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Rodney Sutter
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How to Use This Manual

The Southwest Oncology Group's main goal for the 2009 version of the Clinical Research Manual was to incorporate the changes that have occurred since it was last revised in 2008. Volume I covers administrative and data management issues the Clinical Research Associate and should be used as the primary reference tool on a day-to-day basis. Volume II consists of disease specific information, organized by disease site.
Ethics in the Conduct of Clinical Research

By Charles A. Coltman, Jr., M.D.

Introduction

"Clinical trials support is important to the National Cancer Institute (NCI) and to me," so says Samuel Broder, M.D., Director of the NCI, at a recent Division of Cancer Treatment, Cooperative Group Chair's meeting. "Clinical trials are a part of science. Data falsification is not tolerable," he adds. "We can accommodate mistakes but not fraud." These remarks were prompted by a series of events that transpired as a result of the much publicized fraud discovered in the clinical research being conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP). The NSABP was placed in receivership with an interim chair and executive officer, a flurry of investigations were launched, and there were numerous meetings resulting in many actions. Now the crisis and the associated closing down of the conduct of all NSABP clinical trials is over.

The NCI took a series of steps designed to re-establish the confidence of public trust and the credibility of an NCI supported clinical trials program. In the August 1994 issue of the Group Newsletter, I detailed a series of steps that are being taken by the cooperative groups to re-establish public confidence in our programs. All of these steps relate directly or indirectly to the ethics of the conduct of clinical trials. One of the mandates was to establish and maintain an ethics training program which will define scientific integrity, discuss the mechanisms for the protection of patient's rights and confidentiality, detail the role of Data and Safety Monitoring Committees in regard to patient safety, and reinforce the need to avoid conflict of interest in the conduct of clinical trials.

There can be no application of respect or beneficence or justice in clinical research without earning the trust of the public that we, as researchers, serve. That trust is earned with our integrity which means the elimination of misconduct and fraud through accurate data collection and reporting, and the elimination of any appearance of any financial bias which could be construed to influence judgment.

Belmont Report

The National Research Act (Public Law 93-348) was signed into law July 12, 1974. This created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Commission was charged to consider the basic ethical principles that should underlie the conduct of biomedical and behavioral research, the boundaries between research and the routine practice of medicine, the role of assessment of risk-benefit criteria, the appropriate guidelines for selection of human subjects, and the nature and the definition of informed consent.

The Belmont Report, developed by this commission, established three basic ethical principles: respect for persons, beneficence, and justice. Respect for persons is the mandate to allow persons to decide health care issues for themselves to the extent to which they are capable. Beneficence is the mandate to treat persons ethically, respecting their decisions and protecting them from harm while making efforts to secure their well being. Justice is the fair and equal distribution of the benefits as well as the burdens of research.
Title 45, Code of Federal Regulations, Part 46, Protection of Human Subjects

The Commission subsequently established a federal policy on human subjects which can be found in the Code of Federal Regulations, Title 45, Part 46, Protection of Human Subjects, hereafter referred to as 45 CFR 46.

Each institution must provide assurance that it will comply with the requirements set out in this policy. This regulation established a National Institute of Health, Office for Protection from Research Risks (OPRR), to oversee the institutions compliance with their assurance.

Each institution is required to establish an institutional review board (IRB) with at least five members, made up of individuals with a diversity of race, gender and cultural backgrounds. The IRB must also include at least one scientist and one non-scientist, and at least one member who is not affiliated with the institution. No member with a conflict of interest may participate.

The criteria for IRB approval of human research are: that the risks to the subjects are minimized, that the risks to subjects are reasonable in relation to anticipated benefits, that the selection of subjects is equitable, that informed consent is sought on each subject and appropriately documented, importantly, that there are adequate provisions for monitoring of data collected to ensure safety of the subjects, and that there are adequate provisions to protect the privacy of subjects and to maintain confidentiality of the data.

Certain requirements for the content of the informed consent were clearly spelled out in the regulation. These requirements are: that the informed consent include a statement that the study involves research and an explanation of its purposes, that the informed consent include a description of any reasonably foreseeable risks or discomfort, that it include a description of any reasonably expected benefit to the subject, and that a disclosure or appropriate alternative procedure be defined.

The informed consent must include a statement describing the extent to which confidentiality of the records will be maintained, a statement as to whether any medical treatments are available if injury occurs, an explanation as to whom to contact for answers to pertinent questions, and a statement that the participation is voluntary and that refusal to participate will involve no loss of benefits, such as continued care.

Thus, the research activity involving humans must be reviewed by a duly constituted IRB in order to assure rational scientific design and patient safety. The second important criterion is that patients may be involved in human research only under circumstances in which they are given adequate informed consent.

Data and Safety Monitoring Policy

As indicated in 45 CFR 46, one of the criteria for IRB approval is adequate provision for monitoring of data collection to ensure safety of subjects. The Data and Safety Monitoring Board was created in order to satisfy the federal regulation in regard to monitoring of clinical trials. Interim evaluations of Phase III cooperative group trials are necessary to monitor for extreme therapeutic results. Routine reporting of study conduct and toxicity, at six month intervals, is necessary to appraise the participating physicians of safety issues and to improve the quality of the study.
This allows all investigators involved in the recruitment of patients to a multi-institution clinical trial to review the toxicity experienced by patients from all institutions participating in the trial. This improves the safety of all patients involved.

Routine reporting of interim therapeutic results is unnecessary and detrimental to study quality because early separation of time-to-relapse curves is not convincing evidence of long-term remission or survival of the superior arm. Furthermore, the probability of a false positive result is greatly increased by allowing repeated testing at the 0.05 level at six month intervals.

An additional source of difficulty is that the presentation of interim therapeutic results can result in the study being stopped informally by investigators who conclude improperly that the early separation of time-to-relapse curves is convincing evidence of long-term remission or survival of the superior arm and, thus, stop registering patients to that clinical trial.

The membership of the Southwest Oncology Group Data and Safety Monitoring Committee includes one person from outside the Southwest Oncology Group, a physician and a statistician from the Cancer Therapy Evaluation Program (CTEP), or from the Division of Cancer Prevention and Control (DCPC) if a prevention trial is under consideration. The physician and statistician from the NCI are non-voting members. Group members who do not have a personal stake in the outcome of the clinical trial may be included as voting members as well, plus the Group's statistician, who is a non-voting member.

Certain members of the Group are excluded from membership in the Data and Safety Monitoring Committee. They are the Group Chair, the associate chair, any Phase III study coordinator, and the disease and discipline committee chairs. These individuals are considered to potentially have a personal stake in the outcome of the trial, are thus presumed in conflict of interest and, therefore, excluded from participation in the Data and Safety Monitoring Committee.

The Data and Safety Monitoring Committee meets in conjunction with each Southwest Oncology Group Meeting. The written status of each Phase III clinical trial will be provided to all committee members by the study statistician three weeks prior to each meeting. The study statistician will present the report to the members of the Data and Safety Monitoring Committee. The study coordinator may also be present at the presentation, upon request of the Committee. Following the presentation, a closed session of the Committee is held, including voting and non-voting members, and their recommendations are reported to the Group Chair. The deliberations of the Committee can be overturned only by the joint decision of the Chair of the Cooperative Group and the Director of CTEP at the NCI. No member of the Data and Safety Monitoring Committee can be in perceived or actual conflict of interest.

Conflict of Interest

Title 42, Code of Federal Regulations, Part 50, is a proposed set of rules dealing with objectivity in research. In this proposed regulation, investigators are required to disclose to an official, designated by the institution, or the Group, a listing of significant financial interests. The official will review these disclosures and determine the acceptability of the reported financial interests and act to protect Public Health Service (PHS) funded research from bias that is reasonably expected to arise from those interests.
The proposed regulations limit the disclosures that must be made to *significant financial interest*, any interest or monetary value exceeding a defined threshold of value ($5,000), or a percentage of ownership (5% or more) that would reasonably appear to directly and significantly affect the design, conduct or reporting of research funded by the PHS.

The proposed rules specifically state that the requirements constitute a condition of award and, as such, could be enforced through the suspension or termination of a grant or cooperative agreement.

*Significant financial interest* means anything of monetary value including, but not limited to: salary or other payments for services (e.g., consulting fees or honoraria), equity interests (e.g., stocks, stock options or other ownership interests), intellectual property rights (e.g., patents, copyrights and royalties from such rights).

*Significant financial interest does not include* income from seminars, lectures or teaching engagements sponsored by public or non-profit entities; income from service on advisory committees or review panels for public or non-profit entities; and financial interests in business enterprises if the value of such interests does not exceed $5,000 per annum in salary, fees or other continuing payments, or represent more than 5% ownership of any one enterprise, when aggregated, for the investigator, spouse and dependent children.

Each institution, or Group, must inform investigators of the policy and the investigator's reporting responsibility. Also, it must designate an official to solicit and review disclosure statements and ensure that the investigators have provided a listing of *significant financial interests* prior to the time a PHS application is submitted.

Each institution, or Group, must provide guidelines to identify *significant financial interests* and take actions to ensure that such financial interests will be managed, revised or eliminated. They must maintain records of financial disclosures and establish procedures for violation of financial conflict of interest policy.

Each institution, or Group, must certify, in each application for funding, that a written and enforced policy exists; that the institution has or has not found *significant financial interest* and certify, if found, actions taken to manage, reduce or eliminate the interest; and must make information available, upon request, to the Department of Health and Human Services, concerning all *significant financial interests* identified.

Management of a financial interest that could potentially bias a project may include recognition by the institution, or Group, that a potential conflict exists, and monitoring the progress of the research to ensure that financial interest does not bias the project.

Other approaches to the management of potential or actual conflicts of interest include: public disclosure, monitoring of the research by independent reviewers, modification of the research plan, disqualification from participation in all or a portion of the research, divestiture of significant financial interest, and finally, severance of relationships that create potential or actual conflicts of interest.
The Southwest Oncology Group was the first cooperative group to establish a Conflict of Interest Policy. This Policy Memorandum No. 35 was created in April 1991, and most recently revised in April 1994. It is the model which has been distributed to other cooperative groups for their emulation. The Conflict of Interest Policy is applicable to the Group Chair, associate chair, Executive Officers, statisticians, disease committee chairs, discipline committee chairs, all study coordinators, member of the Conflict of Interest Committee, members of the advisory boards, and members of the Data and Safety Monitoring Committee.

All applicable Group participants complete a Conflict of Interest Disclosure Form identifying "possible" or "potential" conflicts of interest. This disclosure is reviewed by the Group Chair to determine the acceptability of the information.

Following disclosure, potential conflicts of interest are entered into a memorandum on which the participant accepts responsibility for avoiding both potential and actual conflicts of interests by rescuing him/herself from discussions of issues relating to the identified potential conflict of interest(s). The applicable participants in the Southwest Oncology Group have all responded to such disclosure forms and have signed the memorandum committing themselves to avoiding potential or actual conflicts of interest.

**Fraud in Clinical Research**

1. **NSABP Problems**

In June 1990, NSABP discovered two identical operative reports on a patient from Montreal showing two different dates. One date made the patient eligible for the lumpectomy study and one ineligible. In September 1990, NSABP audited six additional charts and suspicions increased.

In January 1991, NSABP conducted a more thorough audit and additional cases were found. In February 1991, the suspected fraud was reported to the NCI and an immediate NCI and Office of Research (ORI) Integrity audit occurred. The ORI embargoed all discussion of potential fraud. In May 1991, Dr. Poisson admits data fabrication to the ORI and to the FDA. In July 1991, the NCI was told that the B-06 clinical trial results had not changed as a result of reanalysis of the data, expunging the Montreal data.

In March 1992, study B-06 was re-analyzed and presented to the ORI. Both the NCI and the ORI recommended republication of the re-analysis. In June 1993, the ORI reported audit results in *The Federal Register*. They had discovered 115 instances of fraudulent manipulation of data involving some 99 patients among 1,500 patients enrolled. NSABP was instructed to re-analyze the study and to republish the results. In February 1994, re-analysis was provided to the NCI for a review.

In March, CTEP, in a review of the NSABP Operations Office, discovered a September 1993 audit report indicating suspected fraud in another patient from a different Montreal hospital, registered on the Breast Cancer Prevention Trial. A crude cut-and-paste of a six-month old mammogram report was used to make the patient eligible.

CTEP audited the records of the second Montreal hospital in March 1994 and confirmed fraud. The ORI investigated the second investigator. Dr. Ron Herberman, Director of the Pittsburgh Cancer Institute, was appointed Interim Chair of the NSABP.
On March 31, 1994, there was an emergency meeting of the cooperative group chairs and on April 26, 1994 there was an emergency meeting of the division of cancer treatment, board of scientific counselors.

A series of deficiencies in NSABP operations including auditing and quality assurance were identified. There was failure to establish a required Data and Safety Monitoring Board in December 1992. There was suspension of all treatment trial audits in April 1993 because of the volume of work related to the Breast Cancer Prevention Trial. There was also failure to provide the NCI with requested audit schedules in 1993. Then there was a six month delay in reporting evidence of a second fraud case to the NCI in March 1994; a greater than six month delay in reporting a problem audit in New Orleans, and a failure to report audit results of the Prevention Trial for 1993 and 1994.

In regard to the St. Luc's fraud case, St. Luc's being the first Montreal hospital mentioned, NSABP failed to publish St. Luc's fraud case and re-analyses of important breast cancer trials. They failed to notify NSABP membership of fraud at St. Luc's Hospital. They failed to expunge St. Luc's data from the NSABP data files, and they failed to exclude St. Luc's data from publications. They also failed to re-analyze, and submit for publication, previously published major trials containing St. Luc's data.

2. *Scientific Misconduct*

This section addresses the new NCI Manual, Chapter 1303, Findings of Scientific Misconduct, dated May 12, 1994. Scientific misconduct means fabrication, falsification, plagiarism, or other practices that seriously deviate from those that are commonly accepted within the scientific community for proposing, conducting or reporting research. It does not include honest error or honest differences in interpretations or judgments of data.

The ORI is the PHS office empowered to accept the finding of scientific misconduct by an institution or conduct an investigation on their own into allegations of misconduct in science.

If the investigation of fraudulent activity involving a cooperative agreement indicates that the data and/or publications emanating from that research may be unreliable, then the whole project may be presumed to be tainted in the first and all future years from the point of misconduct. On that basis, financial recovery generally will be pursued for the full amount as permitted by law.

It is incumbent upon the authors and their employees to take remedial action to correct their own mistakes. It should be the policy of the NCI, as permitted by law or regulation, to assure notification of editors of journals where internal NCI or ORI analysis indicates retractions or corrections of previously published data may be necessary.

The names of the individuals guilty of fraud or misconduct are published in the NIH Guide for Grants and Contracts, in the Office of Research Integrity Newsletter, in *The Federal Register*, and in an "On-Line" alert list provided by the federal government.
Additional notifications include the Office of General Counsel of Health and Human Services, the NCI Executive Committee, the editor of the Journal of the National Cancer Institute, the Chief of the Grants Administration Branch, the Chief of the Research Contracts Branch, the Associate Director for Cancer Communications, the Director of the International Cancer Information Center, the legislative liaison at the NCI, and the Director of the Office of Technology Development at the NCI.

Additional actions include suspension and/or termination of the award, removal of the employee from involvement in any PHS-funded project, imposition of special conditions on award(s), recovery of funds spent on the project tainted by misconduct, the debarment of the investigator and/or institution, and notification of the FDA and the OPRR. (There has been considerable comment that the definition of scientific misconduct is far from clear.)

3. Southwest Oncology Group Audit Program

All Southwest Oncology Group institutions are at risk for audit at least once every three years and study centers are at an annual risk.

The institution is notified of the quality assurance audit verbally 30-60 days in advance. The Drug Accountability Report Forms (DARFs) are sent to the Operations Office six weeks prior to the audit; the case list is provided to the institution 10 working days in advance of the audit in order to allow the clinical records to be pulled for comparison with the research records.

The audit team includes Southwest Oncology Group investigator(s) and quality assurance representative(s) from the Operations Office. Also, observers from the Clinical Trials Monitoring System of the NCI attend a random 10% of audits (and more recently observe all audits). Also attending are observers from the Group Statistical Center and Operations Office.

The regulatory issues that occur at each quality assurance site visit deal with the IRB approval, consent forms, and the investigational drug accountability.

The IRB records are checked for initial and continuing approval of each protocol audited, any protocol changes, and any adverse drug reaction reports.

The patient must have signed an IRB-approved consent form that contains all the required elements, and it must have been signed prior to registration and treatment of the patient.

Investigational drug accountability involves a preaudit of the DARFs in the Operations Office, followed by an on-site review of the DARFs and a physical inventory of the drug(s) to verify quantity and lot numbers.

The second portion of the audit concerns compliance and accuracy. The patient's clinical record and the patient's research record are compared in regard to their compliance to the protocol, with specific attention to whether the data on the research record are clearly and accurately documented in the original clinical record.
Compliance and accuracy involve evaluation of patient eligibility and evaluability, treatment administration, response assessment, and laboratory and toxicity reporting. The quality assurance audit result is reported to the NCI and to the principal investigator.

Follow-up audit actions include: if the audit is acceptable, notification that the institution is to be put in the normal audit rotation. If the audit was unacceptable, a repeat on-site or off-site audit will be conducted, depending on the nature of the unacceptability.

The following steps are taken in instances of major problems identified at site visits: after requesting a written clarification, and following review of the case by the cooperative group and/or CTEP, appropriate measures will be applied if the original assessment is confirmed.

In instances of major problems, some of the potential options for action include a letter of warning, probationary status, suspension of patient entry privileges, and/or an immediate repeat site visit. Additional options for action include removal of access to investigational drugs and notification of the FDA if investigational drugs are involved. The FDA may also conduct its own investigation.

The following are actions that are taken only in instances of fraud or severe misconduct: immediate notification of the NCI and the ORI; the replacement of the principal investigator; termination of the grant or contract; reanalysis or retraction of published results and formal NIH investigation; debarment of the investigator from future participation in NIH clinical trials, and refunding of all prior grant support; and finally, notification to the university and/or hospital leadership or board, notification to county and state medical societies, and notification to the State Board of Medical Examiners.

Proposed Revised Terms of Award

These actions are all reflected in the proposed new terms of award which the headquarters, statistical center and the institutional cooperative agreement will be required to adhere. The terms of award are part of the award statement for the Group that is funded by the NCI. Acceptance of the award and its funding is contingent upon compliance with the terms of award.

The revised items of award mandate establishment of auditing timelines and guidelines. The routine audit reports must be submitted to the NCI within six weeks. In cases of serious data irregularities, the Clinical Trials Monitoring Branch, CTEP, must be notified within 24 hours.

In cases of scientific misconduct, the Group Operations Office must provide notification of the Group Data and Safety Monitoring Committee, the NCI, all collaborators, the IRB, and funding sponsors of the trial. The Group must also notify any journal involved and must perform a re-analysis of results after deleting falsified or suspect data within 90 days. It must also submit re-analyzed results to the original journal within 90 days; the NCI may distribute published reanalysis as broadly as deemed necessary. All data files shall be made available to the NCI upon request and the NCI retains the right to re-analyze data affected by scientific misconduct or data integrity or affecting patient safety.
The proposed revised terms of award require notification of all involved parties of any adverse drug reaction (not just the investigational new drug holder), immediate notification of the NCI project officer, responsibility of all participating investigators, and responsibility of headquarters to educate all participating investigators.

**CAUTIONS**

With respect to clinical research associates, I would caution you:

**DO NOT BE AN ACTIVE OR PASSIVE PARTICIPANT IN THE FALSIFICATION OF DATA!!!!**

**I WOULD ALSO CAUTION CLINICAL RESEARCH ASSOCIATES THAT IF ASKED TO FALSIFY DATA, YOU MAKE AN IMMEDIATE ANONYMOUS TELEPHONE CALL TO THE OPERATIONS OFFICE, 24 HOURS A DAY.**

210-677-8808

And finally, to any Southwest Oncology Group investigator:

**DO NOT EVEN THINK ABOUT FALSIFYING SOUTHWEST ONCOLOGY GROUP DATA!!!!**

**IF YOU DO, YOU ARE IN FOR A WORLD OF HURT!!!!!**

**Affirmation of Integrity**

Finally, we will be asking each individual that comes in contact with Southwest Oncology Group research data to sign an Affirmation of Integrity (refer to last page) thereby making a commitment to protect the principles outlined here.

**Summary**

This discussion of the ethical principles of the conduct of clinical trials is designed to share with all members of the Southwest Oncology Group the basic principles, rules and regulations which undergird the conduct of human research, and which are the steps that are critical to help re-establish public confidence in the NCI-supported clinical trials. I have reviewed the Belmont Report, OPRR Regulations for the Protection of Human Research Subjects, the justification and function of the Data and Safety Monitoring Committee, as well as policies for identifying and avoiding potential conflicts of interest. I then reviewed the problems identified in the NSABP clinical trials program, defined scientific misconduct and the consequences of its discovery and verification. I reviewed the Southwest Oncology Group audit program, designed, in part, to detect scientific misconduct, as well as the procedures designed to act upon such findings. As a result of these events, there has been proposed a revision of the terms of award that put the responsibility on the institution, Group, and its investigators.
I trust that this discussion on *Ethics in the Conduct of Clinical Research* will help you to understand the principles, rules and regulations that guide the use of human subjects in clinical research. Hopefully, your understanding of these issues will allow the Southwest Oncology Group to maintain its reputation as an organization that has respect for persons, beneficence and justice in our research activities. With your help we will be able to re-establish public confidence in our research.
References:

1. The Belmont Report, Ethical Principle Guidelines For The Protection Of Human Subjects In Research, as Revised April 18, 1979.


5. Southwest Oncology Group Policy Memorandum No. 35, Conflict Of Interest Policy (Revised April 1994).


SOUTHWEST ONCOLOGY GROUP

AFFIRMATION OF INTEGRITY

IN THE SUBMISSION OF CLINICAL TRIAL

RESEARCH DATA

In signing this document, I affirm my awareness of and compliance with the policies of the Southwest Oncology Group relating to the submission of falsified data and other scientific misconduct.

1. I recognize that the clinical research of the Cooperative Groups is a publicly supported endeavor that is critically dependent upon the trust of the American people. Submission of falsified data is scientifically abhorrent and can destroy the public trust that is necessary for successful clinical research.

2. I recognize that the penalty for submission of falsified data by myself or by others from my institution may include: inability of myself or my institution to participate in Cooperative Group activities, and repayment by my institution of National Cancer Institute funds that had been used in collecting and submitting the falsified data.

3. If I suspect falsified data submission from my institution or other Group members, I understand that Group Policy #41 requires that I make an immediate telephone call, which may be anonymous, to the Headquarters Office, 24 hours a day at:

   734-998-7173

(Signature)  (Date)

(Name – Please Print)

(Institution)