Investigational Trials of Anticancer Drugs: Establishing Safeguards for Experimentation

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Synopsis

The National Cancer Institute since 1955 has been charged with responsibility for discovering new anticancer agents and bringing them to clinical trial. These activities are carried out by NCI's Developmental Therapeutics Program, which has established systems for discovery, experimental testing, bulk synthesis, formulation, and toxicological testing of candidate drugs, and by the Cancer Therapy Evaluation Program, which conducts initial trials to establish safe doses of new agents and to determine their utility in treating specific forms of cancer. These clinical trials are conducted both at NCI in Bethesda, Md., and at selected cancer centers throughout the United States.

This paper describes the safeguards that NCI has built into the clinical trials system in the past decade—safeguards that ensure the safety of patients and the accuracy of data collected and at the same time allow efficient testing of each promising new agent in the fight against cancer. Recent improvements in cancer survival leave little doubt that patients are indeed benefiting from extensive efforts to discover and develop new drugs for cancer treatment.

FOR THE PAST 29 YEARS, The National Cancer Institute (NCI) has assumed primary responsibility for the discovery and development of anticancer drugs in the United States. Because of the toxic nature of these drugs, the formidable scientific challenge of finding new agents, and their high development cost, few private pharmaceutical firms have been willing to establish major efforts in this area, although private investment in this endeavor has significantly increased in the past 2 years because of recent successes with cancer chemotherapy.

Nonetheless, NCI since 1955 has been charged with the responsibility for discovering new agents and bringing them to clinical trial. These activities are now carried out by NCI's Developmental Therapeutics Program, which has established systems for discovery, experimental testing, bulk synthesis, formulation, and toxicological testing of candidate drugs, and by the Cancer Therapy Evaluation Program, which conducts initial trials to establish safe doses of new agents (Phase I) and to determine their utility in treating specific forms of cancer (Phase II and Phase III) (*1,2*). These clinical trials are carried out both at NCI in Bethesda, Md., and at selected cancer centers throughout the United States.

In this paper, we will describe the safeguards that have been built into the clinical trials system in the past decade to ensure the safety of patients and the accuracy of data collected. These safeguards represent a unique system for monitoring clinical researchers—a system that relies upon both peer review and oversight by the sponsoring agency, NCI.

Background

To understand the factors that led to institution of the monitoring of clinical trials in cancer drug research, it is necessary to know something about the impact of drug discovery and development on cancer treatment between 1955 and 1974, because it was during that period that drugs first proved effective in producing remissions, and in some cases cures, of advanced cancer.

Those early years were primarily devoted to establishing the critical elements of a drug development system. Particular attention was paid to the hypothesis that screening of candidate compounds against murine leukemias (L1210 and P388) could identify new agents with value against human tumors. The number of agents screened for antitumor activity reached a peak of 44,000 in 1974 and led to the identification of 6–10 new drugs per year. These drugs were in turn submitted for clinical trials in patients.

Eleven drugs discovered and/or developed by NCI achieved commercial status as a result of the initial two

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decades of experience in drug development (table). Most of these new drugs were active against hematological malignancies but not against solid tumors. On the basis of these results, the screening system for new compounds was altered radically in the 1970s. Murine solid tumors and human tumor xenografts in nude mice were added to the antitumor screening system in 1976, and in 1979 efforts were begun to test compounds in a human tumor colony forming system, in the hope that these new approaches would identify compounds active against solid tumors (*2–3*). A number of compounds not recognized by the murine leukemias P388 and L1210 have been identified by these new screens, but their clinical activity has not been completely evaluated.

A second major change instituted in the past 3 years was to reduce the number of new compounds tested to 10,000 (*4*). This was done through a computer-based analysis of structure that made it possible to eliminate those compounds that lacked promising molecular features or that duplicated previously tested compounds (*5*).

In parallel with the growing scientific information base for drug development, major strides were made in the period from 1955 to 1974 in demonstrating the ability of drugs to produce remissions in patients with cancer. According to trials conducted in the 1960s, more than 50 percent of patients with acute lymphocytic leukemia of childhood, Hodgkin's disease, and choriocarcinoma could be cured with drugs. A number of other tumors, such as breast cancer, other forms of acute leukemia and lymphoma, and testicular carcinoma, were found to be highly responsive to drugs in these early trials.

This demonstration of effectiveness led to a rapidly growing interest, on the part of medical researchers and clinicians, in the new field of medical oncology, which was first recognized as a medical subspecialty in 1973. The new oncologists were trained in the methods of conducting drug trials during their fellowship programs. They accepted the use of investigational agents as a routine part of the practice of oncology, particularly for patients who had failed conventional therapy, and created a growing demand for drugs under development by NCI.

Before 1974, regulation of the use of these agents had been relatively informal. A practitioner could obtain drugs for specific clinical use simply by placing a written request with NCI, but the side effects and effectiveness of these trials were not routinely reported back to the Institute or to the Food and Drug Administration, the agency ultimately responsible for monitoring the safety of new drug trials.

As sponsor of investigational new drug applications, or "INDs," the NCI was responsible for ensuring safety of patients and accurate reporting of the results of clinical trials to the FDA; however, the widespread use of investigational anticancer drugs, most of which had potent myelosuppressive toxicity as well as other side effects, clearly threatened to escape effective control by NCI or, in turn, FDA. At this point, it was necessary for both agencies to face the following issues:

- Were patients being fully informed about the possible toxicities and the relatively low probability of benefit from treatment during Phase I and early Phase II clinical trials?
- Were the drugs being used by investigators qualified to study their toxicity and beneficial effects, and were adverse reactions being accurately reported to the IND sponsor, NCI, and by NCI to FDA?
- Were clinical investigators accurately reporting the results of their trials to NCI and to the scientific community at large?

Commercial anticancer drugs discovered or developed by the National Cancer Institute

Drug	*Discovery*	*Development*	*Antitumor activity*	*Commercial use approved by FDA*[1]
Pipobroman	NCI	NCI	Lymphomas, leukemia	1966
Hydroxyurea	NCI	NCI	Leukemia	1967
Cytosine arabinoside	Upjohn	NCI	Leukemia	1969
Mithramycin	NCI	NCI	Testicular cancer	1970
o,p'-DDD	NCI	NCI	Adrenal cancer	1970
DTIC	NCI	NCI	Lymphomas, melanoma	1975
CCNU	NCI	NCI	Lymphomas, colon cancer, brain tumors	1976
BCNU	NCI	NCI	Lymphomas, colon cancer, brain tumors	1977
L-asparaginase	Cornell	NCI	Leukemia	1978
Cisplatin	Michigan State	NCI	Testicular cancer	1978
Streptozotocin	NCI	NCI	Islet cell carcinoma	1982

[1] Food and Drug Administration.

- Did NCI's drug development systems provide reasonable protection against the entry of inappropriately toxic drugs into clinical trial, and was the initial entry at a safe dose?
- Were investigational drugs supplied by NCI being used for approved protocols?

In 1974, when the program for trials of new agents was in its major phase of growth, NCI staff recognized the need for new policies and procedures to ensure the safety of patients, to control the distribution of experimental drugs, and to promote improved communication among investigators, the NCI, and the FDA.

In 1975, NCI and FDA officials began regular meetings to discuss matters of policy and regulation. In 1976, representatives of the two agencies signed a "Memorandum of Understanding" that described the mutual goals of NCI and FDA in facilitating the development of new cancer drugs within FDA regulatory requirements. Specifically, NCI agreed to establish, maintain, and periodically update a Drug Master File with the FDA's Bureau of Drugs. This file describes the overall NCI plan for anticancer drug development and the Institute's systems for clinical monitoring, drug distribution, and drug reporting; contains the names of NCI-approved investigators; and includes other essential elements in the drug development process.

Another important measure, initiated in 1977, helped NCI control the level of distribution of anticancer drugs. A formal drug distribution system was developed that has provided the foundation for the current system. Before that time, experimental drugs were available to all physicians, who could use them without rigorous NCI review of specific protocols and without having to report results back to the Institute.

The new plan established a three-tier system for distribution of NCI investigational drugs, based on the drugs' level of antitumor activity and the status of clinical information on toxicity. It also established clear restrictions on the distribution and use of these agents. Fundamentally, drugs are divided into the following three groups:

Group A. These agents are in the initial stages of testing (Phase I and early Phase II clinical trials); their clinical toxicity and safe dosage are undergoing evaluation and have not been established. Distribution of these drugs is limited to carefully selected clinical researchers, who must seek prior approval from NCI for their treatment protocols and must report all results to the Institute.

Group B. These drugs have an established safe schedule of administration, but the level of clinical antitumor activity has not been established for specific cancers in definitive studies of specific tumor types. Distribution of this group of drugs includes more than 3,000 investigators in the peer-reviewed clinical cooperative research groups and the cancer centers. Again, all results must be reported to NCI.

Group C. When clear antitumor efficacy against specific cancers has been established, drugs are reclassified, with FDA concurrence, as Group C for those tumor types. It is expected that commercial marketing of these drugs will be approved in the future by FDA. Group C drugs can be distributed for treatment of individual patients not in research trials and can be made available to any physicians qualified to use anticancer drugs.

Clinical Trials Monitoring

In 1976, the Master File included a plan for monitoring Phase I and Phase II clinical investigators. This system of monitoring consisted of presentation of Phase I data at meetings attended by NCI and FDA staff and review by NCI staff of Phase II and Phase III protocols from cooperative groups and cancer centers. The system was underpinned by a policy that made successful peer review mandatory.

In order to verify that NCI-sponsored studies of new drugs were being conducted within a framework of adequate patient protection and were providing accurate research data, the Institute in 1979 initiated an expanded system of onsite review of clinical trials within the Eastern Cooperative Oncology Group. This system was called "site visit monitoring" because it entailed an onsite examination of research records and patients' records by a team of outside reviewers.

In 1980, the monitoring of Phase I trials was expanded to include onsite inspection of all Phase I research groups supported by NCI. In 1982, in anticipation of new FDA requirements for clinical trials monitoring, the site visit procedures were standardized throughout the 14 clinical cooperative groups supported by NCI, and each funded investigator was notified that he or she would be visited at least once every 3 years on a random basis.

Each investigator is at risk of being site-visited during any given year and may be site-visited more than once during the 3-year period. We do not know at this time that this frequency constitutes an "adequate" level of monitoring, but we expect to make an informed decision about the frequency of site visits on the basis of the findings from the site visits currently being performed.

Critical elements reviewed during these site visits include approval of protocols by local institutional review boards, procedures for handling and accounting for investigational drugs, and audit of randomly selected cases. Each audited case is checked to ensure that a valid

consent form was signed, that the research record is an accurate reflection of the primary medical record, and that all relevant information about eligibility, treatment, and adverse effects has been included in the research record.

Between June 1982 and June 1983, 228 site visits were conducted. Two instances of serious infractions were found, each case involving inaccurate reporting of research results. In both instances, the responsible investigators were suspended from the clinical trials group and their investigational drug privileges were revoked. NCI and FDA staff attended a site visit in each instance to audit the records in question and reported their findings to the FDA. The Office for Protection from Research Risks, National Institutes of Health, was notified in the one instance in which problems were found regarding informed consent violations. In the one case in which the investigator was receiving research support, funding has been suspended pending final action.

In addition, specific guidelines have been established by NCI for affiliation of subsidiary investigators (or satellites) with a cooperative group and for supervision of the affiliates by the parent group. Each must have its protocols reviewed by an appropriate institutional review board, and its performance must be monitored as part of the site visit process. NCI further expanded its clinical trials monitoring in July 1983 to include all investigators at cancer centers, holders of clinical research grants, and investigators who recently had been awarded grants in the new Community Clinical Oncology Program, as part of an overall plan to standardize site visit procedures.

Adverse Drug Reactions

Antitumor drugs often have unpleasant side effects, such as nausea or loss of hair, that are expected and are not considered adverse reactions in the normal sense. Other reactions to the drugs may be life threatening. The challenge to the physician is to recognize and separate the unusual and potentially serious adverse reactions from side effects that are expected or symptoms that are part of the disease process.

Physicians involved in the evaluation of new agents must be careful to balance the risk of side effects and the benefits of antitumor activity, without overemphasizing the side effects. For example, there was little initial enthusiasm for clinical trials of cisplatin because of its renal toxicity; however, dramatic responses were subsequently observed in patients with advanced testicular cancer. Testicular cancer—the leading cause of deaths from cancer among young men—is now curable in 98 percent of patients with localized disease and in more than 70 percent of patients with widespread metastases. This dramatic improvement in cure rates has occurred within the past 5 years and is directly related to use of cisplatin in combination with other agents effective against this disease.

Because of increasing use of cancer drugs nationwide by a growing number of physicians, NCI has further refined and simplified its system for reporting potential adverse reactions. To facilitate rapid reporting of untoward reactions, the Institute has established a 24-hour hotline so that investigators can report all serious reactions immediately. All such reports, written or oral, are reviewed within 24 hours by an NCI staff monitor, who immediately reports serious, unexpected reactions to the FDA. The monitor then further evaluates the situation and makes a complete written report to FDA within 30 days of first receipt of the investigator's notification. (All serious reactions, such as heart and kidney toxicity, are reported in writing within 15 days.) Investigators in NCI's clinical trials system are notified of any serious new adverse reactions as quickly as possible through a mass mailing from the Institute.

In addition to the review of each reported reaction by the individual drug monitors, reports are reviewed a second time at a regular monthly meeting of a committee of NCI staff. This group, known as the Adverse Drug Reaction Committee, is currently headed by one of the authors (R.W.).

The committee carefully examines each reported reaction and determines its probable relationship to the experimental drug. Committee members determine whether further actions, such as notification of investigators and amendment of consent forms, are needed. In 1982, NCI mailed 23 such notifications of adverse reactions to investigators. Copies of these warning letters routinely go to the FDA. In addition, in regular meetings with Phase I and Phase II investigators, NCI staff have continued to emphasize the importance of prompt reporting of all adverse reactions and, through site visits, have evaluated the investigators' promptness in reporting reactions. The adverse drug reaction guidelines are revised annually and are sent to all investigators.

Informed Consent

Another important issue is the adequacy of informed consent procedures associated with cancer drug trials. Informed consent procedures were first required by the Public Health Service in 1966, but FDA and Department of Health and Human Services (HHS) guidelines for these procedures have undergone considerable change since that time, most recently in 1981.

To ensure compliance with new FDA and HHS regulations regarding the informed consent process, NCI in September 1982 instituted a policy of systematic review of the informed consent forms accompanying each sub-

mitted protocol, in order to verify that each includes the elements required by regulation. The scientific review of each protocol is accompanied by a review of the consent document, and these documents are sent to the investigator. As previously noted, examination of patients' records for the presence of valid informed consent forms is performed during site visits.

Accountability for Drugs

The widespread use of anticancer drugs is the major factor responsible for the decrease in mortality from cancer in patients below 45 years of age. However, this widespread use presents NCI staff with problems regarding accountability for drugs.

In the past, investigators receiving experimental drugs from NCI occasionally used these agents for patients who were not participants in approved drug trials. At times, drug supplies were used by investigators other than the investigator of record. A system for recording the receipt and distribution of drugs, with use specified on a patient-by-patient basis, was required to establish accountability.

New accounting systems were developed by NCI over a 3-year period and in 1982 underwent 3 months of pilot-testing and evaluation at six major cancer research centers in the United States. The new system was formally implemented nationwide in January 1983.

All NCI-sponsored clinical investigators are now required to record the receipt and distribution of NCI-supplied investigational agents. These drug logs are reviewed as an integral part of the site visit process, to ensure that drug supplies are being used only by approved investigators and only for approved protocols.

Risks and Benefits

Despite the complexity of the process of drug development and the considerable information transfer required, we believe that NCI's present systems for conducting investigational drug trials provide every reasonable protection for patients and at the same time allow efficient testing of each promising new agent in the fight against cancer. But are the risks and toxicities that attend Phase I trials of new drugs balanced by the benefits of discovering effective new treatments?

The pace of drug discovery, while admittedly slow, nonetheless continues to provide concrete improvements in cancer treatment. In the past 3 years, clinical trials of the following active agents have yielded positive results:

- m-AMSA, in acute leukemia and lymphoma (*6*);
- mitoxantrone, in breast cancer (*7*);
- aziridinyl benzoquinone (AZQ), in brain tumors (*8*);
- VP-16, in lymphomas, testicular cancer, and lung cancer (*9–10*); and
- deoxycoformycin, in lymphocytic malignancies (*11*).

In addition, agents developed for the treatment of cancer find other valuable uses—for example, the stimulation of fetal hemoglobin synthesis by 5-azacytidine in patients with sickle cell anemia and beta-thalassemia (*12*). Many of these agents have been licensed by pharmaceutical firms and will be commercially available in the near future.

Cancer drug development continues to have a strong impact on cancer patient survival, as revealed in recent data from the NCI Survival, Epidemiology, and End Results survey of cancer registries, which covers 12 percent of the U.S. population. According to 1980 data, 5-year survival of cancer patients nationally has risen to 48 percent, compared with 41 percent in 1973 (*13*). Patients with Hodgkin's disease, testicular cancer, ovarian cancer, and diffuse non-Hodgkin's lymphoma experienced a 30 percent or greater decrease in mortality in the 10 years from 1969 to 1979.

These improvements can only be explained by the introduction of effective drug treatments for patients with advanced disease. Thus, there is little doubt that patients are indeed benefiting from the extensive efforts to discover and develop new drugs for cancer treatment. With the recent changes in the clinical trials apparatus outlined in this paper, we feel confident that clinical trials of new agents are being conducted in the safest possible setting.

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Nitrosamines in Bacon: a Case Study of Balancing Risks

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Synopsis

Nitrite has been used for centuries to preserve, color, and flavor meat. Today, about 10 billion pounds of cured meat products are produced annually, accounting for some one-tenth of the American food supply. Regulators became concerned about the safety of using nitrite in the early 1960s when studies showed the presence of carcinogenic nitrosamines in cured meat products. In the early 1970s, a study at the Massachusetts Institute of Technology implicated nitrite itself as a carcinogen. As studies have raised concern over the safety of nitrite, regulators have had to weigh the potential risk from cancer against nitrite's proven role in protecting consumers from deadly food poisoning bacteria.

Today there is little scientific support for the theory that nitrite is a direct carcinogen. To deal with the nitrosamine problem, the U.S. Department of Agriculture (USDA) lowered the permissible amount of nitrite in cured meats to that level considered necessary for botulism protection. Regulators, however, found it necessary to take additional steps with bacon because nitrosamines were found consistently in fried bacon samples. In addition to lowering the amount of nitrite that could be added to "pumped bacon" (cured by injecting liquid curing agents in the pork belly), USDA required the addition of nitrosamine inhibiters and began an intensive monitoring program in processing plants to ensure that fried bacon did not contain confirmable nitrosamines. The cooperative effort between Government and industry resulted in the virtual elimination of confirmable nitrosamines in pumped bacon by 1980.

USDA is continuing its efforts to reduce nitrite in meats wherever possible. It is involved in active research programs in the Federal Government, academia, and industry.

THE USE OF NITRITE TO CURE MEAT dates back thousands of years. Every year, about 10 billion pounds of meat products are cured with nitrite. These products—including such traditional items as bacon, ham, and hot dogs and other sausages—account for about one-tenth of the American food supply.

Nitrite serves an important function in addition to coloring and flavoring the meat. It inhibits the growth of *Clostridium botulinum* spores and the formation of its toxin. The toxin causes botulism, a rare but often fatal form of food poisoning.

Responsibility for regulating nitrite is divided between the Food Safety and Inspection Service of the U.S. Department of Agriculture (USDA) and the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services. Acting under authority of the Federal Meat Inspection Act, USDA formally approved the addition of nitrite to meats as a curing agent in