

The Scientific Data Verification
and Auditing System of the
Cancer and Leukemia Group B
(CALGB)

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Why Do
Audits?

Stem-cell Transplant for Breast Cancer

- Bezwoda WR, 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 do not report verifiable data, and 9 other publications coauthored by the PI 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.

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. In a document recently sent to his colleagues, Bezwoda acknowledged that he 'committed a serious breach of scientific honesty and integrity' by misrepresenting the results of that trial. Bezwoda has resigned his position at the university.

"ASCO regards these developments with the utmost seriousness."
Joseph S. Bailes, MD

Case Summary

In a drug co. study of a toxicity protectant:

- The CRAs at 4 participating institutions falsified at least one QOL document to be completed by the patient.
- Three completed the form and signed the patient's signature.
- One used one form signed by the patient, changed the date with white-out, and submitted it as the form for a later date.

Case Summary

- Event published in the Federal Register in March 2004.
- 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 ca. prevention.
- The Clinical Trials Monitoring Branch and the Office of Research Integrity is currently investigating multiple other reports of scientific misconduct in the coop groups in past several years.

Case Summary---CALGB

- A CALGB affiliate site entered 41 patients in 2003-2006, and about half had one or more instance of deceptive information being submitted.
- Six consents were cut and pasted to make it appear the patient declined to allow submission of blood samples and pathology materials.
- Some radiology reports were cut and pasted to make it appear a study done *after* entry was done *prior* to entry.

Case Summary---CALGB

- One patient was started on Treatment B before randomization, and then when the randomized treatment was A, information was submitted to SWOG claiming that “computer problems” were the reason for this error and the wrong regimen was relayed to the site staff by CALGB.
- Seven patients had the Eligibility Checklists completed with information that certain required pre-enrollment tests were done, when they, in fact, were not done.

The Washington Post, Tuesday, September 19, 2000

Penn Researchers Sued In Gene Therapy Death

Teen's Parents Also Name Ethicist as Defendant

CALGB Data Audit
Committee

Motto

“In God We Trust
All Others We Audit”

Reasons to Do Audits

- To discourage fraud & find its rare instances.
- To *educate & prod* investigators regarding protocol adherence & data collection.
- To find and correct errors.
- To assure all required patient-protection measures and pharmacy procedures are followed.
- To help provide assurance the study results are valid.

Who Does Audits?

- Each cooperative group.
- NCI contractor (Theradex Corp.).
- Major cancer centers.
- NCI Intramural Program.
- Pharmaceutical companies.
- Others (General Accounting Office and Food & Drug Administration).

CALGB Data Audit System Personnel

- Data Audit Committee (DAC): approx. 20 members, half are MDs and half CRAs.
- DAC Chair is the only paid member.
- A designated statistician (Jeff Johnson).
- A designated administrative assistant in the Central Office (Sally Scherer).
- Ad hoc auditors (CALGB MDs and CRAs who are not DAC members).

CALGB Data Audit System Selection of Institution

- All institutions entering at least one 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.
- All institutions are subject to audit during any one year.

CALGB Data Audit System Selection of Institution (cont'd)

- Re-audits are done when patient accrual is sufficient to make them worthwhile, but in 12-18 months usually.
- Institutions leaving CALGB are still subject to audit of their entries since the previous audit.
- Geographical and weather considerations may affect scheduling.

CALGB Data Audit System Notification Lead Time for Audit

- Date is selected 3-4 months in advance & is arranged, as much as possible, for mutual convenience of the Team Leader and the local staff.
- Patient list arrives 30 days in advance.

CALGB Data Audit System

Audit Teams

- 1-5 MDs and 1-5 CRAs make up teams and almost always work in pairs.
- Team Leader is always a DAC member.
- DAC members are those individuals with demonstrated audit interest and skill.
- Ad hoc auditors participate as an educational experience & always work with DAC member.
- Geographical and other considerations.

CALGB Data Audit System

Patient Selection

- Patients entered on 8-20 protocols representing a cross-section of diseases and stages, especially when there are special data submission requirements. 2-10 studies will involve NCI-supplied drugs.
- Patients at risk for audit are primarily, but not exclusively, those entered since the previous audit.
- At least one patient will be unannounced.

CALGB Data Audit System Patient Selection (cont'd)

- The number audited depends on the number entered by the institution. Main institutions are at least 15-20%, and affiliates vary from 20% to 100%.
- An attempt is made to select at least one entry from each participating MD.
- The percentage of entries to any one study audited within the whole Group varies from 5% to 40%.

New NCI Requirements for Audits

- There are no more new intergroup studies. CTSU now fulfills this role.
- CTSU studies will be audited just as if they were a CALGB study, but they will be segregated into “endorsed” and “non-endorsed” cases. Thus, samples from each category will be selected for review.
- If >3 CTSU cases are to reviewed, CTSU staff will augment the Audit Team.

New NCI Requirements for Audits (cont'd)

- The CTSU cases will be included in the 24-hour Preliminary Report and the Final Audit Report along with the CALGB cases.
- Comments in the audit reports in the Patient Case reviews now go to the lead group on a case-by-case basis for the non-CALGB studies, for action.

CALGB Data Audit System Data Management Center Duties

- Make copies of all submitted data forms for use by auditors.
- After audit report is final & submitted to all concerned parties, any needed changes in the database are made.

CALGB Data Audit System Audit Preparations at Institution

- Review audit-preparation information in Policies and Procedures Manual, in the letter to the PI, and on the CALGB website.
- Assemble all relevant IRB-review items (initial, annual, update, and SAE reviews) and put in chronologic order by category.
- Assemble all inpatient and outpatient records for the patients to be audited.

CALGB Data Audit System Audit Preparations at Institution

- Inform the pharmacy staff of the impending audit and request they have all records (drug logs, NCI-shipping & return invoices, etc.) available and in chronologic order. A knowledgeable person must be available at the audit.
- Be prepared to locate the medical records for the unannounced patient(s).

**CALGB Data Audit System
Administrative Elements Audited
IRB**

- Were the protocols being audited fully approved prior to the first patient entry and were the annual reviews done annually (i.e., interval of <366 days).
- Were protocol Updates reviewed w/n 90 days & were consent revisions implemented
- Were local & broadcast Serious Adverse Events reviewed as required.

**CALGB Data Audit System
Administrative Elements Audited
Consents**

- Were the consents signed and dated on or before the date of registration.
- Were all local IRB requirements (witness, blanks, initials on pages, etc.) fulfilled.
- A sample of at least 3 consents are reviewed for completeness using the CALGB 28-item checklist (available on CALGB website).

**CALGB Data Audit System
Administrative Elements Audited
Pharmacy**

- Are the NCI Drug Accountability Record Forms (DARFs) being used.
- Does drug income and dispensing match.
- Does the supply on the shelf match the log count.
- Is there any misuse of NCI-supplied drug for a non-study patient.

**CALGB Data Audit System
Administrative Elements Audited
Pharmacy (cont'd)**

- Were commercial supplies (if available) substituted for NCI-supplied drug and was NCI-supplied drug repaid to the commercial supply.
- Is drug storage secure with limited access.
- Were transfers of drug supplies approved by NCI & was excess drug handled correctly.
- 1-3 drugs will have unannounced reviews.

CALGB Data Audit System Protocol Elements Audited

- Were the pre-therapy baseline pathologic, radiologic, laboratory, and other required assessments properly performed and did they meet protocol minimums.
- Did the patient meet *all* eligibility requirements.
- Were stratification and randomization correct.

CALGB Data Audit System Protocol Elements Audited

- Was the correct treatment given at the correct dose and schedule for all cycles.
- Was all treatment toxicity properly assessed, graded, and reported.
- Was the antitumor response (none, partial, complete) properly measured (often done with review of the relevant radiographs).

CALGB Data Audit System Protocol Elements Audited

- Was the patient monitored after completion of therapy according to the requirements of the protocol.
- Were all required data forms submitted to the CALGB Stat. Center Data Operations.
- Were all required ancillary submissions (pathology items, XRT data, blood/marrow samples, etc.) completed and on schedule.

CALGB Data Audit System Audit Reports

- The 3 components are each rated as being Acceptable, Acceptable Needs FU, or Unacceptable.
- An Unacceptable rating requires a re-audit; an Acceptable Needs FU may require one, depending on the issues.
- An Unacceptable rating in IRB/consent category results in suspension of patient registration until the problem is corrected.

Avoidable Errors in IRB

- All Updates/Amendments must be reviewed by the IRB within 90 d. of implementation.
- All SAEs broadcast in the monthly mailing from the CO must be acknowledged by the IRB within 90 days of implementation.
- Annual renewals must be done within 365 days of the previous renewal.
- All closed studies with patients still in active FU must have annual renewals also.
- All “Action Letters” must be reviewed.

Avoidable Errors in Pharmacies

- Using a local version of the NCI DARF.
- Substituting commercial agents for INDs when the consent tells the patient the drug will be provided free by the NCI.
- Not returning unused drugs when a study closes or transferring to another open study with NCI authorization..
- Having vials of drug unaccounted for.
- Satellite pharmacies must use DARFs too.

Avoidable Errors in Consents

- Failure to include CALGB personnel (i.e., auditors) among those authorized to review records.
- Failure to include the Alternatives in exact same text as in the Model Consent.
- Failure to include **all** side effects present in the Model.
- Failure to include the new info present in the Updates.

Avoidable Errors, Consent Signing

- No consent available at all or only a copy (only originals will be reviewed).
- Boxes not filled in with information. The Yes/No responses for companion studies not completed.
- All IRB-required signatures not present and/or not dated.
- IRB-required initials on every page not present.

Avoidable Errors in Eligibility

- Auditors will declare a patient ineligible only when a specific protocol criterion is not followed.
- Close attention to the details of the pathology report is essential.

Avoidable Errors in Stratification

- When registering the patient, please be sure that the stratification is correct. Example of 2 common errors: # of nodes involved for the adjuvant breast cancer studies and the ER status.

Avoidable Errors in Data Management

- Participants in cancer control studies are not patients, and thus source documents must be created for each patient contact.
- Keep a “tickler file” for sample collection time points and ancillary data such as XRT and blood/urine/marrow specimens.

Avoidable Errors in Data Submission

- For complex studies (e.g., 10105) with multiple required blood/marrow/serum sample submissions, it is useful to develop a one-page set of directions for local use.
- For participation in CALGB 8461 a local cytogeneticist must be approved by CALGB to participate before study activation and patient entry.

Avoidable Errors in Data Submission

- The pathology materials are not submitted at all or in proper fashion (check LabTrak).
- The pathology materials are submitted to the wrong place (one must pay attention to the requirements that apply to CALGB sites stated in the protocol).
- If the correct items cannot be submitted, the PCO, QARC, or LTB should be notified regarding the reason why.

Avoidable Errors in Audit Follow-up

- Site response must be submitted to CTMB within 45 days of submission of the Audit Report. It must be submitted to the Central Office within 30 days.
- Be sure to respond with specifics, not just “we’ll do better in the future.”
- When a re-audit is necessary, the corrective measures should have been put in place and improvements actually made.

Audit Preparations

- **PLEASE** read the Audit Announcement Letter and distribute it to all involved personnel including those at the relevant affiliate(s).
- **PLEASE** make sure all preparation directions in the letter are followed.
- Sending personnel to affiliates to assist with, and supervise, audits is **very** useful.
- CALGB Website has the Audit Preparation Workshop available for review.

CTMB Reminders for PIs

- The PI is responsible for ensuring all required IRB reviews are performed.
- The PI is responsible for pharmacy activities with INDs.
- The PI is responsible for all CRA activities.

CALGB Data Auditors

**Nitpickers,
Ad Nauseum**

CALGB Data Audit
Committee

**Club Med for
Type A Personalities**

Since When Is
Obsessive-Compulsive
Considered A Disorder?