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.
Semin Oncol 42:686-692

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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Conflicts of interest: none.
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0093-7754/ - see front matter

http://dx.doi.org/10.1053/j.seminoncol.2015.07.011

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

Principal Investigator of the Community Clinical Oncology Program or an extramural auditor.

This program was started in 2008. In 2007, 17 of 25 investigators had met the minimum standards. This left 8 investigators at risk in 2008. However, in 2008 six of the eight investigators exceeded the minimum performance standard requirements. The annual average accrual increase for these six investigators increased from 0.75 patients to six patients. The average accrual for all investigators was 14 patients. However, in 2008, two investigators did not meet the performance standards, and their clinical trials investigator status was dropped. In 2009, 25 of 29 investigators achieved the minimum accrual performance standards. One investigator did not meet the performance standards and lost his clinical trials investigator status. Three investigators were allowed a 90-day probation in 2010 to accrue two patients out of the four minimum accrual standards, and this was successful. This 90-day probationary period was added to the clinical trials performance standards in view of the fact that there were circumstances where a specific disease site clinical trial was not available or the investigator fell short of the minimum standard by one patient. In 2009, the 25 active investigators averaged eight patients accrued. Lastly, there were four internal audits over the 2-year period, which resulted in a decline of major deviations with no major deviations in the fourth audit late in 2009. In conclusion, the clinical physician investigator minimum performance standard can successfully be implemented resulting in increased quantity and quality of trial activity and with a minimum dropout rate of underperformers.

In 2014, the challenges for community cancer research have changed again. With relatively less funding coupled with an explosion in new molecularly driven initiatives, the NCI has focused on smaller phase II treatment and chemoprevention trials, many of which incorporate the study of biomarkers. This typically adds significant complexity to a trial. For example, a patient may, after consent, undergo an additional biopsy with the fresh tumor tissue required before starting therapy. In trials testing an intervention to reduce the risk of developing cancer, the impact of the intervention on a biomarker (eg, breast density) may act as a surrogate marker for risk reduction. Such studies can more quickly determine if there is a signal present suggesting that the intervention may work on a larger scale, but these smaller studies are done much faster and at dramatically less cost to the NCI. However, the impact of these new studies at ground level means that there is much more physician and clinical research associate work performed for each patient accrued.

RECENT INITIATIVES

Over the last decade the NCI also launched a different community research initiative, known as the National Community Cancer Centers Program (NCCCP). NCCCP was based in large community hospitals that had annual cancer incidence in excess of 1,000 new cases per year. The program was intended to become a delivery model, with cancer care administered by multidisciplinary teams supported by patient navigators that would reduce system inefficiencies while lowering cultural barriers to clinical trial participation. The program was well resourced, and an early evaluation confirmed that many sites had achieved the goal of increased multidisciplinary care.

In 2010 following the release of the Institute of Medicine's alarming report entitled "A National Cancer Clinical Trials System for the 21st Century: Reinvigorating the NCI Cooperative Group Program," the NCI embarked to redesign the cancer clinical trial system. The report highlighted many inefficiencies and redundancies in the current system and provided a roadmap for changing the system to a more modern, flexible and faster national research enterprise. As part of this transformation, the NCI combined the CCOP, Minority-based CCOP, and NCCCP systems into one new enterprise, the National Community Oncology Research Program (NCORP). Applications for this new system were received in January 2014 and initial funding of seven new NCORP science research bases, 34 community sites given monies for accrual and infrastructure, and seven new community minority/underserved sites commenced August 1, 2014. In addition to the creation of the NCORP, the NCI has also re-aligned academic medical centers, cancer centers, and other cancer research organizations into the National Cancer Treatment Network (NCTN), also turning the former Cooperative Groups into Network Groups. This new organizational structure allows for the first time accurate measurement of all NCI-sponsored cancer clinical trial activities. NCORP sites will function as main members of the NCTN and will be the primary conduit of clinical trials out to the community, where 85% of Americans receive their cancer care.

NCI's Community Oncology Research Program (NCORP), is a community-based national network designed to provide access to state-of-the-art multicenter clinical trials in treatment and imaging, prevention, cancer control, health-related quality of life, and screening and in cancer care delivery research studies. The five NCTN Groups and two cancer centers are required and challenged to develop questions in a new era of cancer research that are clinically relevant. While sustaining the legacies of successful clinical trials accrual in community

settings, engaging investigators in the process of implementing scientific advances in the general public, and building infrastructures for research across the continuum of cancer care, NCORP represents oncology practices that are adapting to a dynamic health care environment. NCORP is composed of integrated systems in which oncology specialists are in proximity to primarily care services; systems composed of primarily oncology practices from hospital acquisitions; large distributed practices; and, small single oncology practices. Collectively, the network includes over 800 components and subcomponents for cancer care throughout the country. This large and diverse network also broadens access to individuals at risk of cancer in primary care settings.

NEW AND EXISTING CHALLENGES TO COMMUNITY RESEARCHERS

Investigators in the community setting are being forced to re-evaluate their practices, staffing, workloads for staff, and the management of NCI-supported clinical research in the new era of genomically driven medicine. To meet the needs of future cancer research, community sites will also need to consider the following:

- Engagement of disciplines (eg, surgery, pathology) to ensure that biospecimens are processed appropriately and available to meet the time-lines for interpretation that are imposed by trial designs.
- Ways to partner with NCORP NCTN and Cancer Center Research Bases in the planning of research questions that are feasible and in which their participation will improve the uptake of evidence-based advances in care and the quality of care for patients.
- Strategies to produce appropriate accrual rates for diverse organizations and populations.
- Requirements for participating investigators that support the overall goals of providing broad access to NCI-supported clinical research.
- Strategies to successfully engage the participation of an increasing number of minority and underserved populations that are rapidly changing the demographics in NCORP catchment areas.

New areas of interest in clinical trials include mechanistic approaches in studies to ameliorate treatment-related toxicities and cancer and host symptoms. NCORP has the expertise to develop concepts to determine the most effective surveillance modalities for cancer patients treated for curative intent. NCORP is also a resource for studies evaluating the over diagnosis of cancers in several disease sites (Figure 1).

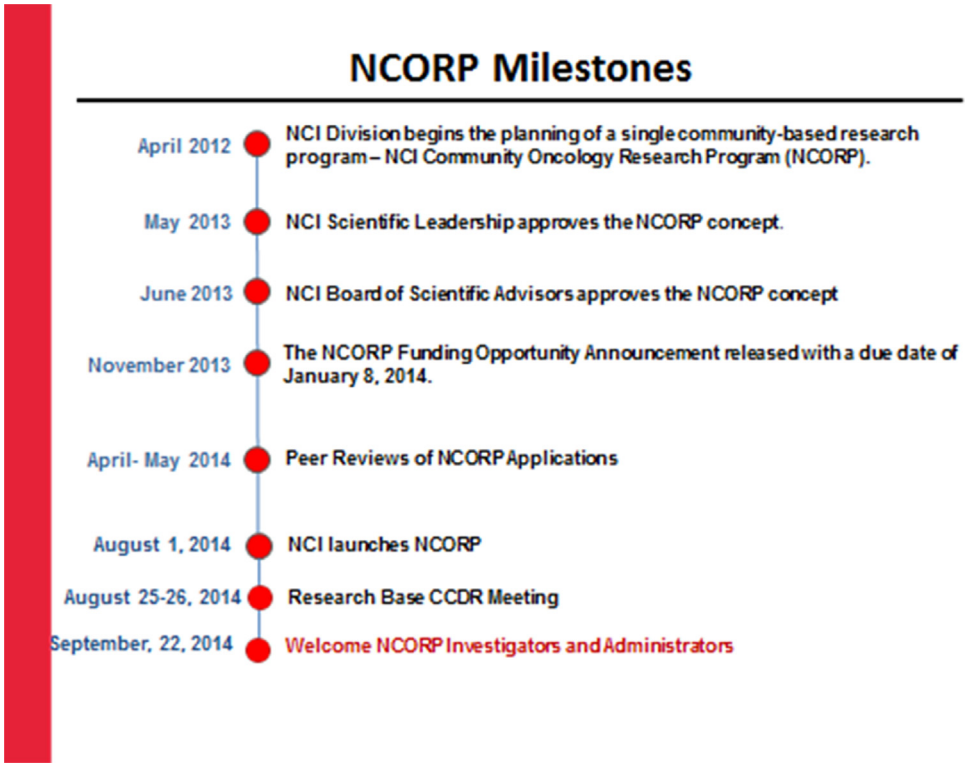

Figure 1. NCORP milestones.

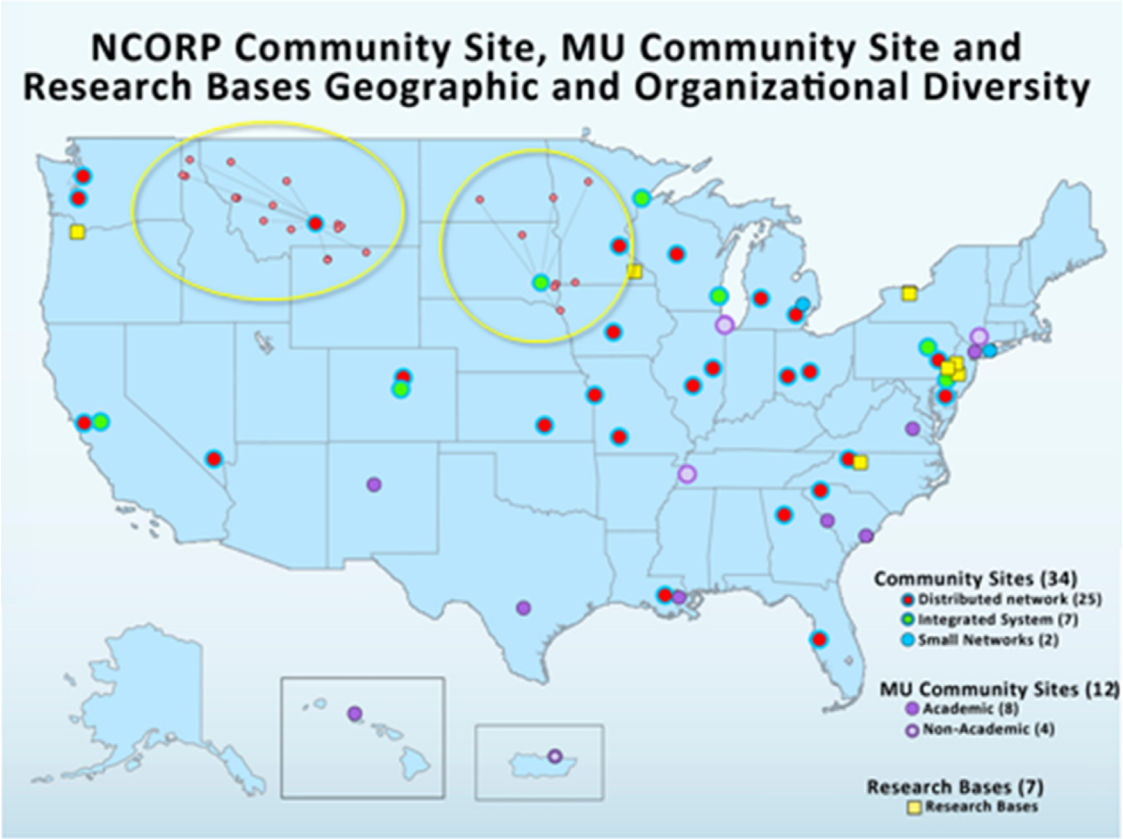

Figure 2. NCORP community site, MU community site, and research bases geographic and organizational diversity.

CANCER CARE DELIVERY RESEARCH

The means by which cancer care is delivered in the community setting is an expanded component of research in NCORP. The delivery of cancer care in the United States is often fragmented, resulting in an urgent need for evidence on how national policies and other care organizations influence patient outcomes and disparities in care. Cancer care delivery research within NCORP is defined as a multidisciplinary field of scientific investigation that studies how social factors, financing systems, organizational structures and processes, health technologies, provider and individual behaviors affect cancer outcomes including access to cancer care, quality and cost of cancer care, and ultimately the health and well-being of cancer patients. Importantly, its focus includes individuals, families, organizations, institutions, providers, communities, populations, and their interactions (Figure 2).

Over the past few years, community investigators have identified challenges faced by reimbursement for trials, hospital acquisitions, and the uncertainties about how their organizations will accommodate the new generation of clinical trials and cancer related research. NCORP Research Bases have proposed their CCDR priority areas for the program and the Community and Minority/Underserved Sites have identified at least one component to participate in cancer care delivery research studies. CCDR studies will include three major categories of studies: descriptive observational studies to capture prevalence and variability of cancer care delivery models and approaches; analytical observational studies to understand how the patient, provider, and organizational characteristics of cancer care delivery models influence quality, outcomes and access; and, intervention studies to test new models an approaches to improve quality, outcomes, and access. It is expected that this area of research will mimic the process of community input into study design that has been characteristic of the process used historically in clinical trials between academic and the community investigators. As the infrastructure is assessed and developed within the community sites, the most important CCDR questions are identified as feasible within the NCORP, and the management and peer review organizational structures are formalized, NCORP will be well poised to engage all of its stakeholders in the development of a successful CCDR program. As NCI supports research in clinical trials that are expected to result in clinically meaningful and practice changing outcomes, CCDR studies must also be designed to be practice changing in

design, structure, content, or processes of cancer practices at the provider, practice, system, or policy levels.

NCORP provides an opportunity, as a network of "real world" practices and investigators to evaluate the influence of the current health care system on the successful conduct and implementation of a new era of research and to be at the helm of research that is designed to ensure equitable cancer care for all populations. NCORP sites are charged with continuing their traditional participation in NCI-sponsored treatment and cancer control, prevention and health related quality of life research studies. The clinical trials agenda includes screening and post-treatment surveillance.

A RECIPE FOR SUCCESS?

Successful NCORP sites must excel in three broad areas: efficiency, engagement, and execution. NCORP sites must fulfill their responsibilities with modest financial resources. It is imperative that each program (investigators and administive staff) carefully review its procedures and work flow processes, and reduce as much as possible redundancies and inefficiencies in their operations. In the Midwest, the Heartland NCORP is undergoing such a review. Heartland NCORP is the result of the merger of three historically strong CCOPs; Heartland CCOP of St. Louis, Central Illinois CCOP, and the Illinois CancerCare CCOP of Peoria. Heartland NCORP is one of the larger NCORP sites. Its service area covers three quarters of both Illinois and Missouri and also draws patients from Kentucky, Tennessee, and Arkansas. Its service area has a population of over 7 million and includes 120 counties. Many of its 140 investigators serve both larger cancer centers in metropolitan areas as well as in rural small clinics in many small towns. The logistics of bringing NCI-approved cancer clinical trials to all these areas is a challenge. Operational issues include opening studies in regions served by different Investigational Review Boards (IRBs), making sure that all study documents are up to date, insuring that local clinical research associates are trained on all new studies opened, that standard policies and procedures are in place to track all study-related investigational agents, and that the protocols are followed correctly and that the data is collected and submitted on time. In the year-long planning process to develop the Heartland NCORP, all administrative tasks of the three programs were identified and distributed using a virtual "central office" model. This model assigned key functions to staff at key offices throughout the organization.

Heartland NCORP learned of its grant award August 1, 2014. It held its first implementation meeting in mid-August. It is fortunate to have the strong backing of several hospital systems and the Illinois CancerCare Foundation of Peoria to help cover the costs that exceed the NCORP grant award. It is also fortunate to have a team of very experienced administrators from the three historic programs who are dedicated to making Heartland NCORP a success. It became clear that there must be only one consent and one IRB approval for each protocol for the system. To reach that goal, the administrative team met with seven regional IRBs. All agreed to accept the NCI Central IRB for studies covered under their assurance and the Decatur Memorial Hospital IRB for all other clinical trials that were not reviewed by the NCI CIRB. Next, all Heartland components agreed to use the web-based protocol posting site CREATE developed by the Central Illinois CCOP. The CREATE website, funded by an American Society of Clinical Oncology (ASCO) Conquer Cancer Foundation Community Oncology Research Grant, hosts all approved studies plus all supporting documents including the most recent version of the consent form. This allows one-site uploading and maintenance for all approved studies. Finally, all components will utilize a uniform protocol tracking system to maintain up to date information on when data is due for each step in every study. These changes should make Heartland NCORP more efficient. It is hoped that each year a thorough self-exam will help Heartland NCORP continue to function more efficiently, even with fewer resources.

Additionally, the Heartland NCORP utilizes a distributive local leadership model to bring the research program in to every practice. Heartland NCORP has designated a regional sub-Principal Investigator (sub-PI) for its main component and sub-component sites. The Heartland NCORP PI and the regional sub-PIs hold a weekly teleconference to review accrual data and to select new studies. New protocols are evaluated by their appropriateness for the patient population, the complexity and data management requirements, and a determination of whether the study overlaps or competes with protocols already open. The discussion leads to consensus from all participants. Newly approved protocols are presented weekly, raising awareness of new studies immediately after open. In addition to protocol presentations, each weekly meeting reviews accrual progress to date, both for the local physicians as well as for the entire network. This way all investigators are continuously exposed to the accrual performance of their peers and the progress to the annual accrual goal, with attention to one of the primary barriers to clinical trial participation, the lack participation by the treating cancer specialist.[2]

The Heartland NCORP, like the Delaware NCORP, has a minimum accrual participation level that is an annual requirement for ongoing participation. Medical Oncology/Hematology investigators are required to place at least three patients on a clinical trial every year. All other investigators, ie, surgeons and radiation oncologists, are required to place at least one patient on a clinical trial every year. All investigators see each week how they and their colleagues are progressing, which creates an increased sense of engagement for all physicians across the network. In addition, Heartland NCORP will continue the tradition of at least one annual meeting of all investigators to meet one Saturday in winter. This annual retreat facilitates a review of the protocol menu, a sharing of successful accrual strategies, and a problem solving meeting to address specific protocol implementation problems that can occasionally arise. So far, this approach has been quite successful and Heartland NCORP accrual is ahead of its annual projection, with accrual coming from a broad segment of the physician membership.

CONCLUSIONS

The NCORP program will succeed only if the protocols are followed and all the data are reported accurately, which should be possible, given that the CCOPs all demonstrated excellent data quality and protocol compliance. Each site must also stress accuracy, clarity, and adherence for every patient accrued to a study. Clinical research associates (CRAs) must be very familiar with the nuances of each new study to which he or she registers and enrolls patients. That task is made more challenging because the larger NCORP sites will have a very wide protocol menu, which also leads to greater accrual.[3] NCORP sites will need to strengthen internal quality control and data quality oversight mechanisms to meet this increased workload level. Physician investigators will also need a higher level of familiarity of each protocol they utilize. As CCOPs, MB-CCOPs, NCCCPs, and new organizations come together to create NCORP, their success in implementing modern NCTN trials will be assured if each organization spends some time on these three important themes; efficiency, engagement, and execution. In the future clinical trials will become more complex and heavily biomarker-driven, ie, the Lung MAP Trial. If every new NCORP succeeds in these three basic areas, this newest version of NCI-sponsored community clinical trials will become a resounding success.

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