Introduction to Alliance Audit

Scott Okuno, MD
Audit Committee Chair

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Why Do Audits?

- Investigators of clinical trials have an obligation to take appropriate steps
  - To protect human subjects who participate in research studies
  - To protect the integrity of the science of cancer studies

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Components

- Regulatory
- Pharmacy
- Case Review

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Goal of Audit

- Quality Assurance
- Rule of Fraud/Falsification
- Educational

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Data Set
Integrity of Science

- The integrity of a data set is a function of the entire process
  - Data collection
  - Data analysis
- Detailed plans and systems are needed to assure
  - Protocol adherence
  - Uniform collection of data

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Audit: Quality Improvement

- Detect honest errors
  - Systemic – repeated errors
    - Misunderstanding of what is to be entered
    - Misunderstanding of how the study is to be conducted
  - Random – data entry errors
    - Data from wrong dates
    - Transposition of numbers
    - Missing data
    - Data just does not make sense

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Data Submission Human Subjects/Integrity of Science

- Is the Time Table for data submission being followed as specified in the protocol
  - With each cycle?
  - Within specified weeks / months of study entry, treatment or completion of all study therapy?
- Are the specified data being submitted?
  - Operative reports, path reports, flow sheets, forms, etc.
- Are the data just not submitted?
- Has the site been timely in response to queries?

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Detection of Falsification

- Hopefully rare event, however….
- Bezwoda et al: High-dose chemotherapy with hematopoietic rescue as primary treatment for metastatic breast cancer: A randomized trial. J Clin Oncol 1995, 13: 2483-9
  - "[High dose chemotherapy]…results in a significant proportion of CRs and increased survival in patients with metastatic breast cancer"

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Falsification

- Weiss RB, et al: An on-site audit of the South African trial of high-dose chemotherapy for metastatic breast cancer and associated publications. J Clin Oncol 2001; 19:2771-7.
  - "the multiple publications of this study do not report verifiable data, and 9 other publications co-authored by the principal investigator contain at least one major untrue statement"
- Bezwoda in a document sent to his colleagues:
  - Acknowledged that he committed a serious breach of scientific honesty and integrity by misrepresenting the results of that trial
  - Resigned his position at the university

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Other Examples Falsification

- A CRA was found guilty of falsifying the data in the study records of 35 patients on the SWOG SELECT trial for prostate cancer prevention
- Drug Company Study of a toxicity protectant
  - The CRAs at 4 participating institutions falsified at least one QOL document that was to be completed by the patient
  - Three CRPs completed the form and signed the patient's signature
  - One CRP used one form signed by the patient, changed the date with white-out, and submitted as the form for a later date

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Audit for Cause

- Any time concerns are raised regarding the conduct of clinical trials at a site there can be an “audit for cause”
  - This involves a more thorough scrutiny, e.g.
    - All subjects entered on all protocols
    - All subjects entered on a specific protocol
    - Drug accountability, etc.
  - Clinical Trials Auditing Branch (CTMB) of the NCI is notified and is present at the Audit
  - Charges may be brought against individuals or institutions and may result in
    - Fines, sanctions (e.g. loss of NIH funding)
    - Loss of employment, Loss of Licensure, etc.
    - Imprisonment depending on nature of fraud

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Audit = Quality Assurance
Dr. Curtis Meinert defines QA as:

- Any method or procedure for collecting, processing, or analyzing study data that is aimed at
  - Maintaining or enhancing their reliability and validity
- Includes prevention, detection, and action from the beginning of data collection through publication of the results to assure
  - Unbiased treatment assignment
  - Adequate assessment of eligibility
  - Compliance with protocol treatment
  - Compliance with regulatory requirements
  - Complete collection of data on the primary outcome measures

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AUDIT
Could/Should = Educational Process

- Audit team members should share practices that have been successfully implemented at other institutions
  - Clinical practice techniques
  - Data management systems
  - Quality control systems
- Goals of the local staff
  - Use the results of the on-site audit to identify operational areas where improvements could be made
  - Corrective and Preventative Action Plan
    - In response to written findings of the audit
    - To incorporate “best practices” in conduct of clinical trials

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Alliance - Audit Program

- Follow CTMB Guidelines and Code of Federal Regulations
- Utilize Alliance Policies and Procedures
- All institutions entering at least one (1) patient are subject to audit at a maximum interval of 36 months
- New main member institutions are audited within 18 months after entry of the first patient, unless accrual has been robust

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Alliance - Audit Program

- Institutions withdrawing are still subject to audit of their entries since the previous audit
- All institutions are subject to audit during any one year
- Re-audits are done when accrual is sufficient to make them worthwhile, generally within 12 months
- Special Audits / Audits for Cause
  - Irregularities in quality control procedures
  - Allegations of scientific misconduct

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Alliance - Audit Program

- Date of Audit is arranged ~4-6 months in advance
  - Mutually convenient time
  - Geographical & other considerations may affect scheduling
- Audit team usually comprised of a CRP/RN, or MD/CRP
- Team leader –a member of the Audit Committee (AC)
  - Ad hoc auditors are invited to participate
  - Ad hoc auditors always work with a AC member

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Alliance - Audit Program

- NCI representative may also be present
  - More commonly with Re-Audits
  - Audit the work of the auditors
  - Audit the process of the audit
- NCI representative always there if
  - Audit for cause
  - Special Audit

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Alliance - Audit Program Protocol Selection

- Statistical Office selects protocols for review
  - Minimum of three protocols representing studies conducted at the site
  - May include:
    - IND trials – e.g. investigational drug in use
    - Multi-modality studies
    - Designated prevention trials
    - Trials with high accruals
    - CTSU studies

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Alliance - Audit Program Protocol Selection

- A minimum of 10% of patients accrued since last audit will be reviewed (10% each from Alliance, CTSU, DCP, Advanced Imaging)
- Most selected from patients accrued since previous audit
  - However, any patient case is eligible for selection
- At least one (1) unannounced case will be reviewed (per NCI site code) if the total accruals warrant selection of unannounced cases
  - May elect to do limited review (e.g. eligibility, consent, data quality etc.) or full review of the unannounced case
  - If limited review, does not count towards the minimum of 10% rule noted above

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In summary
Why Do We Do Audits?

- To assure all patient protection measures are followed
  - IRB following the Code of Federal Regulations (CFR) mandates
  - ICC complete and follows model consent
- To assure all pharmacy procedures are followed
- To help provide assurance the study results are valid
  - To find and correct errors
  - To find missing data, if it exists
- To discourage fraud and find its rare instances
- To educate all involved in clinical trials research regarding protocol adherence and data collection

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2016 Group Meeting

November Chicago, IL