



Introduction to Data Auditing

David Hurd, M.D.
Interim Chair, Data Audit Committee
Wake Forest University School of Medicine

CALGB CRA Orientation, April 2008

For CALGB Participants Only

How did we get here??

- National Cancer Institute is the 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

For CALGB Participants Only

Slide 2

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

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

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 Group's monitoring program which includes auditing as one component

Clinical Trials Monitoring Branch 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

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

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

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

Why Do Audits??

- Detect honest errors
 - systemic or random
- Detect falsification
 - hopefully rare event, however....

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”
- 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”

Cancer researcher admits falsifying trial results

- Trial results presented at ASCO’s annual meeting misrepresented treatment in the control group
- The University of Witwatersrand Medical School
 - Investigated 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

Other Examples

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

Data 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

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

CALGB Data 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

CALGB Data 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

CALGB Data 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

CALGB Data 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
 - Limited review (e.g. eligibility, consent, data submission)
 - If limited review, does not count towards the minimum of 10% rule noted above

CALGB Data 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

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!!!!!!!!!!!!!!!!!!!!!!**

