspection Focused Areas

- Comparison of line listings with source documents and verification of reported data and quality
- Review of enrollment process and signed consent from(s)
- Review of IRB oversights
- Review of monitoring activities
- Review of reporting to sponsor
- Review of compliance with applicable regulations (e.g., financial disclosure and updates as indicated)
Close Out Meeting

- Discuss major inspectional findings
- Issue FDA Form 483 (if appropriate)
- Provide Post-inspectional Instruction

FDA Form 483

- Issued at the conclusion of an inspection when an investigator(s)
  has observed any conditions that in their judgment are objectionable
  (may constitute violations of the Food Drug and Cosmetic (FD&C)
  Act and related Acts)
- Discussed with clinical investigator
- Clear, specific and significant
- Investigators are encouraged to respond to the FDA Form 483 in
  writing with their corrective action plan and then implement that
  corrective action plan expeditiously

After the Inspection

FDA considers all information to determine what further action, if any,

- Establishment Inspection Report
- All evidence or documentation collected on site
- Clinical investigator’s response to FDA Form 483

GCP Compliance Classification

- No Action Indicated (NAI)
  - correspondence acknowledges investigator’s/sponsor’s basic compliance
    with pertinent regulations
- Voluntary Action Indicated (VAI)
  - correspondence will identify the issues & when needed, state that FDA
    expects prompt, voluntary corrective & preventive action (CAPA) by the
    investigator/sponsor
- Official Action Indicated (OAI)
  - correspondence will request to submit a detailed corrective & preventive
    action plan (CAPA). Disqualification proceedings may proceed if the
    investigator does not respond appropriately

Potential Penalties of Noncompliance

- Warning Letters
- Disqualifications, restrictions, or debarments
  - Available to the public
  - Related to repeated and deliberate failure to comply with regulations
- Criminal prosecutions
Warning Letters

- Notifies a responsible individual or firm that the Agency considers one or more products, practices, processes, or other activities to be in violation of the Federal Food, Drug, and Cosmetic Act (the Act), its implementing regulations and other federal statutes
- Issued for violations of regulatory significance, i.e., those that may actually lead to an enforcement action if the documented violations are not promptly and adequately corrected
- One of Agency's principal means of achieving prompt, voluntary compliance
- Informal
- Advisory

Disqualifications, Restrictions

Prohibition against conducting any clinical investigation that supports an application for a research or marketing permit for products regulated by FDA

Clinical investigator has repeatedly or deliberately:
- failed to comply with applicable regulatory requirements
- submitted false information to the sponsor or, if applicable, to FDA, in any required report

Debarment

Prohibition against a person or company from submitting or assisting in the submission of an application for a new drug

- Applies to firms or individuals convicted of a felony under Federal law for conduct relating to development or approval of any drug product, or otherwise relating to any drug product under the Federal Food, Drug, and Cosmetic Act
- Penalty set forth in a 1992 amendment to the Act
- As of April 2009, the FDA has debarred 73 persons
- FDA Debarment website

Ideal Investigator Site at Inspection

- Cooperation throughout inspection/data audit
- Documented training of CI and research staff for the study by sponsor and monitor(s)
  - Re: the protocol, CRF, treatment administration, IP accountability, adverse events reporting, concomitant medications, protocol deviations, monitoring visits
- Demonstrated Investigator's responsibilities and oversight of the conduct and knowledge of all critical aspects of the study, including delegation of responsibilities, study enrollment procedures.
- Records of protocol/amendments and IRB approvals before implementation in the study site
- Evidence of complying with the protocol, reporting events and protocol deviations to sponsor and, as necessary, to the IRB

Ideal Investigator Site at Inspection (cont’d)

- Complete source documents and related case report forms from screening to each study visit, with no missing required records
- Maintained monitoring records and documentation of data queries and their resolution
- Complete records of investigational product accountability and handling
- Complete information on Investigator’s and sub-investigators’ credentials and financial disclosure
- Signatures for all required documentations and records
- Retention of records for appropriate length of time

Summary

- GCP in clinical investigations has specific requirements
- Clinical investigators are responsible for conduct of studies in accordance with study protocols, compliance with applicable regulations, and protection of study patients.
- Inspection readiness results from investigators’ knowledge of regulations and their real-time oversight of the conduct of studies, including adequate training and supervision of study staff
- Be proactive in prevention and correction of errors or deficiencies identified
Status of Inspections at OSI/CDER

Overall inspections conducted in FY 2018 (including GLP, BE, and IRB inspections)

- For PDUFA/BsUFA related applications, 384 inspections conducted (as of 7/30/2018): 86% for CIs

PDUFA/BsUFA Applications, FY 2018

- Clinical Investigator 86% (343)
- Sponsor 10% (40)
- Contract Research Organization 4% (14)

Frequency of Most Common GCP Related Inspection Findings, CDER FY 2015-2017

- Investigator Drug Accountability: 27%
- Failure to Obtain Informed Consent: 18%
- Falsification Informed Consent: 12%
- Failure to Report Adverse Events: 12%


- U.S. Inspection
- Non-U.S. Inspections
Special Thanks

• Dr. Max Ning, providing opportunity to speak to ASCO and contribution of some slides
• Dr. Kassa Ayalew, GCPAB Branch chief, contribution of slides, editing of presentation

Useful Links

• Clinical Investigator Responsibilities at CFR: https://www.ecfr.gov/cgi-bin/text-idx?SID=85342f2ba7659ad8b9a1868a43c888&mc=true&node=sp21.5.312.d&rgn=div6
• Guidance on Investigator Responsibilities: https://www.fda.gov/media/77765/download
• Guidance on Financial Disclosure: https://www.fda.gov/media/85293/download
• Use of Electronic Records and Electronic Signatures in Clinical Investigations: https://www.fda.gov/media/105557/download
• FDA Good Clinical Practice Contacts: CDER-OSI-GCPReferrals@fda.hhs.gov

When the FDA Calls or Arrives Unannounced

What to ask?
• Which study is under review?
• What type of audit is it?
• What is the inspector’s name?
• When would they like to visit?
• What is anticipated length of inspection?
• Who will be coming with inspector?
• What records will they review?

Are you ready?

• Notify all study staff
• Pull all ORIGINAL research records
  • CRF And Source Documents; Including Signed Informed Consents
  • Clinic Charts-certified copies or ensure access to EMR
  • Regulatory Binder-IRB Approvals, Correspondence, Drug Shipping And Return Information, Site Signature Log, Monitor Visit Log, 1572, CV’s, etc.
  • May need: subject and staff schedules, telephone logs, subject sign-in sheets, temperature logs, calibration logs
• Review protocol
• Review CRF/source documents and informed consents for all subjects
• Review SAEs
Are you ready?

- Review regulatory binder - especially correspondence
- Organize documents if necessary
- Identify a conference room or private space for the Inspector
- Appoint a point person to make copies and escort the inspector

The Inspection

- Familiarize the Inspector with the surroundings; restroom, cafeteria
- Check in with the Inspector from time to time
- Make duplicate copies; one for Inspector, one for you
- Call your sponsor/institutional official at the end of each inspection day or as agreed upon
- Meet with the Inspector at the end of each day
- Confirm the day and time for the next day’s visit

The Interview…… Do’s and Don’ts

- Don’t be defensive
- Don’t get emotional
- Listen carefully and repeat the question or ask it to be repeated if necessary
- Answer completely, directly, and honestly
- Do not guess or make up the answer
- Do not provide your opinion, only the facts
  - What Do You Think? What Is Your Best Guess?
- Do not volunteer more information than necessary
- Never question the Inspector’s authority (remember, they have a badge!)
- Never argue or raise your voice
- Do not answer for someone else
- Do not agree or volunteer to change a policy without first discussing with PI and/or Site Director
- There is no such thing as “off the record”
- It is OK to say “I do not know or I do not remember”
- Take notes of questions asked
- Expect what you say to be documented in a FDA field notebook
- Leave as soon as the interview is over
Interview Questions for the PI

- How many studies have you been involved in?
- How many other studies were you involved in during this trial?
- How many active studies
- What percentage of time did you devote to this project?
- How did the sponsor choose you?
- How were you trained on the protocol?

Interview Questions for the PI

- How did the sponsor communicate your responsibilities?
- As PI, what are your responsibilities?
- How were sub-investigators and staff trained on protocol?
- How do you delegate responsibility?
- How did you recruit subjects?
- What did the consent process involve?

Interview Questions for the PI

- Where was study drug stored?
- Who had access to the study drug?
- Did you see subjects at each visit?
- When did you review the source docs and CRFs?
- Who determined subject eligibility?

Interview Questions for the PI

- How many subjects did you enroll?
- Who assessed AEs?
- Any SAEs?
- How often did the monitor visit?
- Did you meet with the monitor at every visit?

Interview Questions for the PI

- Study specific questions and findings
  - This will give you an opportunity to address issues and MAYBE keep them off the 483
    - Were you aware of
    - I found 3 missing consents, etc.

Interview Questions for the Study Team

- How were you trained on this protocol?
- Was the PI available when needed?
- Who determined eligibility?
- Who assessed AEs?
- How did you recruit patients?
- How often did the sponsor monitor the study?
- Who had access to the study drug?
Communication

- Keep the lines of communication open between the PI, the study staff, and the Sponsor/Institutional Official
- The PI, Sponsor and/or Institutional Official may request a daily update and should be available for a daily check in
- Always check in at the end of each inspection day

Inspection Close-Out

- Exit interview will go over findings
- Many investigators receive a form 483
- This will go over in detail the results of the inspector’s findings
- Make sure you understand what the 483 contains
  - Listen, absorb, do not argue
  - Send a copy of the 483 to your sponsor
- Response Letter

Inspection Results

- The FDA Inspector will write and establishment inspection report (EIR)
- The EIR will be used by the FDA district office to classify the site’s compliance and details the inspection, exit interview and items listed on the form 483
- A copy of the EIR will be sent to you after the inspection

Inspection Close-Out

- Schedule inspection post mortem
- Review what went well and opportunities for improvement
- Share learnings with everyone

Case Study

Leslie Byatt, CPHT, CCRC | New Mexico Cancer Care Alliance
Katie Goodman, RN | Florida Cancer Specialists

Time to roll up our sleeves!
A Phase 2 open label study for HER2+ breast cancer has been recruiting for over 2 years at 20 sites. Currently, 75% of the 100 expected patients have been enrolled.

Great Outcomes Hospital has enrolled 15 patients. PI, Dr Hugh Raye has had very positive feedback from their patients and have reported one SAE and no endpoint data. Crystal Ball, CRC received a phone call from FDA Inspector Mr. Dick Tate, requesting a date and time for a two day inspection.

A two-day FDA inspection has been scheduled at Great Outcomes Hospital in five business days. This is the first time Dr. Hugh Raye and his team have been FDA inspected.

Answer: New Drug Applications/Routine Inspection

- Routine selection based on a % of all clinical data submitted with New Drug Application (NDA) OR
- Site with notably high or fast enrollment
- Site conducting multiple studies or large pivotal trials
- Site conducting study supporting a submission to FDA for NDA, marketing, license, etc.

Before the FDA Arrives

- Schedule pre-audit review meeting with internal team to discuss strategies
- Determine inspection accommodations
- Develop roles and responsibilities of staff during inspection
- Review study documentation and organize
- Prepare to welcome the inspector
- Sponsor/CRO communication plan

Inspection Preparation Checklist

Knowing the Roles and Responsibilities of your Team

- Review who is currently responsible for each step of the study process
- Review who was historically responsible (if applicable)
- Ensure staff understands on-going responsibilities
- Ensure pertinent staff are available
Do You Have Everything?

- All required documents (organized, complete and current?)
- Review study team documentation (qualifications, training and delegations?)
- Review pertinent dates
- Review pertinent study team members
- Review findings of recent monitors visits
- List shortcomings for further discussion before the inspection

During the Inspection:
When they arrive

- FDA investigator(s) should present credentials; if not, you may ask to view them
- FDA Form 482 – Notice of Inspection
- Entrance Interview with PI, Dr Hugh Raye and the study team

Exit Interview

- Ensure PI, Dr. Hugh Raye is available and invite other crucial departments as needed (i.e., Compliance, Leadership, etc.)
- FDA Inspector, Mr. Dick Tate will discuss oral “suggestions” or “discussion items.” If there are significant, serious findings, the FDA may issue a Form 483
- Be sure to ask for clarification as needed
- Correct significant factual errors in discussion items during the exit conference since there is still the opportunity to keep them out of the Inspector’s report
- LISTEN AND LEARN!!

During the Inspection
What to expect when inspected

- If requested, be prepared to give a guided tour of the facility
- Documents: Only give what is requested by the inspector
  - Assign one staff member to manage all document requests. This includes maintaining a record of all documents provided to the FDA inspector
  - Designate plans for inspector communication
  - PI communications plan, ensure frequent communication on inspection status
  - Plan a daily update with your sponsor contact

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It’s over…what just happened?

The Form 483 lists observations made by the FDA representative(s) during the inspection.

If the inspection does not yield any objectionable conditions or practices, a 483 will not be issued.

However, if the agency does issue one or more 483s at the conclusion of the inspection, it is always better to select "promise to correct" rather than "under consideration" in response to each 483 observation.
It's over…what just happened?

**Warning letters** are issued to manufacturers or other organizations that have violated some rule in a federally regulated activity, i.e., violations of regulatory significance.

A warning letter is one of the agency's primary means of achieving prompt voluntary compliance with the FD&C Act.

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**Response Cover Letter**

Ms. X, District Director  
Food and Drug Administration

Dear Ms. X:

I am writing in response to the 483 issued following the FDA inspection of our facility, Great Outcomes Hospital, conducted by Dick Tate, Inspector, between 25 October 2018 and 5 November 2018. My staff and I carefully reviewed the inspector's observations. In this letter we have provided responses to each observation, including clarification and further information on some of the observations. I respectfully request that the information in the letter be taken into consideration in the agency's review of the inspector's observations.

**OBSERVATION 1**

Failure to report promptly to the IRB all unanticipated problems involving risk to human subjects or others 21 CFR § 312.64(b)

**DURING AN INSPECTION OF YOUR FIRM I OBSERVED:**

We understand the importance of SAE reporting and have reviewed each of the observations and believe that the deficient SAE reporting was a result of clinical staff failing to alert the research staff of the SAE. As a result, we have reviewed with our research coordinators, research staff, and all physicians that participate in our research program the importance of prompt reporting of any hospitalizations, serious adverse events, and deaths. We have reviewed this with our hospitalists and mid-levels on the inpatient service as well.

We are engaging with our education department to prepare an instructional slide deck that must be completed to maintain research and hospital privileges. Additionally, we are modifying our electronic medical record to clearly indicate when a patient is enrolled on a clinical trial the EMR is viewed by any providers that interact with the patient to ensure it is clear that additional reporting is required. Each of these actions will be completed by November 1, 2019. Lastly, we will perform a process audit of our own SAE reporting processes in 6 months to ensure this change has ensured ongoing compliance.

**SITE RESPONSE TO OBSERVATION 1**

Specifically,

Subject D01-002 received C2D28 scans on 07/15/2016 which is 10 days out of window
Subject D01-009 started investigational product on 07/15/16. CT scans performed on 10/6/16 which documented progression of disease however, was continued on study therapy for 6 months
Subject D01-005 had dose reduction at C3D1, dose increases at C5D1 and C6D1 without documentation of protocol rationale.

**OBSERVATION 2**

An investigation was not concluded in accordance with the signed statement of investigational plan CFR §312.60

**DURING AN INSPECTION OF YOUR FIRM I OBSERVED:**

Specifically,

Subject D01-007 received C2D28 scans on 07/15/2016 which is 10 days out of window
Subject D01-009 started investigational product on 07/15/16. CT scans performed on 10/6/16 which documented progression of disease however, was continued on study therapy for 6 months
Subject D01-005 had dose reduction at C3D1, dose increases at C5D1 and C6D1 without documentation of protocol rationale.
SITE RESPONSE TO OBSERVATION 2

We understand the importance of following the protocol and strive for compliance at all times. There are different reasons why each of the observations above occurred, each is noted below.

Subject D01-007: Since the time that this study was conducted, we implemented a centralized scheduling process for all radiology exams. These schedulers receive special training on the importance of adhering to ordered scan schedules of research patients. This process is outlined in attachment A.

Subject D01-009: We have conducted retraining with all research coordinators, research staff, and physicians that patients on a research trial who meet criteria for disease progression must cease taking study drug. The patient must be listed as progressing on the study and end-of-study procedures must be initiated.

Subject D01-005: We have also conducted retraining on the importance of adherence to dosing and dose modification tables must be followed as per protocol. Physicians are not to make arbitrary dosing decision in patients on research protocols.

SITE RESPONSE TO OBSERVATION 2 (cont’d)

To ensure ongoing communication, we are instituting a weekly mandatory research meeting for all physicians, mid-levels, and coordinators in our research program. At this meeting each currently active patient will be reviewed and any communication between the study PI and sub-I's and/or coordinators will be documented. All these meetings important protocol changes, amendments, etc. will be reviewed and documented. The minutes of our weekly meeting is attached as attachment B.

DURING AN INSPECTION OF YOUR FIRM I OBSERVED:

OBSERVATION 3
Failure to obtain informed consent in accordance with 21 CFR Part 50 from each human subject prior to drug administration

Specifically,

Subject D01-009 restarted on study drug on 10/15/16 prior to being consented with Liver Toxicity Consent Form which was signed on 11/12/16.

SITE RESPONSE TO OBSERVATION 3

We understand the importance of ongoing consent and overlooked the timely reconsent of this subject. Since the inspection we have reviewed our process of obtaining re-consents and have implemented at the above mentioned weekly mandatory research meeting a standing agenda item where all in attendance will review all amendments and revised consents. This will ensure that any patients with appointments the following week will have the reconsent processes completed. The minutes of our weekly meeting is attached as attachment B.

DURING AN INSPECTION OF YOUR FIRM I OBSERVED:

OBSERVATION 4
Investigational drug disposition records are not adequate with respect to dates, quantity, and use by subjects.

Specifically,

Three vials of study drug (101598, 101601, 101602) are not accounted for in the study accountability log.

SITE RESPONSE TO OBSERVATION 4

Since the inspection we reviewed our records in greater detail and medication administration records have been identified and attached (attachment C) which document the administration of vials 101598, 101602, and 101602. Late entries have been added to the accountability log (attachment D). Additionally, we will implement a process where each drug accountability log will undergo review on a quarterly basis to ensure complete documentation.
Toolkit

- What additional tools or resources would be helpful?

Key Takeaways

- If it's not documented it did not happen
- Conduct every study as if it will be audited
- Share your ideas and resources – comment cards, email, online forum
- Complete the workshop feedback survey

Thank you!