



Introduction to Alliance Audit

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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

Components

- Regulatory
- Pharmacy
- Case Review

Goal of Audit

- Quality Assurance
- Rule of Fraud/Falsification
- Educational

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

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

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?

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”

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

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

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

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

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

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

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

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

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

Alliance - Audit Program Protocol Selection

- Statistical Office selects protocols for review
 - Minimum of 4 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

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)
- At least 1 case per NCI code for registration trials
- Most selected from patients accrued since previous audit
 - However, any patient case is eligible for selection
- At least 1 unannounced case per NCI code will be reviewed if the total accruals warrant
- May conduct limited review (e.g. eligibility, consent, data quality etc.) or full review of the unannounced case
 - Limited review, does not count in minimum 10%

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



2016 Group Meeting

November Chicago, IL

