

SPECIAL ARTICLE

THE NATIONAL CANCER INSTITUTE AUDIT OF THE NATIONAL SURGICAL ADJUVANT BREAST AND BOWEL PROJECT PROTOCOL B-06*

MICHAELE C. CHRISTIAN, M.D., MARY S. MCCABE, R.N., EDWARD L. KORN, PH.D., JEFFREY S. ABRAMS, M.D., RICHARD S. KAPLAN, M.D., AND MICHAEL A. FRIEDMAN, M.D.

Abstract Background. The National Surgical Adjuvant Breast and Bowel Project (NSABP) Protocol B-06, a clinical trial sponsored by the National Cancer Institute (NCI), has provided evidence of the value of lumpectomy and breast irradiation for treating women with breast cancer in an early stage. Publicity generated by the discovery that the study included fraudulent data on patients enrolled by St. Luc Hospital in Montreal aroused concern about the overall accuracy of the data and conclusions. To address this concern, the NCI conducted an audit of other participating institutions.

Methods. In 1994, data on 1554 of the 1809 randomized patients (85.9 percent) enrolled by centers other than St. Luc Hospital were audited at 37 clinical sites in North America. The audit included data on eligibility, survival, disease-free survival, the length of time to a recurrence of cancer in the ipsilateral breast, and documentation of signed informed consent.

Results. End points were assessed for all 1554 patients, and eligibility was assessed for 1507 patients; 47 patients were excluded because their forms were not complete or not returned. A total of 1429 patients had their eligibility status verified. Of a total of 7770 data points examined with respect to the number of positive

nodes at base line, treatment characteristics, first events (excluding death), recurrence of cancer in the ipsilateral breast, and survival, 7577 (97.5 percent) were verified, 123 (1.6 percent) could not be verified, and 70 (0.9 percent) were discrepant with the NSABP file. Of the 1554 patients, 1340 (86.2 percent) had all audited items (including eligibility) verified, 69 (4.4 percent) had at least one discrepant item, and 113 (7.3 percent) had at least one unverified item (as a result of missing or incomplete data); 32 (2.1 percent) were not assessed for eligibility but had no other discrepant or unverifiable items. Written informed consent was documented for 1098 patients before surgery and 210 after surgery; no date appeared on the signed form for 137. The informed-consent status was not verified for 71 patients and could not be determined for 38. The rates of verification of end-point data and documentation of written informed consent were similar among the total-mastectomy group, the lumpectomy group, and the group treated by lumpectomy and breast irradiation.

Conclusions. The audit confirms the adequacy of the data on which the reanalysis of Protocol B-06 and the results after 12 years of follow-up are based. (N Engl J Med 1995;333:1469-74.)

THE National Surgical Adjuvant Breast and Bowel Project (NSABP) Protocol B-06, a federally sponsored clinical trial that compared segmental mastectomy (lumpectomy) plus axillary dissection, with or without irradiation of the breast, with total mastectomy plus axillary dissection for women with stage I or II breast cancers ≤ 4 cm in size (tumor, node, metastasis classifications, T1 or T2, N0 or N1, M0), accrued patients between 1976 and 1984. The initial results were reported in 1985¹ and updated in 1989.² The most recent analysis appears elsewhere in this issue of the *Journal*.³

In 1991, the NSABP detected scientific misconduct by an investigator who had been a major contributor to Protocol B-06. After an investigation, the Office of Research Integrity of the Public Health Service determined that Dr. Roger Poisson, of St. Luc Hospital in Montreal, had fraudulently enrolled 99 patients in

NSABP protocols,⁴ including 6 in Protocol B-06 for whom eligibility data were falsified or fabricated.

Two therapeutic options — mastectomy or conservative surgery plus breast irradiation — are currently available to women with breast cancer in an early stage. Several randomized trials^{5,6} of these two approaches have yielded similar outcomes. Protocol B-06 was the largest of these studies, and any change in the results of this study could affect prevailing treatment recommendations.⁷ In early 1994, publicity surrounding the inclusion of fraudulent data in the study aroused public concern about the overall quality of the data and the validity of the conclusions.

To assess the accuracy of the data base as a whole and to address the public's concern, the National Cancer Institute (NCI) audited the Protocol B-06 data. Although the auditors looked for evidence of fraud, the primary focus was on verifying the accuracy of the data on which the study's original analysis and conclusions were based.^{1,2} Attempts were made to distinguish between deliberate falsification and error. The purpose of the audit was to assess independently sufficient eligibility and outcome data to permit a reanalysis based only on audited data.

Details of the design of Protocol B-06, including eligibility criteria, treatment plans, and statistical methods, have been published previously.¹⁻³ Major study end

From the Cancer Therapy Evaluation Program, Division of Cancer Treatment, National Cancer Institute, 6130 Executive Blvd., Rm. 715, Rockville, MD 20892, where reprint requests should be addressed to Dr. Christian.

*The complete report of the NCI audit of NSABP Protocol B-06, the 1995 EMMES reanalysis of NSABP Protocol B-06, and the Expert Panel's Report on the NCI's Audit and Reanalysis of NSABP Protocol B-06 will be available after December 1, 1995, from the NCI's CancerFax (fax: 301-402-5874) and CancerNet (CancerNet@icicc.nci.nih.gov) or through the International Cancer Information Center (Internet address: <http://www.icic.nci.nih.gov/>).

points included disease-free survival, survival free of disease at distant sites, overall survival, and the length of time to the recurrence of tumor in the ipsilateral breast.³

METHODS

Audit Methods

In Protocol B-06, 2163 patients underwent randomization at 89 institutions. The exclusion of the 354 patients enrolled by St. Luc Hospital decreased the number of patients available for the audit to 1809. The NCI audit targeted all hospitals or clinics that had enrolled at least 10 eligible patients, except St. Luc Hospital in Montreal, and Royal Melbourne Hospital in Melbourne, Australia (because of geographic distance). Ultimately, two additional institutions were excluded: Letterman Army Hospital in San Francisco, which had closed, and Michigan State University, a consortium of eight institutions in Michigan, each of which had accrued three or fewer patients. This plan targeted 1554 of 1809 patient records (85.9 percent) (Table 1). Site visits were conducted between March 28, 1994, and July 20, 1994, at 37 of the 89 institutions that had enrolled patients in the study.

Audit teams were composed of NCI personnel and professional auditors contracted through Theradex (Princeton, N.J.). Fifty-four NCI auditors participated — 36 physicians, 8 nurses, 8 pharmacists, and 2 doctors of philosophy (1 in nursing and 1 in immunology, both of whom had extensive experience with clinical trials) — and 22 outside auditors. A physician was assigned as team leader at each site.

After gaining experience in the initial site visits, the NCI revised the audit forms. The outcome-assessment form was clarified, and the eligibility-assessment form was shortened from a 25-point checklist to a list of 11 criteria deemed critical to the outcome of the study. The eligibility criteria (Table 2) focused on key physical and pathological characteristics of the tumor and lymph nodes and the patients' status with respect to prior therapy for breast cancer and concomitant malignant conditions.

The outcome-assessment form included 12 questions on the randomized treatment, the date of surgery, the actual surgical procedure, surgical findings (number of positive nodes and presence of tumor at the surgical margins), first events (date and site of recurrence), the date of the most recent follow-up, the date of death, the date of recurrence of tumor in the ipsilateral breast, and the informed-consent process. The form used to review data on outcomes yielded information on three of the four major end points: disease-free survival, survival, and the length of time to the recurrence of cancer in the ipsilateral breast. Distant-disease-free survival was not covered in the audit because it was considered a surrogate for survival.

The auditors did not attempt to clarify consent issues beyond noting the nature of the consent (written vs. oral) and the date of consent relative to the definitive surgery. Patients were not declared ineligible or unable to be evaluated because of the lack of documentation of informed consent. Institutions were not asked to provide additional information, as they were for other missing or ambiguous items.

The NSABP provided specific information on individual patients (updated through September 1993) from their data base; such information was preprinted on the audit forms. Auditors used any primary-source documentation available at the site to verify data from the NSABP files, including records from hospitals, outpatient clinics, physicians' offices, and separate primary-research records. The NSABP data forms were not considered adequate source documentation and were not used, except to obtain the date of the most recent follow-up visit. Because many of the study participants were no longer being seen, followed, or treated at the institution that had enrolled them in

Table 1. The Patients and Institutions Audited by the NCI.

VARIABLE	NO. OF PATIENTS	NO. OF INSTITUTIONS INVOLVED
Total no. of randomized patients in Protocol B-06	2163	89*
No. of patients enrolled by St. Luc Hospital	354	1
No. of patients available for audit	1809	88
No. of patients subsequently excluded from audit		
Institutions with <10 eligible patients	198	48
Royal Melbourne Hospital	35	1
Michigan State University	12	1
Letterman Army Hospital	10	1
Total no. of patients audited	1554	37
No. of patients audited for eligibility (% of randomized patients, excluding those from St. Luc Hospital)	1507 (83.3)†	—
No. of patients audited for end points (% of randomized patients, excluding those from St. Luc Hospital)	1554 (85.9)‡	—

*The University of Miami had two NSABP institution numbers but only one patient list and data collection at only one site; it was therefore counted as one institution.

†Forty-seven patients were excluded from the analysis because the eligibility-assessment forms were incomplete or not returned to the auditors.

‡For eight of these patients, no information was available on the initial site visit and follow-up institutional queries. Their data were considered to be unverifiable.

the study, these NSABP forms were often the only documentation of the date of the most recent contact. The major audited items used in the reanalysis are described in Table 3.

Each data entry from the NSABP files was compared with the data in the patient's records, and the NSABP file entry was judged to be verified, not verified, or discrepant. The classifications were defined as follows: verified, the original documents confirmed the data in the NSABP file; not verified, the original documents did not address the item in sufficient detail to allow confirmation or were not reviewed, because they either could not be located or did not exist; discrepant, source documents did not agree with the data in the NSABP files. Differences due to extended follow-up (e.g., a report of a recurrence of cancer after the date of the last follow-up visit in the NSABP file) were not considered discrepant, nor were minor differences within defined data categories (e.g., a change of less than 30 days in the date for a first event or a recurrence of cancer in the ipsilateral breast).

All audited data forms were submitted to the EMMES Corporation (Rockville, Md.) for processing, review, and analysis. When data items were identified as discrepant, unverified, or missing, the EMMES Corporation contacted the principal investigators and the chairpersons of the institutional review boards at the participating institutions to request additional relevant documentation. These requests did not provide the data-base values for the items in question. Additional information on survival was obtained by a search of the National Death Index. The NSABP provided copies of relevant documents from its files, such as copies of pathology reports documenting a date or site of first recurrence.

A data-resolution panel composed of three of the authors (Jeffrey S. Abrams, Michael C. Christian, and Richard S. Kaplan) reviewed the data to resolve all remaining questions of eligibility and outcome. Members of the NSABP staff were invited to these meetings and attended two of four meetings.

An advisory committee of experts from outside the NCI was convened to review the audit findings and the end-point reanalysis based on audited data and to assess the overall process.⁸

Statistical Analysis

With respect to the determination of the number of patients to be sampled, the major finding of Protocol B-06 to be verified with the use of audited data was the similar rates of disease-free survival and overall survival in the group treated by mastectomy and the group treated by lumpectomy plus irradiation. On the basis of the reanalysis of the original data⁹ by the EMMES Corporation, the hazard ratio

Table 2. Items Listed on the Eligibility-Assessment Form.*

On clinical examination, the tumor was confined to one breast and ipsilateral lymph nodes.
On clinical examination, the tumor was movable (not fixed to skin, muscle, or chest wall).
On clinical examination, there was no skin infiltration (edema, peau d'orange, or ulceration).
On clinical examination, if palpable lymph nodes were found, they were judged to be ≤ 2 cm in size and movable (not fixed to each other or surrounding structures).
No suspicious lymph-node masses were found on the contralateral side (e.g., axilla, supraclavicular area, or infraclavicular area), or a biopsy proved them benign.
The patient had no history of previous therapy for breast cancer, including irradiation, surgery, chemotherapy, immunotherapy, and hormonal therapy.
The patient had not had a previous malignant condition and did not have a concomitant malignant condition, except effectively treated skin carcinoma (squamous or basal cell).
The pathology report indicated the presence of invasive carcinoma and no other histologic abnormalities (sarcoma, etc.) in the breast.
The pathology report did not indicate the presence of intraductal carcinoma (without invasion of stroma) or lobular carcinoma in situ.
Neither the pathology report nor the clinical examination indicated the presence of inflammatory breast cancer.
Neither the pathology report nor the clinical examination indicated the presence of more advanced disease such as satellite or parasternal nodules.

*These criteria were deemed critical to the outcome of the study.

(relative risk) for survival among eligible patients (excluding patients enrolled by St. Luc Hospital) was 0.88 (95 percent confidence interval, 0.72 to 1.07). The hazard ratio for disease-free survival was 0.91 (95 percent confidence interval, 0.77 to 1.07). These hazard ratios reflect near-equivalence, with a slight advantage for the group treated by lumpectomy plus irradiation.

On the basis of analytic calculations and computer simulations, if a random sample of approximately 80 percent of the eligible patients (excluding patients enrolled by St. Luc Hospital) was analyzed (and the original data were verified by the audits) then, with 95 percent power, the upper limits of the 95 percent confidence intervals for the hazard ratios would be less than 1.20. A value below 1.20 would preclude a hazard-rate disadvantage for survival or disease-free survival of more than 20 percent for lumpectomy plus irradiation as compared with mastectomy. To account for the fact that there would be changes to the data base as a result of the audits (on the basis of a preliminary analysis of the first nine audited institutions), we decided to audit institutions that accounted for approximately 87 percent of the eligible patients randomized in the trial.

A revised data base was constructed through the auditing process. When a difference in a data item was found between the original source and the original NSABP file, the revised audit data base was modified to reflect the original source. In addition, data on some patients were censored because of possible withdrawal of informed consent. The revised audit data base, with a listing of changes from the original NSABP files, was provided to the NSABP to update their analysis files. Other plans, involving sampling of institutions, were considered but eventually rejected because they would have required audits at substantially more than 37 institutions.

RESULTS

Of the 1554 audited patients, 1340 (86.2 percent) had all audited items (including eligibility) verified, 69 (4.4 percent) had at least one discrepant item, and 113 (7.3 percent) had at least one unverified item (with no discrepant items); the remaining 32 patients (2.1 percent) were not assessed for eligibility and had no discrepant or unverifiable items. The rates of verification were similar among the three treatment groups: 84.9 percent for the total-mastectomy group, 85.9 percent for the lumpectomy group, and 87.9 percent for the group treated by lumpectomy and irradiation.

With respect to the five other variables listed in Table 3 — the number of positive nodes, treatment characteristics, first event excluding death, recurrence of tumor in the ipsilateral breast, and survival — 1432 patients (92.1 percent) had all items verified, 68 (4.4 percent) had at least one discrepant item, and 54 (3.5 percent) had at least one unverified item (and no discrepant items). No evidence of systematic attempts to manipulate the data was uncovered by the audit.

Eligibility

Eligibility was assessed in 1507 patients (Table 1), regardless of whether they had been declared ineligible by the NSABP (there were 62 such patients). The eligibility of

47 patients at six sites could not be assessed for a variety of reasons, including failure to provide eligibility-assessment forms to the auditors at one site, which was audited with different forms at different times (21 patients); inaccessibility of data at two sites, where the charts of 16 patients who withdrew consent were sealed; inability to locate the charts of 6 patients at two sites; and inability to locate the audit forms for 4 patients at one site. Because these omissions were discovered late in the auditing process and were not the result of institutional deficiencies, the institutions were not asked to supply additional documentation. These 47 patients were assessed for end-point items but were excluded from the analysis of eligibility.

Eligibility status was completely verified for 1429 patients, or 94.8 percent. The auditors were unable to verify one or more of the eligibility items for 77 patients (5.1 percent), and 1 patient (0.1 percent) classified as eligible by the NSABP was deemed ineligible by the auditors (discrepant result). Verification rates were similar among the three treatment groups: 94.6 percent for the total-mastectomy group, 94.2 percent for the lumpectomy group, and 95.7 percent for the group treated by lumpectomy and irradiation.

Patients' Characteristics, Treatment Assignments, and Outcome

The results of the audit of data on base-line characteristics, treatment, and outcomes for the 1554 patients are presented in Table 4. Overall, 7577 of 7770 data points (97.5 percent) covering the number of positive nodes at base line, treatment characteristics, first events (excluding death), recurrence of tumor in the ipsilateral breast, and survival were verified. A total of 123 data points (1.6 percent) could not be verified. In the case of 70 data points (0.9 percent) from 25 institutions, the audited charts and the NSABP files were discrepant.

Table 3. Areas Covered by the Audit and Definitions of Discrepancies in These Areas.

AREA COVERED	DESCRIPTION	DEFINITION OF DISCREPANCY
Eligibility	Eligibility was verified with use of the criteria listed in Table 2.	For patients considered eligible by the NSABP, failure to meet any of the 11 criteria; for patients considered ineligible by the NSABP, meeting all 25 criteria originally included in the NCI audit.
Number of positive nodes	The number of pathologically positive nodes present at the time of the surgery mandated by the protocol was determined.	A change in the number of positive nodes, according to the categories used in the analysis of Protocol B-06 (0, 1-3, 4-9, ≥10).
Treatment	The date of surgery, whether or not the patient received the assigned treatment, was ascertained.	A change in the date of surgery by >1 wk, or any deviation from the assigned treatment (total mastectomy, lumpectomy, or lumpectomy plus irradiation).
First event, excluding death	The times and sites of first events, including recurrences of breast cancer and the occurrence of all second primary tumors but excluding recurrences of cancer in the ipsilateral breast, were ascertained.	The addition of any event before the first confirmed event in the NSABP data base and before the date of the last follow-up in the data base, or the removal of an event or a change in the date of the first event by at least 30 days, or a change in the site of recurrence.
Recurrence of tumor in the ipsilateral breast	The incidence of a recurrence in the ipsilateral breast or a second primary cancer in the ipsilateral breast was calculated for patients who underwent lumpectomy.	The addition of a recurrence of tumor in the ipsilateral breast before the first confirmed event in the NSABP data base, before the date of any previous confirmed recurrence of ipsilateral breast cancer, and before the date of the last follow-up in the NSABP data base, or the removal of a recurrence of ipsilateral breast cancer or a change in the date of the recurrence of ipsilateral breast cancer by at least 30 days.
Survival	The date of the most recent follow-up and the date of death were ascertained.	A change in survival status (not due to additional follow-up) or a change in the date of death by at least 7 days or the removal of at least 30 days of follow-up from the total listed in the NSABP data base (not as a consequence of the withdrawal of consent).

Verification rates were similar among the treatment groups: 97.8 percent for the total-mastectomy group, 97.5 percent for the lumpectomy group, and 97.3 percent for the group treated by lumpectomy and irradiation.

The greatest numbers of unverifiable results ($n = 42$) and discrepant results ($n = 41$) were associated with first events, which consisted of recurrences of breast cancer (except for recurrences of cancer in the ipsilateral breast, which were handled separately) and the occurrence of second primary tumors. The discrepancies were in the identification or the date of a first event (Table 5).

As a result of the review of case records and the search of the National Death Index, additional follow-up information was obtained through September 30, 1993, which exceeded that available in the NSABP files. The data-resolution panel recommended that any such confirmed additional information be included in the re-analysis but not be considered discrepant.

The distribution of age, tumor size, nodal status, and tumor-margin status was similar among the 1340 patients who had all data verified, the 69 patients who had

at least one discrepant data point, and the 145 for whom no discrepant data points were identified, but for whom some data could not be verified. The 1554 audited patients were slightly older than the 255 patients who were not audited (mean age, 51.8 vs. 50.3 years). Differences in the other variables were minor.

The presence of residual tumor at the margins of the surgical specimen (positive margins), or its absence, after lumpectomy often could not be confirmed because the original pathology reports from the period (1976 to 1984) did not describe the margins precisely. To address this issue, the NSABP had assigned a pathologist at each site to review the specimens and to complete a special form. Although the status of margins was one of the items originally targeted for auditing, there was no reasonable means of verifying this end point without the use of the NSABP forms.

The presence of a signed, informed-consent form or documentation of oral consent was also assessed (Table 6). A total of 1445 patients were verified to have given written informed consent, 1098 (70.7 percent) before surgery, and 210 (13.5 percent) after surgery; the date on which the form was signed was not recorded for 137 patients (8.8 percent). The rates of verification of written informed consent were similar among the three treatment groups. The informed-consent status could not be documented for 71 patients (4.6 percent), and data on informed consent provided by the auditors were inconsistent or insufficient to make an assessment for 38 patients (2.4 percent). Unverifiable

Table 4. Results of the Audit of Data on Base-Line Characteristics, Treatment, and Outcomes for 1554 Patients.

VARIABLE*	VERIFIED	NOT VERIFIED	DISCREPANT
	number (percent)		
No. of positive nodes	1526 (98.2)	19 (1.2)	9 (0.6)
Treatment	1531 (98.5)	22 (1.4)	1 (0.1)
First event, excluding death	1471 (94.7)	42 (2.7)	41 (2.6)
Recurrence of tumor in the ipsilateral breast	1519 (97.7)	29 (1.9)	6 (0.4)
Survival	1530 (98.5)	11 (0.7)	13 (0.8)
Total†	7577 (97.5)	123 (1.6)	70 (0.9)

*The variables analyzed are described in Table 3.

†A total of 7770 items were audited.

Table 5. Types of Discrepancies Found in the Audit of First Events.

TYPE OF DISCREPANCY*	NO. OF ITEMS
Addition of an event before the first confirmed event in the NSABP data base and before the date of the last follow-up in the data base	9
Removal of an event	6
Change in the date of an event	
By <6 mo	10
By ≥6 mo but ≤1 yr	6
By >1 yr	8
Change in site of recurrence	2
Total	41

*The discrepancies are defined in Table 3.

and indeterminate results were found in 22 institutions. A chart review showed that 53 patients gave oral consent before surgery.

The NSABP included 36 patients in the data base who were thought to have provided informed consent, but who later appeared to have withdrawn their consent for further participation. The NSABP used the 1984 date on which it was informed of the withdrawal of the consent of these patients as the date on which further acquisition of data on these patients was censored. Because changing the date on which the data were censored would change the data base on which the reanalysis was based, withdrawals of consent were reviewed by the data-resolution panel. The information provided by the sites sometimes suggested that patients had expressed a reluctance to participate at all or had withdrawn consent at some earlier date.

The panel chose to use the earliest date on which consent may have been withdrawn in order to acknowledge the apparent wishes of the patients with regard to participation. A change in the revised NCI data base resulting from the use of an earlier date (e.g., censoring a patient's data in 1982 instead of 1984) was not considered a discrepancy since it was based on a difference in judgment regarding the appropriate handling of these data, not on a factual disagreement.

DISCUSSION

Discrepancies between the NSABP data and the audit results were uncommon, and most of the items considered in the audit were verified. The rates of verified items, discrepant items, and unverifiable items were similar among the treatment groups, as would be expected in a randomized study. We did not address the relative performance of individual institutions that participated in Protocol B-06, because that was not considered in the design and methods of the audit and because some centers enrolled too few patients (range, 11 to 171) to allow meaningful comparisons.

Because the mandate and primary focus of the audit was to provide an accurate data set on which to base an independent reanalysis of the results of Protocol B-06,

eligibility and end-point data were emphasized and data on informed consent were handled differently. Institutions were not asked to provide additional documentation of signed consent when the auditors could not find signed consent forms during the site visit. In addition, except for cases in which consent was withdrawn, the data-resolution panel did not review informed-consent issues.

The qualitative and quantitative aspects of data monitoring differ from study to study, and there are few published reports of on-site audits of clinical-research trials. Large-scale retrospective reviews of the case records of an entire study population are uncommon. Such audits have been done by the pharmaceutical industry in support of applications for drug approval; however, the results of such audits are usually not published. Most audits involve a more contemporaneous review of the data than ours.

The Cancer and Leukemia Group B reviewed its audits conducted in four periods between 1982 and 1992 and involving nearly 1500 patients at more than 230 institutions; the group noted substantial improvements over time with regard to informed-consent deficiencies involving the content, signing, date, or witnessing of these documents (18.5 percent in cycle 1 vs. 3.9 percent in cycle 4). Overall, the eligibility of 94.5 percent of the patients was verified, the tumor response was verified in 96.4 percent of cases, and the rate of what they considered major deviations from the dosing protocol remained steady at 11 percent.¹⁰ Preliminary results of the review of audits conducted over a seven-year period by the Southwest Oncology Group¹¹ of data on 1751 of their 28,613 patients showed that eligibility was confirmed in 94.8 percent of the patients, treatment compliance was confirmed in 78.5 percent, and response assessment was confirmed in 95 percent.

In 1982 the NCI established a formal quality-assurance program in which its cooperative groups were given the responsibility for auditing participating institutions at least once every three years, according to specific guidelines. The NCI reviewed the results of audits conducted between 1982 and 1984 that involved

Table 6. Assessment of the Signed Informed-Consent Forms for the 1554 Audited Patients.*

INFORMED-CONSENT STATUS	NO. OF PATIENTS (%)
Signed informed consent documented	1445 (92.9)
Before surgery	1098 (70.7)
After surgery	210 (13.5)
Form not dated	137 (8.8)
Signed informed consent not documented	71 (4.6)
Status unable to be determined†	38 (2.4)

*After the initial site visit, institutions were not asked to provide information on missing informed-consent items as they were for outcome and eligibility data, nor were unresolved issues presented to the data-resolution panel. The charts of 53 patients contained documentation that oral consent was obtained before surgery; however, these numbers are not reflected in the table.

†Data provided by the auditors were either inconsistent or insufficient to make an assessment.

812 institutions and 5988 patients enrolled by 17 cooperative groups. The ineligibility rate was 7 percent, serious deviations from the treatment protocol occurred in 12 percent of patients, the response was inadequately documented or incorrect in 6 percent, and the data could not be verified because of a lack of documentation or because of discrepancies in 5 percent.¹²

Protocol B-06 had complicated randomization and consent procedures, involved multiple surgical procedures, and required long-term follow-up even of participants who were no longer being seen at the institutions that had enrolled them in the study. Nonetheless, the verification rates are consistent with those obtained through audits of other trials. The NCI audit confirms the adequacy of the data on which the reanalysis of Protocol B-06 and the results after 12 years of follow-up are based.³

We are indebted to all the investigators and staff members for their cooperation, assistance, and conscientious efforts to locate the necessary records, charts, and follow-up documents.

REFERENCES

1. Fisher B, Bauer M, Margolese R, et al. Five-year results of a randomized clinical trial comparing total mastectomy and segmental mastectomy with or without radiation in the treatment of breast cancer. *N Engl J Med* 1985; 312:665-73.
2. Fisher B, Redmond C, Poisson R, et al. Eight-year results of a randomized clinical trial comparing total mastectomy and lumpectomy with or without irradiation in the treatment of breast cancer. *N Engl J Med* 1989;320:822-8.
3. Fisher B, Anderson S, Redmond CK, Wolmark N, Wickerham DL, Cronin WM. Reanalysis and results after 12 years of follow-up in a randomized clinical trial comparing total mastectomy with lumpectomy with or without irradiation in the treatment of breast cancer. *N Engl J Med* 1995;333:1456-61.
4. Case summary: fabricated and falsified clinical trial data. *ORI Newsletter*. April 1993;1:2.
5. Abrams J, Chen T, Giusti R. Survival after breast-sparing surgery versus mastectomy. *J Natl Cancer Inst* 1994;86:1672-3.
6. Early Breast Cancer Trialists' Collaborative Group. Effects of radiotherapy and surgery in early breast cancer: an overview of the randomized trials. *N Engl J Med* 1995;333:1444-55.
7. NIH Consensus Development Panel. Consensus statement: treatment of early-stage breast cancer. In: Consensus Development Conference on the Treatment of Early-Stage Breast Cancer. *Journal of the National Cancer Institute monographs*. No. 11. Washington, D.C.: Government Printing Office, 1992:1-5. (NIH publication no. 90-3187.)
8. Expert Panel's report on the NCI's audit and analysis of NSABP Protocol B-06. Bethesda, Md.: National Cancer Institute, December 12, 1994.
9. Stablein DM, EMMES Corporation. A reanalysis of NSABP Protocol B-06. Bethesda, Md.: National Cancer Institute, March 1994.
10. Weiss RB, Vogelzang NJ, Peterson BA, et al. A successful system of scientific data audits for clinical trials: a report from the Cancer and Leukemia Group B. *JAMA* 1993;270:459-64.
11. Sunderland M, Kuebler S, Weiss G, Coltman C. Compliance with protocol: quality assurance (QA) data from the Southwest Oncology Group (SWOG). *Proc Am Soc Clin Oncol* 1990;9:60. abstract.
12. Mauer JK, Hoth DF, Macfarlane DK, Hammershaimb LD, Wittes RE. Site visit monitoring program of the clinical cooperative groups: results of the first 3 years. *Cancer Treat Rep* 1985;69:1177-87.