Original Contribution

Early-Phase Clinical Trials In The Community: Results From the National Cancer Institute Community Cancer Centers Program Early-Phase Working Group Baseline Assessment

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Abstract

Purpose: The National Cancer Institute (NCI) Community Cancer Centers Program (NCCCP) formed an Early-Phase Working Group to facilitate site participation in early-phase (EP) trials. The Working Group conducted a baseline assessment (BA) to describe the sites' EP trial infrastructure and its association with accrual.

Methods: EP accrual and infrastructure data for the sites were obtained for July 2010-June 2011 and 2010, respectively. Sites with EP accrual rates at or above the median were considered high-accruing sites. Analyses were performed to identify site characteristics associated with higher accrual onto EP trials.

Results: Twenty-seven of the 30 NCCCP sites participated. The median number of EP trials open per site over the course of July 2010-June 2011 was 19. Median EP accrual per site was 14 patients in 1 year. Approximately half of the EP trials were Cooperative Group; most were phase II. Except for having a higher number of EP trials open ($P = .04$), high-accruing sites (n = 14) did not differ significantly from low-accruing sites (n = 13) in terms of any single site characteristic. High-accruing sites did have shorter institutional review board (IRB) turnaround time by 20 days, and were almost three times as likely to be a lead Community Clinical Oncology Program site (small sample size may have prevented statistical significance). Most sites had at least basic EP trial infrastructure.

Conclusion: Community cancer centers are capable of conducting EP trials. Infrastructure and collaborations are critical components of success. This assessment provides useful information for implementing EP trials in the community.

Introduction

The National Cancer Institute (NCI) Community Cancer Centers Program (NCCCP) is a network of community cancer centers that strives to expand cancer research capacity and deliver advanced care in the community.[1-2] The program was launched in 2007 as a 3-year pilot forming a public-private partnership with 16 community hospitals. In 2010, American Recovery and Reinvestment Act (ARRA) funding enabled the NCI to expand the network to a total of 30 sites.

One of the goals of the NCCCP is to increase capacity for community cancer centers to participate in early-phase (EP) clinical trials (phases I-II) so that patients with cancer do not have to routinely seek opportunities for trial participation outside of their communities. The benefits of achieving such a goal include the ability to offer more treatment options closer to home as well as to help contribute accrual to important trials, as the majority (~85%) of patients with cancer are treated in community settings.[3] Indeed, approximately 65% of patients entered onto NCI Cooperative Group trials are enrolled from community-based practices, such as the NCI Community Clinical Oncology Program (CCOP) and academic medical center affiliates.[4]

Sites did have to satisfy certain baseline performance requirements for entering the NCCCP. For example, sites had to have accrued at least 25 patients per year for the last 3 years to any phase of treatment, prevention, or cancer control trial.

NCCCP sites ranged in their level of experience in EP trials, from sites just embarking on building their EP trial programs, to sites already experienced in EP trials. Two NCCCP projects, supported by American Recovery and Reinvestment Act funding, were specifically geared towards increasing NCCCP involvement in EP clinical trials, one via NCCCP site infrastructure development, and the other via NCCCP site collaborations with NCI-designated cancer centers.

In 2010, the NCCCP, through its Clinical Trials Subcommittee, formed an Early-Phase Working Group (EPWG) to collaborate on expanding efforts to implement EP clinical trials among its member sites. Membership was open to any interested NCCCP site. A range of clinical trialists from a majority of NCCCP sites participated in the EPWG, including site investigators, participating physicians, research nurses, clinical research associates/coordinators, and NCI clinical trial advisors.

Major objectives of the EPWG were to assess the NCCCP sites' EP clinical trials infrastructure by conducting a baseline assessment (BA) to determine how that infrastructure was associated with EP accrual, and to exchange best practices to help expand sites' ability to offer and/or better refer to EP trials. This article describes the results from the assessment.

Methods

Information about each NCCCP site's EP trial infrastructure and performance formed the BA and was gathered from a variety of sources, including site progress reports, existing NCI trials databases, and a questionnaire developed by the EPWG. The time period covered was primarily 2010 for the infrastructure assessment and July 2010-June 2011 for EP trial performance. To determine which data items to include in the BA, literature was reviewed and expert opinion sought, including criteria used by seasoned academic EP investigators to evaluate site capability for participating in multicenter EP trials.[5-11]

Analyses were performed to identify site characteristics associated with higher accrual into EP trials. EP accrual rate per site was calculated as EP accrual per 1,000 new analytic cases seen in a year. High-accruing sites were defined as sites with an EP accrual rate at or above the median. Mann-Whitney and Fisher's exact tests were used to compare continuous and categorical variables, respectively, among subgroups.

Results

Twenty-seven of the 30 sites completed the BA. These sites cared for approximately 56,000 new patients annually and had a substantial population of rural and racial/ethnic minority patients (Table 1). Three sites did not respond to the BA, providing the following reasons: not yet participating in EP trials (two sites) and lack of time (one site).

Infrastructure

Infrastructure characteristics of NCCCP sites are summarized in Table 1. Almost all responding sites reported having at least some basic infrastructure elements for EP trials, such as the capacity for handling biospecimens and pharmacokinetic/pharmacodynamic studies, as well as a pharmacy experienced in the handling of investigational agents. Twenty-four of the 27 sites responded that they had the capability to perform an additional biopsy for trials requiring them, with two of these noting they had a limited ability to do so.

Staff roles identified across the sites included those of investigator, physician assistant/nurse practitioner, research nurse, clinical research associate (CRA)/coordinator (CRC), data manager, biospecimen technician, oncology research pharmacist, and regulatory coordinator. Most sites (89%) had at least one person who performed CRA/CRC and/or research nurse duties for EP trials at least part-time. A minority of sites reported use of nurse or patient navigators and quality assurance personnel specifically for EP trials.

Sites found it challenging to quantify staffing focused only on EP trials in granular ways (eg, "data management"), as staff performed multiple, overlapping roles across different types and phases of studies as well as duties related to standard care. Many individual personnel fulfilled more than one role, such as CRCs also performing the roles of data manager, regulatory coordinator, and/or research nurse, and research nurses also being responsible for regulatory coordination and/or quality assurance, to name a few examples.

Twenty sites provided information about the funding sources for their EP trials. The largest funding source was NCI and other federal support, followed by industry. Hospital, philanthropic, and cancer center funding accounted for much smaller percentages of funding. Across sites, these last three categories, which represent "self-funding" by the sponsoring institution, comprised approximately one third of total funding.

Regulatory Committees

Most (n = 23; 85%) sites used a local institutional review board (IRB). More than half of these sites (n = 12) also used at least one external IRB. Four sites used external IRBs solely, either a non-NCI central or regional IRB, or another institution's IRB. Local IRB protocol turnaround time (median, 45 days) was generally slower compared to both non-NCI central/regional IRB (median of 21 days) and NCI central IRB (median, 7 days; used by three sites), but faster than external institution IRB (median, 70 days). Eight sites (30%) used an institutional biosafety committee.

External Collaborations

All sites reported membership in NCI's Clinical Trials Cooperative Group Program (Cooperative Groups; Table 1). A majority (70%) participated in EP trials through the Cancer Trials Support Unit (CTSU), and half participated in EP trials via the NCI CCOPs. Cooperative Group, NCI-designated cancer center, and industry-sponsored EP trials were available in 93%, 48%, and 81% of sites, respectively.

EP Trial Features

Across sites, there were 291 unique EP trials open over the course of the BA period, with a median of 19 trials per site

Table 1. Site Characteristics: National Cancer Institute Community Cancer Centers Program*

Site Characteristics (N = 27)	Median	Range
Annual analytic cases	1,871	526-3,585
Population		
Urban	71%	0-100
Rural	29%	0-100
Race/ethnicity		
White	81%	25-97
African American	8%	<1-52
Asian	2%	0-54
Hawaiian/Pacific Islander	0%	0-18
American Indian/Alaska Native	0%	0-2
Hispanic/Latino	5%	0-52
Data management		
Electronic medical record	70%	
Clinical data management systems	81%	
Electronic data capture	100%	
Infrastructure, percentage of sites		
Biopsy: additional biopsy capability	89%	
Clinical research unit (for any type of trial, including cancer)	19%	
Freezer: −80°C to −20°C freezer for specimens	89%	
Freezer: standard freezer for specimens	100%	
PK/PD capability	85%	
Pharmacy with experience with investigational agents	100%	
Radiation therapy on site	96%	
Refrigerator for specimens	100%	
Specific inpatient accommodations for clinical trials (eg, dedicated beds)	33%	
Specimens: capacity to collect, handle, and send	100%	
Staffing†		
Regulatory		
Institutional review board turnaround time, days	45	7-71
Institutional biosafety committee utilized, percentage of sites	30%	
Trial sponsors, percentage of sites		
Sites with Cooperative Group EP trials open	93%	
Sites with industry EP trials open	81%	
Sites with NCI-designated cancer center EP trials open	48%	
Sites with local EP trials open	22%	
Collaborations with NCI programs, percentage of sites		
Cooperative Group membership	100%	
Use of NCI Cancer Trials Support Unit for EP participation	70%	
NCI CCOP	48%	
Funding source distribution‡		
Cancer center	0%	0%–50%
Federal	41%	0%–82%
Hospital	0%	0%–99%
Industry	26%	0%–65%
Philanthropy	0%	0%–80%
Trial composition per site		
No. of EP trials open per site during July 2010-June 2011	19	1-66§
Proportion of sponsor's trials per site		
Cooperative Groups	76%	0%–100%
Industry	13%	0%–78%
Local	0%	0%–17%
NCI-designated cancer centers	1%	0%–43%
Other	0%	0%–12%
Accrual to EP trials per site in 1 year		
No. accrued	14	0-67
Rate (No. accrued/1,000 new analytic cases)	7	0-67

Continued on next column

Abbreviations: CCOP, Community Clinical Oncology Program; CTEP, Cancer Therapy Evaluation Program; EP, early-phase; NCI, National Cancer Institute; PK/PD, pharmacokinetic/pharmacodynamic.
* For 27 responding sites.
† Please see Results and Discussion sections.
‡ Three responding sites did not answer this question.
§ Number of open EP trials at a site may also reflect EP trials open at a lead site (eg, a lead CCOP site) with which that National Cancer Institute Community Cancer Centers Program site is affiliated.

(Table 1). ("Unique" trials are counted only once, regardless of how many times the same trial is opened by different sites.) Number of open EP trials at a site may have also reflected EP trials open at a lead site (eg, a lead CCOP site) with which that NCCCP site was affiliated. Eighty-two percent of these trials were phase II, 11% phase I/II, and 7% phase I. Phase I, I/II, and II trials were open at nine, 19, and 26 of the 27 sites, respectively.

Additional EP trial features are shown in Table 2. Almost half (128) of the unique trials were phase II Cooperative Group trials. Most NCCCP EP accrual was to Cooperative Group (43% of a total of 433 EP accrual) and industry (30%) trials, with a fair portion (17%) also going to NCI-designated cancer center EP trials. The top three cancers studied were hematologic, lung, and gastrointestinal. The 10 EP trials with the most NCCCP accrual are shown in Appendix Table A1 (online only).

EP Accrual Rate and Association With Site Characteristics

The median EP accrual was 14 patients per site for the year. The EP accrual rate per site was seven accruals per 1,000 new analytic cases (Table 1). No statistically significant differences were found between high-accruing sites and low-accruing sites in terms of any single site characteristic, such as the number of annual analytic cases, collaborations, funding sources, IRB re-

Table 2. Features of 291 Unique EP Trials Open Across 27 NCCCP Sites Over the Course of July 2010-June 2011

Trial Features	No. of Trials	%
Phase		
I	19	7%
I/II	33	11%
II	239	82%
Total unique EP trials	291*	100%
Sources		
Cooperative Groups	141	48%
Industry	98	34%
Local	14	5%
NCI-designated cancer centers	31	11%
Other	7	2%
Disease site		
Hematologic	64	22%
Lung	50	17%
Gastrointestinal	43	15%
Breast	31	11%
Gynecologic	30	10%
Genitourinary	23	8%
Brain	13	4%
Head and neck	10	3%
Melanoma	8	3%
Other	19	7%
Lead organization (top 10, including ties)		
Southwest Oncology Group	28	10%
Eastern Cooperative Oncology Group	24	8%
North Central Cancer Treatment Group	21	7%
Sarah Cannon Research Institute	20	7%
Gynecologic Oncology Group	20	7%
Radiation Therapy Oncology Group	19	7%
Cancer and Leukemia Group B	18	6%
Eli Lilly	8	3%
University of Wisconsin	7	2%
Children's Oncology Group	6	2%
Providence Health & Services	6	2%
American College of Surgeons Oncology Group	5	2%
University of Nebraska	5	2%

Abbreviations: CCOP, Community Clinical Oncology Program; EP, early-phase; NCCCP, National Cancer Institute Community Cancer Centers Program; NCI, National Cancer Institute.

* Number of open EP trials at a site may also reflect EP trials open at a lead site (eg, a lead CCOP site) with which that NCCCP site is affiliated.

view time, and staffing. The only exception was that high-accruing sites had three times as many EP trials open compared with low-accruing sites (39 *v* 13; $P = .04$; Table 3).

Although not statistically significant (perhaps due to small sample size), sites that were high-accruing were almost three times as likely to be a lead CCOP site when compared with low-accruing sites. Likewise, we found a non–statistically significant though sizable difference in IRB turnaround times between low- and high-accruing sites: turnaround time was shorter for high-accruing sites by 20 days.

Discussion

A major pillar of performance for the NCCCP sites is to increase awareness of and participation in EP clinical trials at community cancer centers. The infrastructure for phase II trials is within reach of most community cancer centers that are experienced in clinical trials. This fact is of growing importance as more targeted agents are being studied using phase II (particularly randomized) designs.[12-13] Although the infrastructure needed for phase I studies is initially more daunting for community cancer centers, some sites within the NCCCP have made progress in implementing phase I trials.[14]

During our EPWG monthly conference calls, we learned that many sites were not initially aware that the CTSU has phase II trials available for cross–Cooperative Group participation, with the number of EP trials available through the CTSU gradually increasing over the years from the first EP trial in 2002, to 25 in 2012.[15] Participation in EP Cooperative Group trials offered on the CTSU is one way community cancer centers can increase their access to EP trials. Collaborations with NCI-designated cancer centers and industry offer additional routes, often after sites have demonstrated successful accrual to Cooperative Group phase II trials. Indeed, our assessment found that sites were partnering with Cooperative Groups, NCI-designated cancer centers, and industry to participate in EP trials. In addition, a few sites conducted their own EP trials.

High-accruing sites were almost three times as likely to be a CCOP lead site, compared with low-accruing sites. Although this difference was not statistically significant, perhaps as a result of small sample size, it is still sizable enough to be potentially practically significant. It could be postulated that the CCOP hospitals participating in the NCCCP had the advantage of using their well-established clinical trial infrastructure to expand into more EP trial activity. Minasian et al have discussed the importance of such infrastructure, reporting on 25 years of successful clinical research in the CCOP community networks.[16] Others have reported an association between CCOP affiliation and higher accrual and/or trial participation.[17-18]

Interestingly, volume of new cancer cases per site was not associated with EP trial accrual. This finding seems to point to institutional commitment to research. Petrelli et al[19] report that 30% of oncologists are responsible for 70% of accrual to NCI trials. The Institute of Medicine similarly reports that only a small percentage of physicians enroll the majority of patients participating in Cooperative Group trials.[4]

Although 85% or more of sites had basic infrastructure for trials, it appears that the infrastructural barriers faced by sites seeking to implement EP trials go beyond the basics of having freezers, refrigerators, a pharmacy with experience in investigational agents, and specimen-handling capability. A survey of oncologists by Meropol et al[20]found that lack of staffing was the most significant practical barrier to participating in clinical trials. The NCCCP sites reported that staff at the sites filled a range of roles, with several instances of one person fulfilling

Table 3. Comparison of High- Versus Low-Accruing Sites

Site Characteristic	High-Accruing Sites (n = 14)		Low-Accruing Sites (n = 13)		*P*
	Median	Range	Median	Range	
Annual new analytic case	1,647	526-3,585	2,400	1,277-3,354	.47
Collaborations					
NCI CCOP membership					
Primary only	43%		15%		.21
Primary or affiliate	57%		38%		.45
No. of Cooperative Groups of which site is member	5	1-8	3	0-6	.15
NCI CTSU participation	79%		62%		.42
Funding source (distribution)*					
Cancer center	0%	0%-20%	10%	0%-50%	.11
Federal	46%	0%-82%	40%	0%-75%	.51
Hospital	0%	0%-99%	0%	0%-75%	.82
Industry	23%	0%-65%	31%	10%-50%	.49
Philanthropy	0%	0%-80%	0%	0%-5%	.85
Institutional review board turnaround time, days	32	7-71	52	10-60	.18
No. of EP trials open (all sources)†	39	6-66	13	0-53	.04

Abbreviations: CCOP, Community Clinical Oncology Program; CTSU, Cancer Trials Support Unit; EP, early-phase; NCCCP, National Cancer Institute Community Cancer Centers Program; NCI, National Cancer Institute.

* Data from 20 sites.

† Over the course of July 2010-June 2011. Number of open EP trials at a site may also reflect EP trials open at a lead site (eg, a lead CCOP site) with which that NCCCP site is affiliated.

multiple roles. This highlights the importance of having sufficient, trained staff, with clearly delineated roles, assigned to research.

If only a small number of physicians at sites do the majority of accruing, then they need highly trained CRAs/CRCs or other dedicated clinical research staff to be able to maintain high levels of research activity. A recent *Journal of Oncology Practice* series underscores this point.[21] The series describes the need for the oncology community to "create a research-centered culture." Such a culture would require commitment from hospital leadership, oncologists, clinicians, and research staff to foster collaborations essential to accessing clinical trials that would allow patients to receive their cancer treatments closer to home and their support networks. It may also mean that sites should examine their IRB turnaround times, which our assessment found to be shorter by 20 days for high-accruing sites.

Our finding that a higher number of open treatment trials was associated with higher accrual is congruent with the findings of Weiner et al,[22] who found number of trials (with at least one accrual) to be a contributing factor to higher accrual in the community setting, when combined with a high number of either new cancer cases or affiliated hospitals or practices.

Limitations to our assessment include the fact that all of the BA data on infrastructure were self-reported; only 1 year of accrual restricted to EP trials was analyzed; the sample size was relatively small; and information on the site's entire clinical trials portfolio, which could affect a site's ability to open EP trials, was not available. Our assessment represents a baseline profile of the NCCCP sites' infrastructure; further follow-up is needed to evaluate site progress and any associations among site characteristics and accrual that could possibly emerge over a longer time frame.

From a methodological perspective, we found that clinical trial staffing may best be examined in terms of total number of staff and in context of the overall portfolio of a site's studies (eg, EP, phase III, cancer control studies, and prevention trials) as opposed to trying to pinpoint full-time equivalents of one particular role (eg, data management) specifically devoted to EP trials. The "fuzzy-set analysis" approach of Weiner et al,[22] in which "recipes" of infrastructural components were examined in combination, as opposed to one particular element in isolation, may be a more appropriate method to describe the complexities of research staffing—or infrastructure in general—at sites.

This assessment does support the published literature documenting community commitment and capability to participate in research to advance cancer care.[4,16,22] In addition to bringing more research to the community at an earlier stage, community site participation in EP trials could also address the increasing need for clinical trials to screen ever more patients as newly identified cancer molecular subtypes further refine and narrow trial eligibility.[4,14] Inherent to this focus on molecular eligibility will be the need for more community sites to collect high-quality biospecimens with annotated data, such as tissue biopsies taken during the trial screening process and possibly other time points when integral to a study design.

In conclusion, community sites represent a key component in our nation's clinical trials system,[4] not only as they participate in more traditional later-phase trials, but also for their potential contributions to EP trials. Community sites can serve

as a resource for aiding accrual to EP trials. Moreover, as the science evolves, EP trials can provide a vehicle for bringing promising new anticancer agents to patients more rapidly. To these ends, community sites should be engaged in EP trials.

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Table A1. EP Trials With the Highest NCCCP Accrual (July 2010-June 2011)

Trial ID	Phase	Cancer	Stage	Intervention	Lead Organization	Sponsor	Accrual from NCCCP Sites*
NCT01106898	II	Breast	I-II	Adjuvant cyclophosphamide, paclitaxel ± trastuzumab	University of Nebraska	NCI-designated cancer center	23
NCT00861705	II	Breast	II-III, ER/PR poor, HER2 negative	Neoadjuvant addition of carboplatin ± bevacizumab to weekly paclitaxel followed by dose-dense doxorubicin/cyclophosphamide	CALGB	NCI	17
NCT00828841	II	Lung non–small-cell	IIIb-IV/relapsed	Cetuximab + platinum-based chemotherapy	Accelerated Community Oncology Research Network	Industry	16
NCT00881361	II	Breast	II-III	Sentinel node surgery and axillary node dissection following neoadjuvant chemotherapy	ACOSOG	NCI	12
NCT00614822	II	Lung non–small-cell	IIIb-IV	Carboplatin, bevacizumab and pemetrexed	Christiana Care Health Services/ Eli Lilly	Industry	11
NCT01295723	I	Breast	I	Intraoperative boost radiotherapy with electrons followed by hypofractionated whole-breast radiation	St. Joseph Hospital of Orange	Institutional	11
NCT00986674	II	Lung non–small-cell	IIIb-IV	Carboplatin and paclitaxel in combination with cetuximab, insulin-like growth factor 1 receptor antibody IMC-A12 or both	ECOG	NCI	10
NCT00928174	I/II	Prostate	Androgen insensitive	Measurement of anti-androgen response with 18F-choline PET/CT in androgen insensitive prostate cancer	Queen's Medical Centre	Institutional/NCI	10
NCT00887159	II	Lung small-cell	Extensive	Cisplatin and etoposide + hedgehog inhibitor GDC-0449 or insulin-like growth factor 1 receptor antibody IMC-A12	ECOG	NCI	9
NCT00603863	I/II	Pancreatic	III-IV	Fractionated ^{90}Y-labeled anti-mucin humanized antibody (^{90}Y-hPAM4) + gemcitabine	Immunomedics	Industry	9

Abbreviations: ACOSOG, American College of Surgeons Oncology Group; CALGB, Cancer and Leukemia Group B; ECOG, Eastern Cooperative Oncology Group; EP, early-phase; ER, estrogen receptor; HER, human epidermal growth factor receptor; NCCCP, National Cancer Institute Community Cancer Centers Program; NCI, National Cancer Institute; NCT, ClinicalTrials.gov identifier; PR, progesterone receptor.
* Accrual shown is from NCCCP sites participating in the BA.