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ORIGINAL ARTICLE

Raymond B. Weiss

Systems of protocol review, quality assurance, and data audit

Abstract The US National Cancer Institute (NCI) is the world's largest sponsor of clinical trials in cancer treatment and biology, and it is responsible for the reliability of data generated by means of its funding. The cooperative groups supported by the NCI consist of main academic institutions and smaller affiliates of these institutions. The size of these groups, their geographical dispersion, and the number of studies accruing patients at any one time make it a challenge to ensure that all requirements of institutional oversight, patient consent, protocol compliance, and data submission and quality are met. Each cooperative group has established various procedures for quality assurance. These include data coordinators at the data management center of the group, study chairs, and statisticians. In addition, each group has a committee of physician-investigators and clinical research associates who make periodic site visits to all member institutions to audit the on-site medical records of a sample of patients entered at that institution. The study records are compared with the medical records for all aspects of protocol management and data generation. In addition, adherence to requirements for consent-form signing and oversight by an institutional review board is assessed. Deviations from the study requirements are evaluated as being minor or major. A written report of the audit result is provided to both the NCI and the relevant administrative components of the cooperative group. The audit process has uncovered rare instances of scientific improprieties in these NCI-funded clinical trials, but more importantly it has educated investigators and support staff to improve adherence to research and data-collection requirements, which has resulted in greater reliability of study results.

Key words US National Cancer Institute · Cooperative groups · Quality assurance · Cancer treatment

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R. B. Weiss
Lombardi Cancer Center, Georgetown University School of Medicine, Washington, DC and the Cancer and Leukemia Group B, Chicago, IL, USA

R. B. Weiss (✉)
Chair, Data Audit Committee, Central Office of Cancer and Leukemia Group B, 208 South LaSalle Street, Suite 2000, Chicago, IL 60604, USA
Tel. +1 301 929 1159; Fax +1 301 929 9377

Introduction

The National Cancer Institute (NCI) supports a large program of clinical trials in cancer treatment and biology. The largest of these enterprises is the cooperative group program, which has now been in existence for 43 years. There are currently 11 of these groups (Table 1), and they consist of main academic institutions and smaller affiliates throughout the USA. Some Canadian institutions and a few in Europe, Australia, and South Africa are also members. The size of these groups varies from several dozen to several hundred institutions, all entering patients on group-wide protocols. Some groups focus on a single disease or disease area and others focus on pediatric patients. Four of the groups are oriented to multiple malignant diseases and annually accrue the largest numbers of patients to ongoing clinical trials (Table 1). Three groups conduct trials not only in phases I, II, and III of treatment development, but also studies of tumor biology, cytogenetics, pharmacokinetics, psychooncology, surgical techniques, pathology, and economic outcomes of cancer treatment. Most of the trials conducted by these groups are performed within the one organization, but when particularly large numbers of patients are required for a study or the disease under investigation is rare, groups often collaborate to conduct a study (ie, intergroup trials). These groups are funded through cooperative agreement grants from the NCI.

Table 1 Cooperative groups funded by the US NCI

Multimodality, multidisease groups
Cancer and Leukemia Group B
Eastern Cooperative Oncology Group
North Central Cancer Treatment Group
Southwest Oncology Group
Disease-focused groups
Gynecologic Oncology Group
Intergroup Rhabdomyosarcoma Study
National Surgical Adjuvant Breast and Bowel Project
National Wilm's Tumor Study Group
Pediatric groups
Pediatric Oncology Group
Childrens Cancer Study Group
Single modality, multidisease group
Radiation Therapy Oncology Group

Each cooperative group has a central administrative office and a data management and statistical center, with each of these entities usually being geographically dispersed. Up to 2000–3000 investigators may be involved, entering patients on as many as 80 studies during any one year. With these large numbers it is difficult to ensure that all requirements of institutional oversight, patient consent, protocol compliance, and data submission and accuracy are met.

Protocol compliance and data quality in cooperative clinical trials sponsored by the NCI begin with physician-investigators and clinical research associates (CRAs; data managers) at the individual institutions. The second level of quality assurance is the central data management office of each group. These offices register and randomize patients, collate the data submitted, review them for completeness, query the institutional investigators for deficient or missing information, and store all the paper records. When fully satisfactory, data are entered into the group's computer system. The third level of data review is the study chairpersons, who assess the submitted patient data for protocol eligibility and compliance with the study requirements. In addition, there may be separate central reviews of pathology materials, reports of surgical procedures, certain radiographic studies, and radiation therapy techniques when relevant to the particular study involved. With these multiple levels of review and analysis, many errors of omission and commission are discerned and, when possible, corrected. For example, a patient may be found ineligible for the study based on the submitted medical information and may be excluded from the study analysis when it is completed, depending on the eligibility issue involved.

These many quality control systems provide reliable data and allow confidence to be placed in the end results of the studies these cooperative groups perform. However, these systems depend on the accuracy, diligence, and honesty of the investigators and the CRAs at each participating institution. Only completed data-collection forms are submitted to the data management center of each group. No one at these centers knows whether the forms are fully accurate and truly reflect what transpired during the protocol therapy. For example, when a partial or complete response is claimed as a result of a particular treatment, did this claimed response truly occur, or if a patient must meet certain requirements for eligibility to the study, did the patient truly meet them? One always assumes the honesty and accuracy of the investigators at each institution, but there have been rare instances of dishonesty by individuals in the trials performed by the cooperative groups [1]. The most common occurrence is simple human error.

The US Food and Drug Administration (FDA) has long performed audits of investigators and institutions conducting clinical trials of new pharmaceutical agents and devices that are to be approved for marketing, but clinical trials sponsored by the NCI were not audited in this manner until an instance of scientific misconduct was brought to light in 1978 [6]. Soon thereafter, the NCI mandated that each cooperative group receiving NCI funding implement a program of periodic on-site audits of patients entered on clinical trials. In 1981 the Data Audit Committee (DAC) of the Cancer and Leukemia Group B (CALGB) was formed. Each of the other NCI-supported groups (Table 1) also has such committees and conducts similar on-site audits. Each year, approximately 900 individual institutions in the cooperative group system are audited, with the CALGB performing approximately 85 of these audits annually. This paper describes some of the procedures used by the CALGB for on-site audits. Results of the first 4 cycles of CALGB audits have been reported previously [9].

CALGB DAC

The DAC is a constituted administrative committee of the CALGB. The chair is partly salaried to make many of the site visits and to organize and implement all of the audits. The remainder of the 20 committee members are CALGB investigators entering patients on study and collecting data on a daily basis, with approximately half being physicians and half CRAs. They make site visits as part of their voluntary contribution to the work and goals of the CALGB, and their salaries are paid by their home institutions. No extra pay is provided for traveling on an audit; DAC members volunteer for the work and are selected based on their interest, commitment to data quality, experience in CALGB research, and willingness to travel 3–8 times yearly.

An audit team is composed of 2–8 people, with half being physicians and half CRAs. When a main CALGB institution is audited, there are usually at least 6 auditors, while smaller institutions may require only 2 people. A CRA and physician usually work together, although for some of the cancer prevention studies, a CRA reviews the medical records alone. However, this CRA can ask a physician-auditor, who is also present and doing audits of treatment studies, if there are questions requiring physician input. The team leader is always a DAC member, but ad hoc auditors are also invited to participate on an occasional basis, not only to distribute the workload but to provide educational experience for CALGB investigators other than DAC members. Almost uniformly, ad hoc auditors later

Table 2 Major audit guidelines in the CALGB

Audit intervals are a maximum of 36 months
All institutions are subject to audit during any year
All institutions will be audited, even if they have entered only a single patient
Patients audited will be primarily, but not exclusively, those entered since the previous audit
Any institution receiving an "unacceptable" rating during an audit is automatically reaudited after an interval of 6–12 months, but reaudits for any deficiency may be recommended
All audit results are made known to the CALGB Membership Committee, the Institutional Performance Evaluation Committee, and the Board of Directors for consideration and action if necessary
All protocols involving patient treatment, cancer control, or cancer prevention are subject to audit

Table 3 Major areas of review during audits of NCI-funded cooperative groups

Compliance with requirements for protocol review by a duly constituted institutional review board prior to entry of the first patient at the institution
Compliance with requirements for annual review, reports of adverse events, and review of protocol revisions
Review of handling, storage, and dispensing of investigational drugs provided by the NCI or a pharmaceutical company
Review of the contents of a consent form sample to verify compliance with required elements and full description of possible adverse effects due to participation in the study
Review of protocol compliance in 6 major areas: consent-form signing; protocol eligibility; treatment; toxicity; outcome/response; and data quality

remark how much they learned about good data collection and protocol adherence as a result of participating in an audit at another institution.

Guidelines for on-site audits

The NCI has implemented a number of guidelines for each of the cooperative groups to follow in the conduct of their audits. In addition, each group has developed its own procedures for doing this work. The Policies and Procedures Manual of the CALGB contains a 26-page section on audit procedures. Table 2 outlines some of the salient features of these procedures. Audits are done at each institutional member of the CALGB at least once every 36 months. Audits may be done more often for institutions accruing large numbers of patients or institutions that fail a prior audit and are recommended to undergo reaudit after making efforts to improve performance. The average interval between audits is approximately 30 months. Special audits may also be done for certain studies accruing unusually large numbers of participants, e.g., $>10{,}000$, such as those involving cancer prevention.

Conduct of audits

The NCI and each cooperative group have established standards for the conduct of audits. During each site visit, 4 major areas of research and regulatory requirements are reviewed (Table 3). Such review entails examining source documents that verify all administrative actions and protocol-related medical care, including consent forms, hospital records, outpatient care records, and radiographs and other diagnostic studies, as well as records of treatment administration.

In the CALGB the principal investigator at the institution to be audited is notified 3–5 months in advance of an upcoming audit. The date set is based on the availability of both the auditors and the investigators at the institution to be audited. A minimum of 10% of the patients entered by the particular institution (and higher percentages for small affiliates) are selected for audit and represent a cross-section of the protocols to which patients have been entered. At least one patient will be audited unannounced, and the institution will be expected to produce the medical records of this patient on the day of the audit without prior knowledge that this record set is to be audited. Patients entered on large phase III trials are particularly chosen for audit, especially when the trial involves complex treatment regimens, central review of pathology materials, radiation therapy and/or surgery in addition to chemotherapy, and/or investigational drugs. For example, an institution may have entered only a single patient on a phase III trial involving protocol-directed radiation therapy, while entering larger numbers of patients on other studies. The one patient entered on the radiation therapy study will be audited while only a sample of the others will be selected. The total fraction of patients audited from any one CALGB study varies from 5% to 40%, with higher proportions (25–40%) applying to high-priority trials that may greatly influence medical practice [2, 7, 10]. However, all CALGB studies involving patients, as opposed to studies of archival pathology samples, for example, are subject to audit.

A physician and a CRA work as a team, with the physician reviewing the on-site medical records and the CRA reviewing the data forms submitted to the CALGB Data Management Center. The audit is thus a process of comparing and verifying the information recorded in the data forms with the details in the various source documents on site. A standard checklist is used to provide guidance in completing review of all elements of patient entry on the study, treatment and follow-up, and data submission. Table 4 lists the major elements reviewed.

In addition to reviewing medical records to verify protocol compliance, the auditors review various regulatory aspects of participation in clinical trials. The contents of a sample number of consent forms are reviewed to verify adherence to both federal government and NCI requirements. Compliance with governmental requirements for clinical trial oversight by institutional review boards is also assessed. Finally, if an institution has used any investigational drugs obtained from either the NCI or a

Table 4 Items assessed during CALGB audits

Did the patient sign a proper consent form dated before registration on the protocol?
If applicable, was the consent properly translated for non-English-speaking persons?
Were all the required pretherapy baselines tests and radiographs completed and results reported on the data forms?
Were protocol stratification and randomization done correctly?
Was the correct treatment administered at the required dose and schedule? Were dose modifications made according to protocol requirements?
Was the tumor response (or lack thereof) properly assessed and categorized? Was the patient monitored after therapy completion according to protocol requirements?
Was any treatment toxicity that occurred properly assessed and reported?
Were all required data forms properly completed and submitted to the Data Management Center on schedule? Were all required ancillary items (pathology materials, radiographs, irradiation data, etc) submitted for central review?

pharmaceutical company, compliance with drug-handling procedures required by the NCI and/or the FDA are reviewed. Each of these administrative aspects is reviewed using a checklist specifically designed by CALGB investigators for audit purposes.

The audit is conducted over 1–2 days, depending on the number of patients accrued at a particular institution. Institutions that are geographically proximate are often audited on each of 2 or 2.5 consecutive days. One pair of auditors can review 8–10 patient records/day in addition to the administrative reviews that must take place. As the records of each patient are reviewed, notations are made on the audit forms regarding any deficiencies. These notes provide the information that is incorporated into the final written report. At the end of the audit, an oral discussion of problems or deficiencies is conducted between the auditors and the investigator staff at the institution being audited (the exit interview).

The team leader later prepares a written report covering all aspects of the audit, including the regulatory review and protocol compliance for the specific patients audited. This report is generated using a format and computer program created by the NCI. All the cooperative groups use this computer program for preparing their audit reports so that the information submitted to the NCI is standardized. In the CALGB, these reports are submitted not only to NCI staff but also to the principal investigator at the institution involved, DAC members, and other administrative committee chairs within the group.

The reports enumerate protocol deficiencies and deviations in both narrative and tabular form. Deficiencies and problems are scored as being either minor (lesser) or major in degree. A lesser protocol deviation is signified when the protocol course is not followed exactly, but the data are usable and valid. Examples are an inappropriate drug-dose reduction in only one cycle of therapy or failure to record minor treatment toxicities. A major deviation is indicated when the variance from the protocol makes the data for a patient questionable. Examples are a patient who is ineligible for the study by protocol criteria or who had an incorrect assessment of tumor response to therapy. Trivial protocol variances are not even recorded at the audit or in the written report. Examples are a patient who had a 1-week delay in therapy due to a scheduling problem or received only 95% rather than 100% of the protocol-directed dose. At the end of the audit report, an overall rating is assigned as follows: acceptable, acceptable – needs follow-up, or unacceptable. Any audit categorized as being "unacceptable" automatically requires that the institution be reaudited. In the CALGB, reaudits are also sometimes recommended for those institutions that fall on the borderline of being unacceptable as a stimulus to improve performance before another audit occurs within 6–12 months.

NCI oversight of audits

As discussed above, NCI staff receive and review all audit reports. If the NCI staff have specific concerns, the administrative personnel of the group involved will be contacted so that the particular issue can be addressed. The NCI staff may request that the audit rating be modified, usually downward, and/or require that a reaudit be performed. In addition, the NCI employs a contractor to attend approximately 20% of audits to monitor audit conduct and report the deviations/deficiencies that were noted independently to the NCI. In cases of particularly egregious problems, the NCI and the FDA may request an immediate additional review of patients entered on clinical trials at the institution.

Results of audits

Results from the first 4 cycles of audits conducted by the CALGB have been reported previously [9]. Over the years of audits from 1982 to 1992, there was a notable improvement in adherence to administrative and regulatory requirements, such as completion of proper, patient-signed consent forms. In addition, verification of protocol eligibility improved from an initially high level of 90% to 95%. A 5% ineligibility rate remains due to occasional and inadvertent human error. The assessment of tumor response or disease progression, as verified by auditors, was initially high (approximately 95%) and improved only slightly over the years. Again, occasional human errors account for the small percentage of deviations. However, a striking aspect of these errors is that they involved approximately equal numbers of upgraded and downgraded responses.

The high rate of verification of data accuracy in the CALGB has also been observed in a special NCI audit of a trial of breast cancer treatment in another (not the CALGB) of the cooperative groups, after a few patients were found to have been entered on the study fraudulently [4]. Among the patients where full on-site records could be reviewed, only one patient who had been declared protocol eligible was found to be ineligible by the on-site auditors. Moreover, only a small minority of patients (41 of 1554 patients

audited) had a discrepancy in first event between the on-site records and the records at the data center of this particular group.

The reason for the NCI performing this special audit of a single trial [4] was the discovery that some patients had been entered on the trial fraudulently at a single institution. The DAC of the CALGB also uncovered 2 instances of scientific improprieties during the audits conducted in the early 1980s [9]. No such events have been found since 1984, which strongly suggests scientific misconduct will be deterred when participants know that their colleagues will be scrutinizing their work within 1–2 years during an audit.

Reports of audit results are rare in the medical literature, but one brief report [3] again emphasizes their value. When an outside audit of a phase I study was performed, some of the tumor responses were found to have been "overstated." This sort of report reinforces the benefit in having such important data points as tumor responses reviewed by objective outside auditors.

Audits not only provide verification of the accuracy of the data, but also serve as an important educational tool, both for the investigators being audited and the auditors themselves. Auditors often show CRAs how their data collection techniques can be improved to provide more accuracy or clarity in the data records or how some administrative recordkeeping practice can be improved. The auditors also observe particular errors in protocol compliance and learn not to repeat the same mistakes when they return to their own institution. Protocol compliance and data accuracy are greatly enhanced by such on-site observations.

Conclusions

The NCI is responsible for the accuracy of data and published reports generated by its funded grantees that perform clinical research. The system of data audits implemented in 1981 has been broadened and modified over the years to meet new needs and requirements. Each cooperative group conducts regular audits of all participating institutions and scrutinizes the records of a sample of patients for protocol compliance, data collection accuracy, and adherence to regulatory and patient safety requirements. Although there have been instances of scientific misconduct in this large clinical trial program [1, 9], fortunately they have been so rare that they have had no effect on the outcome of studies. Protocol eligibility and tumor assessment accuracy have improved from high rates to even higher rates. When an investigator knows that colleagues will be "looking over his/her shoulder" to verify the accuracy of the clinical trial work, quality improves and the accuracy of research results benefits. In addition, both auditors and the investigators being audited learn from each other, with resulting improvements in study quality. When results of trials audited in this manner are published, readers can be confident the results are accurate [8]. Furthermore, the public can be assured that if any scientific fraud has occurred, it is so negligible as to be meaningless; this was not appreciated until a full-scale audit of the involved trial was performed [4, 5] when concerns about fraudulent data arose in one of the NCI-funded groups 3 years ago.

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