NCI Cooperative Research and Development Agreements

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The Cancer Therapy Evaluation Program (CTEP) of the National Cancer Institute (NCI) currently sponsors more than 160 Investigational New Drug applications

Introduction

The Cancer Therapy Evaluation Program (CTEP) of the National Cancer Institute (NCI) Division of Cancer Treatment and Diagnoses sponsors approximately 160 Investigational New Drug applications (INDs), and is involved in approximately 1,600 active protocols. It reviews about 500 new protocols and enrolls more than 33,000 patients annually into ongoing studies. The CTEP has over 9,900 registered investigators, works with approximately 2,000 institutions, and presently, is involved in more than 50 collaborative agreements with pharmaceutical companies.

The therapeutic agents being studied in these programs are developed at the NCI, funded by NCI grants, and submitted by universities, other academic or research institutions, or pharmaceutical companies. The CTEP is involved currently in the domestic development program for oxaliplatin (Eloxatin).

Cooperative Research and Development Agreements and Clinical Trials Agreements

Collaboration between the NCI and institutions or pharmaceutical companies occurs through cooperative research and development agreements (CRADAs) and clinical trials agreements (CTAs). These differ in important respects. Clinical trials agreements are most appropriate for collaboration when the collaborator has a strong patent position, has completed the preclinical studies and IND-directed toxicology required for IND filing, and is supplying only the formulated agent to be used in the clinical study protocols (with no further development of the agent being intended). Clinical trials agreements are not covered by congressional legislation, and no funding is provided for their execution. For rapid implementation, these agreements can be approved and signed by a divisional director at the NCI.

In contrast, a CRADA is a detailed agreement between the NCI and a pharmaceutical company for the co-development of an agent that stipulates terms for a much broader scope of research, usually encompassing preclinical development. Cooperative research and development agreements were created by congressional legislation as a result of the Federal Technology Transfer Act. Their implementation requires National Institutes of Health (NIH) subcommittee review and approval, and their execution allows the NIH to receive financial support for research from the collaborator.

Characteristics of CRADAs

Many potential advantages are associated with collaborating with the CTEP in the development of promising investigational agents, including regulatory expertise. The NCI has been involved in studies that have led to more than 60% of the current indications for cancer for all agents licensed by the US Food and Drug Administration (FDA).

Other advantages include the ability to evaluate investigational anticancer agents in a wide variety of tumor types and disease settings and to expedite trials through the extensive Cooperative Groups clinical trials networks. In this evaluation process, all data on a particular agent are made available exclusively to the NCI collaborator for the agent.

During the application process, either the NCI or the collaborator can submit the initial IND. A filed IND may cross-reference an IND or master file held by the NCI or collaborator. All information in the
NCI IND is shared fully with the collaborator, and manufacturing data can be held confidential.

**Protocol Development**

The activity of the CTEP in the collaboration with the pharmaceutical company begins with discussions of the development plans for the investigational agent, including an exchange of information about sponsored studies. Thereafter, the CTEP is active in developing protocols, monitoring studies, and providing the pharmaceutical company with access to data. Protocol development is typically initiated by receipt of a protocol letter of intent from an investigator to perform a particular study, or by requests from the CTEP for protocol letters of intent. Proposals are reviewed by the CTEP Protocol Review Committee and sent to the pharmaceutical company with an invitation to provide comments, after which a consensus review is performed by the NCI. The final CTEP-approved protocol with all amendments is subsequently forwarded to the pharmaceutical company at the time of submission to the FDA.

In its role as an IND sponsor, the CTEP attends pre-IND meetings, writes and files INDs, monitors adverse drug reactions, submits annual progress reports for each clinical trial sponsored under an IND, sends revisions to FDA letters and phone inquiries, and participates in joint NCI/FDA-sponsored conferences. With regard to study monitoring, the CTEP assumes responsibility for monitoring and reporting to the FDA. For pivotal trials, special arrangements can be made between the NCI and a pharmaceutical sponsor to permit additional or complementary sponsor auditing.

**Guidelines for NCI-Sponsored Trials**

The general guidelines for NCI-sponsored trials are as follows. The NCI oversees a drug master file for the standard procedure involved in clinical trials of investigational agents. It reviews and approves all protocols and is responsible for ensuring that all investigators adhere to the protocol and FDA regulations. It also ensures confidentiality of data and that applicable transfer limitations per the CRADA are observed. Issues regarding ownership of investigator data and intellectual property are written into the agreement. The NCI is responsible for ensuring that such agreements are enforced. Any access to trial data is provided by the NCI and the collaborating company (or companies).

**Issues Raised by Pharmaceutical Companies**

The general issues raised by pharmaceutical companies regarding NCI-sponsored trials include patent rights, publication procedures, data rights, timely access to data, and control of the development of an investigational agent. Patent rights usually arise in the context of the use of patents filed by an individual investigator who has developed a particular method of administering an agent or combination of agents. The NCI policy permits modification of the funding agreement with an "Intellectual Property Option to Collaborator" statement. This offers the right of first negotiation to the company supplying the investigational agent in cases in which an invention using that agent arises.

With regard to NCI publications, the collaborator(s) is given 30 days to review manuscripts prior to submission to ensure that no confidential or proprietary information is released; an additional 30 days for review can be requested in cases in which patent filings are involved. No editorial comments on manuscripts are accepted.

**Clinical Trials Data**

Clinical trials data that are generated in NCI-sponsored trials are made available exclusively to the NCI, the FDA, and the collaborator. The NCI is currently implementing a new informatics system designed to improve the speed with which data are made available to collaborators. At present, approximately 98% of data requested by the CTEP from collaborators are available within 3 to 4 weeks of each quarterly due date; continual improvements are expected in the time required for data collection and availability.
The CTEP is also implementing applications that will allow electronic filing of adverse event data to the NCI, and in turn, to the FDA, as well as electronic protocol submission to the NCI of standard formats of phase I, II, and III trials. As noted, there is joint control of development, with the development process of the investigational agent being a collaborative and natural effort between the NCI and the pharmaceutical company.

**Collaboration Requirements**

A number of documents detailing the requirements for collaborations in addition to providing information on collaborations are available to collaborators (or potential collaborators). One provides sections of standard language required in any NCI-sponsored protocol covering issues such as access of new investigational agents to women and minorities, filing of regulatory information, and investigators’ responsibilities in conducting the study and handling data and potential publications.

The "Terms of Award Option to Collaborator" document is in the funding agreement of all institutions involved in clinical trials of investigational agents. The "Sponsored Research Agreement" document outlines the basic procedures for investigators collaborating directly with the pharmaceutical company and provides language that does not conflict with NCI funding agreements. Finally, the "Collaborative Clinical Development of Investigational Anticancer Agents With the NCI" document is a notebook that contains detailed information on the Cancer Therapy Evaluation Program model agreements, and other documents pertinent to successful collaboration with the NCI.

**Oxaliplatin Studies Under the CRADA Program**

The NCI is currently participating in a number of clinical studies of oxaliplatin, a new cytotoxic agent from the diaminocyclohexane platinum family. Further information on the oxaliplatin clinical trials sponsored under the CRADA agreement are listed and described on the following websites: [http://cancertrials.nci.nih.gov/](http://cancertrials.nci.nih.gov/) and [http://cancernet.nci.nih.gov/](http://cancernet.nci.nih.gov/).

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