

# ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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## The National Cancer Institute's Experimental Therapeutics Clinical Trials Network



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### **H&O** What is the purpose of the Experimental Therapeutics Clinical Trials Network (ETCTN)?

**SPI** The purpose of the ETCTN is to perform early-phase clinical trials using investigational drugs. The National Cancer Institute (NCI) participates in the development of these drugs and holds their Investigational New Drug (IND) application. This program is grant funded, with 13 grants awarded to 29 investigators at sites across the United States. The recent redesign of the ETCTN involves using multiple investigators across many institutions to develop and perform single clinical trials, in order to meet the demands of the rapidly changing and expanding field of drug development.

### **H&O** Could you give some historical context for the ETCTN?

**SPI** The NCI has had some type of experimental therapeutics program since the late 1950s. The details of this program have changed and evolved over time, but the program has existed for many years as a grant-funded program. The ETCTN was recently transformed to adapt to the changes in drug development that have occurred in the last 7 to 10 years. It has become increasingly obvious to us that single or "siloe" institutions are no longer able to perform large clinical trials. In many instances, patients are selected based on a specific biomarker or molecular characteristic even in early-phase clinical trials. Thus, no single institution would

have enough patients to accrue and complete a study in a reasonable period of time (ie, approximately 1-1.5 years). We therefore needed some kind of network to obtain a national catchment area for the clinical trials, rather than a small regional area. Another factor that influenced this decision was the need for specialized expertise, because close to 100% of the trials through the ETCTN are biomarker-driven studies. The institutions needed the ability to perform tumor biopsies in order to understand the drug's effect on the molecular target, its mechanism of action, and/or whether the patient develops resistance to therapy.

### **H&O** What are the primary goals of the ETCTN?

**SPI** Our primary objectives are: (1) to perform research and development for new cancer treatments; (2) to focus on tumor characterization and biomarker development; (3) to enhance our understanding of cancer biology contemporaneously with the conduct of the clinical trial; and (4) to educate and train young investigators in clinical cancer research and early-phase therapeutic studies. This final objective is perhaps the most important.

### **H&O** How are the investigators chosen?

**SPI** Every 5 years, we release a request for applications in a funding opportunity announcement. The submissions undergo a peer-reviewed grant assessment that is conducted by the National Institutes of Health (NIH) and

the NCI. We have a relatively steady group of investigators who have been with us for many years—some for more than 30 years. Every 5 years, we also identify 1 or 2 new sites to incorporate into the program that may not have been working with us directly.

In order to choose the investigators, we examine how they described their program, their skill, their experience, their track record with early-phase trials, and their ability to do cutting-edge experimental therapeutics research. The investigators and institutions are specifically chosen based on their ability to meet the primary goals and objectives of the ETCTN.

### **H&O** How do the clinical trials designed by the ETCTN differ from other trials?

**SPI** The physical structure of the clinical trial is not different. The real difference is that we have the opportunity to work with the best academic investigators in clinical therapeutics across the United States. This makes the ETCTN a very academic program, and allows our clinical trials to be driven by basic science, proof of principle, and mechanism of action.

A relatively large number of clinical trials are performed by the pharmaceutical industry. In general, their approach is to get a drug to market in the most expeditious way possible. If they are successful, their studies eventually will lead to a change in the standard of care. Our approaches and goals are similar, but we also examine new indications for drugs and focus on identifying rare tumors or rare subgroups of patients who may also benefit from an investigational therapy. Our goal is to change practice and standard of care broadly across the United States.

### **H&O** What support do investigators receive from the NCI, in addition to the monetary grant?

**SPI** First, we provide a Web-based system for protocol development, design, and reporting. This recent addition is particularly important for our network-based system, because the transfer of data between multiple sites within a single study is common. This data sharing system allows sites all over the country to enter their data in a reasonable time frame. The principal investigator and statisticians for the study can access data through the Web-based portal at any time, which makes it easier to perform network-based clinical trials. In addition, the system made it easier for us to track the development of adverse events and toxicities.

We also have implemented a central Institutional Review Board (CIRB) for both protocol review and amendment review. Each site relinquishes to the CIRB the responsibility for being the IRB of record for the study. Therefore, any time a study is changed or modified,

it only requires one IRB review rather than separate reviews for each participating institution, which would entail massive amounts of iterative change and take many months. The CIRB drastically decreases the administrative burden of work. Although we have only used it for a short time, the new system has streamlined work for a lot of our investigators.

### **H&O** What challenges do you expect for the program?

**SPI** I think there are a number of challenges. First, even though some of our investigators have had successful collaborations with colleagues at other institutions, most of them were very used to working as a single institution. The challenge is to have investigators view each of the studies as a network study rather than their own study, even if they are leading it. The second challenge is that we recently moved from an investigator-centric development process to a team-based development process, which has necessitated a relatively steep learning curve for all of us.

### **H&O** Could you describe this team-based development process?

**SPI** When we first bring a new drug into the NCI through the Experimental Therapeutics Program (NExT), we set up an internal project team. This team discusses the preliminary development of the drug using expertise from across the NIH and NCI, along with some additional basic science investigators. When we have that preliminary plan, we then create a project team for the drug based on short applications submitted by our investigators.

The project team has 3 components: clinical researchers, translational researchers, and basic science researchers. These investigators work together to begin defining the best initial development plan for the new drug at the NCI. In this group, they determine how the clinical trials should be designed, which trials should be done first, which diseases should be evaluated, which biomarkers are the most appropriate for patient selection and monitoring, and how to identify those biomarkers.

The final plan, usually consisting of 3 to 5 clinical trials, is presented to the Investigational Drug Steering Committee, an external group with some degree of oversight for the program. This committee reviews and critiques the team's general plan for the initial drug development. After that process is complete, we ask the clinical leads of the project team to submit a letter of intent to perform the study.

Using a team-based development process is beneficial in multiple ways. In the past, we identified new trials by providing our investigators with descriptions of possible

projects, and we would get 75 to 100 letters of intent to perform those studies. Very consistently over the last 20 years, we approved approximately 30% of those applications, meaning that the investigators put in weeks of work to write a 20- to 100-page letter of intent with a 70% failure rate. With this new system, the application requires less effort and the chance of approval is more than 90%.

Another great aspect of this setup is the deliberate involvement of young investigators, which is the fourth goal of the ETCTN. Out of 20 studies, all but one included a “cradle investigator” (ie, someone less than 7 years out of fellowship) as a project leader. These young investigators come in with a mentor, propose the trial, and lead the study.

Although we have gone through the team-based process with only 3 groups so far, I think we have been quite successful. We have not done enough to say definitively that this process is the best, but there has been an enormous amount of participant buy-in. I think that our investigators have enjoyed working closely with a group of their peers, because they were often working alone in the past. They also have enjoyed the interaction with others outside of their expertise. Although I currently do not have enough data to declare that this process will be successful, I think that we are absolutely headed in the right direction.

### **H&O** What are the challenges with this team-based development approach?

**SPI** The major problem is that, at academic institutions, promotion and tenure for a professor is based on grant funding and successful peer-reviewed research, which is an individual contribution. Almost every academic institution affirms the importance of participating in team science, and some of the greatest advances—mainly in physics and similar fields—have come from team science. However, the medical profession is still very tied to individual researchers. Therefore, for the team-based approach to be successful academically, it must be clear what each individual contributed. We are very conscious of this challenge, and we make sure to clearly define what each team member has contributed and how much merit that contribution has.

### **H&O** What progress has been made in the newly designed ETCTN so far?

**SPI** Most of the grant recipients are approximately 9 months into their program. During this time, the investigators’ main task has been to learn to use the Web-based portal. One year prior to the start of this grant cycle, we developed and tested our protocol-building and monitoring tool known as Medidata Rave. We have built 15 protocols, so we now have a number of open protocols that are

utilizing the system, and I think that is going reasonably well. Additionally, we have implemented 5 clinical trials since the grants were awarded, which is a little less than one every other month.

We have also set up a formal system to test the success of the ETCTN’s new design. Using an NCI/NIH internal grant, we have developed 2 different systems to review and evaluate network functionality for the ETCTN. It will examine the acceptability of the new process, so at the end of 3 years, we should be able to define whether we made greater than incremental gains and improvements in our clinical trials process.

### **H&O** How do you define success for the ETCTN?

**SPI** If we identify new research potential, perform practice-changing clinical trials, and have our trials lead to practice-changing phase 3 investigations, then we can declare our operation very successful. If we can achieve these goals, I think the ETCTN will warrant future funding.

### **Suggested Reading**

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