Cooperative Group Trials in the Community Setting

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Over the last 40 years the National Cancer Institute (NCI) has created a vibrant public-private partnership for the implementation of NCI-sponsored cooperative group (Network) clinical trials throughout the United States and Canada. Over these four decades, the cancer clinical trials process has become more complex more precise and more resource intensive. During this same time period, financial resources to support the NCI community research initiative have become more constrained. The newest manifestation of NCI-sponsored community based cancer clinical trial research, known as the National Community Oncology Research Program (NCORP) began initial operation August 1, 2014. We describe several key strategies that community sites may use to not only be successful but to thrive in this new financially austere research environment.
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Over the last 40+ years the National Cancer Institute (NCI) has endeavored to build a clinical trial delivery system that accesses broad and diverse patient populations from across the country. These efforts initially began as limited proof of principle demonstration projects. In 1978 the Cooperative Group Oncology Program (CGOP) was begun to evaluate community hospitals' ability to participate in NCI-sponsored clinical trials. In 1981 the Community Hospital Oncology Program (CHOP) was instituted to assist community hospitals adoption of management guidelines in cancer treatment. The first request for applications (RFA) for the Community Clinical Oncology Program (CCOP) was announced in 1983, with grants initially awarded in 1984. Over the following 30 years, the program grew and matured, becoming a key contributor to NCI-supported cooperative group clinical trials. Numerous studies of the CCOP demonstrated that the data collection and quality was excellent, and that trial adherence was equal to that measured at academic medical centers.[1,2] The CCOP became a powerful vector for the diffusion of new knowledge throughout the medical oncology community. In 1990 the NCI-sponsored the related Minority-Based CCOP (MB-CCOP) initiative. M-B CCOPs were required to serve underserved and minority populations, and were created to help increase clinical trial participation in these groups that had been underrepresented in clinical trial accrual historically. Although similar in many ways to the CCOP program, M-B CCOPs could have primary academic medical center affiliations. The M-B CCOPs were a great success and minority accrual to clinical trials significantly improved as a direct result of this new initiative.

In the 1990s the NCI, through the Cooperative Group Program, embarked on a broad chemoprevention initiative. Four large national chemoprevention studies were launched and completed on schedule. These large chemoprevention trials were successful because of robust recruitment from CCOPs and MB-CCOPs. At the end of the decade, after enormous NCI investment, chemoprevention to reduce cancer morbidity had shown only modest success. Unfortunately, the positive lessons learned from these studies have only been moderately adopted by primary care providers. These large chemoprevention trials amassed a treasure trove of biospecimens that were annotated to real clinical outcomes. The basic science investigation using this data to study oncogenesis and disease evolution is only now underway.

In spite of the CCOP, MB-CCCOP, and other clinical trials programs, only between 2% and 7% of

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adults with cancer participate in NCI-sponsored clinical trials reducing the application of advances to the general population. Added to this fact is the problem of underrepresented populations in NCI-funded clinical trials. These populations include African-American men, Hispanics, Pacific Islanders and Asian, American Indians/Alaskan Natives, adults 65 years of age and older, individuals living in rural areas and those of low socioeconomic status.[3,4] This latter problem decreases the opportunity for discovering both preventive and treatment successes that could be relevant to a particular underrepresented population.[5,6] In a publication in 2007 by Meropol et al[7,8] barriers to participation in treatment trials were summarized among oncologists in the state of Pennsylvania. Eligible patients in this survey report were adults at least 18 years of age with cancer who were undergoing follow up by a medical oncologist in the state. There were 137 oncologists and 170 patients who completed the survey. It was noted that 84% of patients were aware of clinical trials. In addition, both the patients and oncologists agreed that clinical trials were important to improve cancer treatment. In reviewing potential barriers to clinical trials, the two most common issues mentioned were random assignment and fear of receiving a placebo. These barriers were related by both patients and the medical oncologists. However, patients themselves identified fear of adverse side effects whereas oncologists ranked this issue as of least importance to their patients. CCOPs across the country addressed this shortcoming with a variety of strategies.

For example, one program, the Delaware Christiana CCOP, was very successful in improving clinical trial accrual. The Delaware Christiana CCOP was initially funded in 1987. Accrual to NCI clinical trials from the associated Cancer Center was 9.9%, but it reached 23.1% in 2013. There are several reasons for this dramatic increase in clinical trial accrual over the time period, which represents five to six times the national accrual average to NCI clinical trials. These include the establishment of multidisciplinary disease site centers and placing clinical research nurses in the private practice offices of the oncologists.

Interestingly, despite the improvement in clinical trials accrual, an administrative team identified a core of physicians participating in the Cancer Program whose track record to NCI clinical trial accrual was particularly poor, despite the fact more than 100 clinical trials were available for their patients, covering most major disease sites, and having available infrastructure support to help in recruitment. These individuals were designated members of the NCI Cooperative Groups and several had membership in cooperative groups prominently featured on their curriculum vitaes. Analysis suggested there was inequity in the system, in that the same recognition (clinical trial investigator) and resources were given regardless of whether said individual recruited one or two patients per year or 20 to 30 patients over that same time period.

Therefore, in 2008, the Helen F. Graham Cancer Center & Research Institute put into place specific criteria to define a clinical trials investigator who participates in NCI-sponsored clinical trials,[3] which had also been done by the Southeast CCOP. Although the Christianna CCOP criteria differed from those used by the Southeast CCOP, the successful model encouraged other physician practices involved in NCI clinical trials to establish criteria in their own environments for defining a clinical trials investigator participating in NCI adult clinical trials. The goals of establishing clinical physician investigator performance standards were to increase annual accrual per physician investigator, to increase the overall accrual to the Community Clinical Oncology Program, and to improve quality of research monitored by internal audits. Specifically, the following physician investigator performance standards were established in 2008:

1. Clinical trials investigators are required to recruit to NCI clinical trials a minimum of four patient accruals per calendar year.
2. Clinical trials investigators are strongly encouraged to attend a minimum of one NCI Cooperative Group or Community Clinical Oncology Program research-based meeting every other year.
3. If four patients per calendar year are not accrued, the physician will lose his/her clinical trials investigator status, but will be expected to continue to submit follow-up data on all patients as required. The following requirements must be met for reinstatement as a clinical trial investigator:
   a. A 1-year waiting period
   b. A letter of intent from the investigator to the principal investigator of the Community Clinical Oncology Program stating renewed interest in research participation
   c. Completion of the NCI membership application with a membership fee of $500.00
   d. Attendance at an NCI Cooperative Group or research-based meeting
4. All investigators will undergo a medical records internal audit as part of preparation for NCI Cooperative Group site visits. These internal audits are to be performed monthly by the Medical Director of the Cancer Program and the