

Introduction to Audit

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Chair
Audit Committee

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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

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Why Do Audits??

- 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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Why Do Audits??

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

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Why Do Audits??

- Detect late data
 - Time table for data submission
 - Weeks
 - Months
 - Specific time points outlined in protocol
 - Data just not submitted
 - Response to queries
- Detect falsification
 - Hopefully rare event, however....

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Breast Cancer Clinical Trials

- 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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Breast Cancer Clinical Trials

- 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 to not report verifiable data, and 9 other publications co-authored by the principal investigator contain at least one major untrue statement”

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Cancer researcher admits falsifying trial results

- Trial results presented at ASCO's annual meeting misrepresented treatment in the control group
- JOHANNESBURG – The University of Witwatersrand Medical School is investigating Werner Bezwoda, MD, PhD for scientific misconduct for allegedly lying about the results of a clinical trial on high-dose chemotherapy and stem cell support for breast cancer
- 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

- A CRA at Decatur Memorial Hospital 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 CRAs completed the form and signed the patient's signature
 - One CRA 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 = 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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GOAL: PREVENT PROBLEMS

- Selection of responsible investigators and research staff
- Implementing routine monitoring procedures to detect
 - Random errors
 - Systemic errors
 - And do it in a timely and effective fashion

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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
- Goal of the local staff
 - Use the results of the on-site audit to identify operational areas where improvements could be made

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How did we get here??

- National Cancer Institute - World's largest sponsor of clinical trials of investigational anti-neoplastic agents and cancer clinical trials.
- NCI must ensure that the research data generated under its sponsorship are
 - High Quality
 - Reliable
 - Verifiable

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How did we get here??

- 1955 - Monitoring policies for Clinical Trials have been in evolution since the start of the Clinical Trials Cooperative Group Program
- 1963: Harris-Kefauver amendments to the Food, Drug, and Cosmetic Act required:
 - FDA to oversee investigational new drug (IND) testing in humans subjects
- 1977: FDA published proposed regulations on
 - Responsibilities of sponsors and monitors of clinical trials
 - "Annual site visit of each investigator"
 - Most sponsors conform to these proposals

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How did we get here??

- 1982 – NCI made on-site monitoring a requirement for
 - Clinical Trials Cooperative Group Program
 - Cancer Centers
 - Community Clinical Oncology Program (CCOP)
 - Other investigators conducting clinical trials under its sponsorship
- NCI delegated much of the responsibility for on-site monitoring of investigational agents and clinical trials to the Cooperative Groups

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FDA regulations require

- Division of Cancer Treatment and Diagnosis (DCTD) to maintain a monitoring program
 - Clinical Trials Monitoring Branch (CTMB) of the Cancer Therapy Evaluation Program (CTEP)
 - CTMB - provides direct oversight of each Cooperative Groups monitoring program which includes auditing as one component

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Clinical Trials Monitoring Branch (CTMB)

- Purpose of Audit
 - To document the accuracy of data submitted to the Cooperative Groups
 - To verify investigator compliance with protocol requirements
 - To verify investigator compliance with regulatory requirements
 - To provide an opportunity for the audit team to share with the institution staff
 - Information concerning data quality
 - Information concerning data management
 - Other information on the aspects of quality assurance

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CALGB - Audit System

- All institutions entering at least one (1) patient are subject to audit at a maximum interval of 36 months.
- New institutions are audited by 18 months after entry of the first patient, unless accrual has been robust
- All institutions are subject to audit during any one year
- Re-audits are done when accrual is sufficient to make them worthwhile, generally 12-18 months
 - CTMB guidelines state 12 months
- Institutions leaving CALGB are still subject to audit of their entries since the previous audit
- Special Audits / Audits for Cause
 - Irregularities in quality control procedures
 - Allegations of scientific misconduct

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CALGB - Audit System

- Date of Audit is arranged 3-4 months in advance
 - Mutually convenient time
 - Geographical & other considerations may affect scheduling
- 1-5 MDs and 1-5 CRAs / Research Nurses
- Team leader is always a member of the DAC
 - Ad hoc auditors are invited to participate
 - Ad hoc auditors always work with a DAC member
- NCI representative may also be present to
 - audit the work of the auditors
 - audit the process of the audit

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CALGB - Audit System Protocol Selection

- Statistical Office selects protocols for review
 - Minimum of three protocols representing studies conducted at the site
 - Emphasis should be given to the following
 - IND trials
 - Multi-modality studies
 - Designated prevention trials
 - Potential licensing trials
 - Trials with high accruals
 - CTSU studies

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CALGB - Audit System Protocol Selection

- A minimum of 10% of patients accrued since the last audit will be reviewed
- Most will be selected from patients accrued since the previous audit
 - However, any patient case may be at risk for selection
- At least one unannounced case will be reviewed if the total accruals warrant selection of unannounced cases
 - May elected to do limited review (e.g. eligibility, consent, etc)
 - If limited review, does not count towards the minimum of 10% rule noted above

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CALGB - Audit System CTSU Patient Accruals

- No longer “inter-group” trials. Patients entered on studies through the CTSU are categorized as:
 - Endorsed
 - Non-endorsed
- Depending on number of CTSU cases, an additional individual may be sent from the CTSU to augment the audit team
- CTSU cases will be included in the
 - 24 hour Preliminary Report
 - Final Audit Report along with the CALGB Cases
 - Pieces of the audit reports now go to the lead Group (e.g. ECOG, SWOG, etc) on a case-by-case basis

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Why do we do audits?

- To assure all patient protection measures are followed
- To educate all involved in clinical trials research regarding protocol adherence and data collection
- To find and correct errors
- To assure all pharmacy procedures are followed
- To help provide assurance the study results are valid
- To discourage fraud and find its rare instances, and finally
- **BECAUSE WE HAVE TO!!!!!!!!!!!!!!!!!!!!!!**

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**Cancer and Leukemia Group B
Fall Group Meeting
2008 Tampa, FL
November 13-16**