Publicly Funded Clinical Trials and the Future of Cancer Care

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Disclosures of potential conflicts of interest may be found at the end of this article.

ABSTRACT

Publicly sponsored trials, conducted primarily by cooperative groups sponsored by the National Cancer Institute, and commercially sponsored trials are necessary to create new knowledge, improve the care of oncology patients, and develop new drugs and devices. Commercial sponsors launch clinical trials that will result in drug approval, label extension, expansion of market share, and an increase in shareholder value. Conversely, publicly sponsored trials seek to optimize therapy for a particular disease, create new knowledge, and improve public health; these trials can also result in label extension of a drug and even in initial drug approval. Publicly sponsored trials may combine and/or compare drugs developed by different commercial sponsors, develop multimodality therapies (e.g., the combination of chemotherapy and radiation), or develop novel treatment schedules or routes of drug administration (e.g., intraperitoneal chemotherapy). Publicly sponsored trials are more likely to focus on therapies for rare diseases and

to study survivorship and quality of life; these areas may not be a priority for commercial entities. Screening and prevention strategies have been developed almost exclusively by the public sector given the large sample size and long follow-up period needed to complete the trial and, therefore, the lack of short-term commercial gain. Finally, given the public nature of the funding, clinical investigators are expected to publish their results even if the outcomes are unfavorable for the investigational therapy. With the ongoing reorganization of the cooperative groups to form a national clinical trials network, opportunities exist to create a robust platform for biomarker discovery and validation through the expanded collection of well-annotated biospecimens obtained from clinical trial participants. Thus, publicly funded trials are vital to developing and refining new cancer treatments and disseminating results to the medical community and the general public. *The Oncologist* 2013;18:232–238

INTRODUCTION

There are two main sponsors of cancer therapeutic trials in the U.S.: (a) publicly sponsored trials, conducted primarily by the cooperative groups sponsored by the National Cancer Institute (NCI), soon to be known as the National Clinical Trials Network (NCTN) and (b) commercially sponsored trials. Both types of trials are necessary to create new knowledge, advance the care of oncology patients, and develop new drugs and devices. Despite these similarities and a common mission to improve outcomes for patients with cancer, the goals of public and commercial sponsors ultimately diverge (Table 1). Commercial sponsors launch clinical trials that will result in drug approval, label extension, expansion of market share, and an increase in shareholder value. Publicly sponsored trials seek to optimize therapy for a particular disease, create new knowledge, and improve public health; these trials can also result in label extension of a drug and even in initial drug approval. Because publicly sponsored trials often depend on the availability of commercialized drugs and technologies, these studies may be performed in collaboration and with support of a commercial sponsor. A report issued by the Institute of Medicine on comparative effectiveness research noted that “publicly funded clinical trials play a vital role by addressing questions that are important to patients but are less likely to

be top priorities of industry” [1]. In general, commercial sponsors have little interest in studying the optimal dosing of commercially available or generic agents, the integration of combined modality therapies into treatment paradigms, or comparing the effectiveness of established therapies. Studies of radiation and surgical therapies also often lack commercial sponsors.

Publicly sponsored trials often seek to directly compare the effectiveness of various treatment options. They may combine and/or compare drugs developed by different commercial sponsors, develop multimodality therapies (e.g., the combination of chemotherapy and radiation), or develop novel treatment schedules or routes of drug administration (e.g., intraperitoneal chemotherapy for ovarian cancer). Publicly sponsored trials are more likely to focus on therapies for rare diseases and to study survivorship and quality of life; these areas may not be a priority for commercial entities. By collecting and banking biospecimens, these trials may be able to identify patient and tumor subsets that are most likely to benefit from the intervention being studied or experience severe toxicities or poor outcomes. Given the public nature of the funding, clinical investigators are expected to publish their results even if the outcome is unfavorable for the investiga-

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Table 1. Goals of therapeutic clinical trials

Commercial sponsor	Public sponsor
Register drug	Optimize treatment
Label extension	Label extension
Expand market share	Create new knowledge
Create shareholder value	Improve public health

tional therapy. Finally, screening and prevention strategies have been developed almost exclusively by the public sector given the large sample size and long follow-up period needed to complete the trial and, therefore, the lack of short-term commercial gain (Table 2).

IMPACT OF THE COOPERATIVE GROUPS

The publicly funded cooperative group program was established in 1955 with the goals of conducting clinical trials of new cancer treatments, studying cancer prevention and detection, and assessing quality of life during and after cancer treatment. At the time of their formation, virtually all cancer drug development was supported by the NCI because the pharmaceutical industry had not yet assembled the necessary research and development infrastructure to develop anticancer drugs. From their inception, the cooperative groups have had an established infrastructure with administrative and data management centers that are organized to develop and conduct trials, as well as quality assurance programs to ensure protocol adherence and accurate data. With the inclusion of the Community Clinical Oncology Program, many trials are conducted in settings that are similar to those in which the intervention will be employed in practice [2]. The cooperative group program includes more than 14,000 oncology professionals working at more than 3,100 unique sites, enrolling patients that are representative of the U.S. population as a whole [1]. With its biorepositories, image archives, and reference laboratories, the cooperative group program is able to collect high-quality biospecimens and images for research that will allow investigators to further develop personalized cancer care. Publicly funded clinical trial groups also operate internationally, such as the National Cancer Institute of Canada (NCIC) Clinical Trials Group, and the European Organization for Research and Treatment of Cancer, these groups are funded by philanthropy as well as government; and through foundations such as the Multiple Myeloma Research Foundation and Stand Up to Cancer.

Publicly funded clinical trials are well suited to compare effective and promising regimens with each other as well as to the standard of care. Studies that directly compare prevailing treatment regimens or agents that are recently introduced by different sponsors for the same indication are unlikely to be performed by commercial firms but generate information that is of high interest to patients and physicians. An early example comes from the treatment of non-Hodgkin lymphoma (NHL). Cyclophosphamide, vincristine, doxorubicin, and prednisone (CHOP) was the first combination chemotherapy regimen for NHL with proven efficacy in a cooperative group trial. In the decade following its introduction, alternative regimens with six or eight different drugs were developed by academic institutions that reported higher response rates and seem-

Table 2. Role of publicly funded trials

Compare the effectiveness of various treatment options
Combine/compare drugs developed by different sponsors
Develop therapies for rare diseases
Address optimal dosing
Test multimodality therapies, such as radiation therapy in combination with drugs
Identify patient and tumor subsets most likely to benefit from interventions
Study screening and prevention strategies
Focus on survivorship and quality of life
Publish negative results
Assess cost and cost-effectiveness
Provide "gold standard" databases for registry studies

ingly improved survival. The Southwest Oncology Group launched a phase III study in 1986 comparing CHOP to (a) methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone; (b) cyclophosphamide, doxorubicin, etoposide, cytarabine, bleomycin, vincristine, methotrexate, and prednisone; and (c) methotrexate with leucovorin rescue, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin in patients with advanced stage diffuse large B-cell lymphoma. Despite promising single-institution experience with each of these regimens, CHOP was determined to be the superior treatment as it had a similar response rate and overall survival compared to the other regimens and was notably less toxic [3].

In 1996, the Eastern Cooperative Oncology Group (ECOG) reported results of a phase III trial comparing four different platinum-based doublet chemotherapy regimens that had been developed for treatment of advanced non-small cell lung cancer (NSCLC). The ECOG study randomized over 1,200 patients to receive cisplatin/paclitaxel, cisplatin/gemcitabine, cisplatin/docetaxel, and carboplatin/paclitaxel, with a primary endpoint of overall survival [4]. It is important to note that three of the drugs (paclitaxel, docetaxel, and gemcitabine) were being developed by three different pharmaceutical companies for use in NSCLC as part of a platinum doublet, yet there was little data comparing the effectiveness of these regimens to each other. The ECOG study established that none of the four regimens offered a significant advantage over the others in terms of response rate or survival but differed significantly in toxicity profile. Although this study did not lead to a clear advance in treatment of NSCLC, it provided important information to help physicians and patients make informed decisions about the optimal treatment regimen based on patient preferences, comorbidities, and tolerances.

More recently, the Cancer and Leukemia Group B (CALGB) completed study 40502, a randomized trial of weekly paclitaxel compared to weekly nanoparticle albumin-bound (nab)-paclitaxel or ixabepilone with or without bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer. The study sought to understand which of three anti-microtubule agents approved by the U.S. Food and Drug Administration improved progression-free survival in combination with bevacizumab for the first-line treatment of metastatic breast cancer. CALGB 40502 compared the standard of care, weekly

generic paclitaxel, with two novel branded agents, albumin-bound nab-paclitaxel and ixabepilone, that are marketed by different pharmaceutical companies and are considerably more expensive than generic paclitaxel. Two preplanned analyses of the primary endpoint (progression-free survival) by the CALGB Data and Safety Monitoring Board in June and November 2011 determined that neither experimental arm was likely to be superior to generic paclitaxel [5]. Importantly, the biospecimens collected as part of this trial may enable studies that provide insights into which group of patients are most likely to benefit from each treatment arm based on expression of a number of putative predictive biomarkers.

Publicly funded clinical trials are also an important mechanism to develop novel therapies for rare diseases with small commercial markets and to optimize the dosing and scheduling of commercially available agents. 5-Azacitidine, the first FDA-approved treatment for myelodysplastic syndrome, was developed entirely through a series of publicly funded trials conducted by investigators at the Mount Sinai Medical Center in New York City with the pivotal phase III trial performed by the CALGB. The study showed clear clinical benefit for 5-azacitidine compared with best supportive care in event-free survival, time to progression to acute myeloid leukemia (AML) and patient quality of life [6]. Cooperative group studies also demonstrated the superiority of intraperitoneal chemotherapy over intravenous treatment for stage III ovarian cancer [7] as well as the favorable impact of “dose-dense” chemotherapy as adjuvant treatment for stage II breast cancer [8]. These studies changed the standard of care simply by optimizing the delivery of available drugs. Nowhere has this been more evident than in treatment of pediatric acute lymphoblastic leukemia, for which a series of well-designed and efficiently conducted publicly funded clinical trials improved the cure rate of children with this disease from less than 10% to more than 80% over four decades of clinical investigation [9].

Studies of combined modality therapy, such as chemotherapy plus radiation, are generally of little interest to commercial companies and thus have been primarily pursued through the public sector. Many of these studies have been practice changing and have improved patient survival or quality of life, such as the use of chemoradiation following surgery which established a new standard of care for patients with early-stage gastric cancer [10], and the addition of cisplatin chemotherapy to radiation to enable organ preservation in patients with laryngeal cancer [11].

Just as importantly, cooperative group studies have sometimes moved the field away from more aggressive therapy by demonstrating similar outcomes and less toxicity for simpler treatment approaches. For example, in an era when thousands of women with breast cancer were seeking high-dose chemotherapy and stem cell transplantation based on the results of single-institution, nonrandomized trials, the CALGB and other cooperative groups completed prospective randomized clinical trials that proved that such toxic and expensive therapy was not superior to more standard chemotherapy approaches [12], essentially putting an end to the use of high-dose chemotherapy for treatment of breast cancer.

Cancer prevention studies have primarily been sponsored by the public sector because commercial sponsors are generally not interested in such studies that typically require a large sample size and a long time to reach the primary endpoint of

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cancer prevention. The National Surgical Adjuvant Breast and Bowel Project P2 study compared tamoxifen with raloxifene for the prevention of invasive breast cancer (Study of Tamoxifen and Raloxifene [STAR] trial) in a population of women determined to be at high risk for invasive breast cancer [13]. At the time the study was conducted, tamoxifen had been approved for the reduction of breast cancer risk (as well as the treatment of breast cancer); raloxifene, a second-generation selective estrogen receptor modulator, had been developed as a drug to treat osteoporosis. In 2006, the study investigators published results showing that raloxifene was as effective as tamoxifen in reducing the risk of invasive breast cancer but had a lower risk of thromboembolic events and cataracts, with a median follow-up time of 47 months. The results of this study lead to FDA approval of raloxifene for the prevention of breast cancer in postmenopausal women. The STAR trial was updated in 2010 after a median of 81 months follow-up time. Interestingly, the updated results indicated that although raloxifene still had decreased toxicity in comparison to tamoxifen, it no longer appeared as effective in preventing invasive breast cancer [14]. The updated results revealed that although raloxifene had a decreased incidence of uterine cancer, the rate of invasive breast cancers was 24% higher than in patients treated with tamoxifen. Both drugs can be considered good preventive choices for women at high risk of breast cancer depending on a woman's individual cancer risk, bone health, and gynecologic history. This type of trial likely could have been performed only in the cooperative group setting; although it resulted in a label extension for raloxifene, the duration of the study and large sample size (nearly 20,000 randomized patients) limited the interest of commercial entities in conducting such a trial.

In recent years, the rapidly rising costs of health care have focused the attention of patients, physicians, and payers on improving health outcomes, enhancing value in health care and improving health care delivery to individual patients. As the second leading cause of death in adults in the U.S., cancer is a disease that affects many Americans and their families. The delivery of cancer care requires multiple medical specialists, complex medical systems, and toxic drugs; therefore, the

cost of cancer care is increasing more quickly than health care costs in general. By conducting economic analyses alongside clinical trials, publicly funded studies have been able to shed light on the costs of cancer care in a way that commercially sponsored studies are often unable or reluctant to do. For example, a cost-effectiveness analysis of *Kras* mutation testing to guide administration of cetuximab was performed based on data from NCIC study CO.17. The analysis revealed a cost-effectiveness ratio of \$199,742 per life year gained when cetuximab is administered to all patients with advanced colorectal cancer, which could be reduced to \$120,061 per life year gained if the drug is administered only to patients with *Kras* wild-type tumors [15].

COMPARATIVE EFFECTIVENESS RESEARCH

In 2009, the Institute of Medicine (IOM) published a report delineating the goals and promise of comparative effectiveness research (CER). Their report defined CER as the “generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat and monitor a clinical condition, or to improve the delivery of care. The purpose of CER is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population levels” [16]. Table 3 outlines the goals and methods of CER described by the IOM.

Oncology has a rich history of improving clinical outcomes and advancing research through randomized controlled trials (RCTs). As described above, RCTs for oncology indications have led to the development of new drugs that can potentially cure or improve survival of patients with cancer, refined the methods of delivery and scheduling of oncology drugs, identified subpopulations of patients that are most likely to benefit (or be harmed) from a specific therapy, and established the utility of combining different treatment modalities to treat patients. Many of these studies, often conducted by the national cooperative group program, fulfill the goals of CER as described by the IOM. These trials also provide investigators with a platform to prospectively study patient-reported outcomes and quality of life, as well as to collect economic data for cost-effectiveness analyses and economic modeling. Thus, RCTs can be considered not only the criterion standard of efficacy research but the cornerstone of CER.

Comparative effectiveness research primarily seeks to evaluate the applicability and/or superiority of a particular therapy among the existing options in real-world settings. For example, in recent years, minimally invasive surgical techniques such as robotic and laparoscopic procedures have been developed and replaced more invasive, open procedures. As new surgical innovations generally do not require regulatory approval, newer techniques are often adopted in clinical practice without comparative research or RCTs. For surgical oncology, it is important to determine that the surgical innovation not only decreases surgical morbidity but also produces at least equivalent cancer-related outcomes. Laparoscopic colectomy was initially introduced for resection of colon cancer in the early 1990s. Subsequently, a randomized noninferiority trial comparing laparoscopic colectomy to open colectomy was conducted with 872 patients enrolled at 48 institutions by the Clinical Outcomes of Surgical Therapy

Table 3. Goals and methods of comparative effectiveness research

Goals
Directly inform a specific clinical decision from a patient perspective or a health policy decision from the population perspective
Compare the intervention under study to the best/most commonly used alternatives in practice or development (not necessarily placebo)
Describe results at the population and subgroup levels
Measure outcomes (both benefits and harms) that are important to patients
Employ methods and data sources appropriate for the decision of interest
Be conducted in settings that are similar to those in which the intervention will be used in practice
Methods
Pragmatic clinical trials
Prospective observational studies
Prospective or retrospective registries
Meta-analyses
Literature review
Technology assessments
Adapted from [16].

(COST) Study Group [17]. After a median follow-up time of 4.4 years, rates of tumor recurrence (the primary endpoint) and overall survival in the two arms were found to be similar with a hazard ratio of 0.86 (95% confidence interval: 0.63–1.17), with the laparoscopic patients experiencing a 16% rate of recurrence and overall survival rate of 86%. The patients in the laparoscopic group also had a faster perioperative recovery and shorter hospitalization.

The success of laparoscopic colectomy was also demonstrated in the U.K. Medical Research Council’s CLASSIC (Conventional Versus Laparoscopic-Assisted Surgery in Colorectal Cancer) trial, a randomized trial comparing laparoscopic versus open colectomy [18]. These two RCTs, both performed in selected institutions with experienced surgeons, provide conclusive evidence that laparoscopic surgery is an efficacious treatment for colon cancer. The translation of laparoscopic colectomy to the general population was recently analyzed by Billmoria et al. [19], who examined the National Cancer Database to determine the outcomes of laparoscopic versus open colectomy. The analysis demonstrated that laparoscopic colectomy is an effective option; among some groups of patients, it was associated with improved survival in comparison to open colectomy. However, the 3- and 5-year rates of overall survival in the analysis (74.9% and 64%, respectively) were not as good as those obtained in the COST trial (86% and 76.4% overall survival rates at 3 and 5 years, respectively). This discrepancy in survival outcomes illustrates the difference between efficacy and effectiveness that may occur when a novel surgical technique is applied in clinical practice.

Of course, not all advances supported by clinical trial evidence lead to changes in clinical practice. Uptake of intraperitoneal chemotherapy for treatment of advanced ovarian cancer has been constrained by the technical diffi-

Figure 1. Reconfiguration of the adult cooperative groups. The Cancer and Leukemia Group B, North Central Cancer Treatment Group, and the American College of Surgeons Oncology Group have merged to form the Alliance for Clinical Trials in Oncology. The National Surgical Adjuvant Breast and Bowel Project, the Radiation Therapy Oncology Group, and the Gynecologic Oncology Group have joined forces to form N-R-G. The American College of Radiology Imaging Network (ACRIN) and the Eastern Cooperative Oncology Group (ECOG) have merged to form ACRIN-ECOG. SWOG (formerly the Southwest Oncology Group) has remained independent.

culty of the approach. Also, acceptance of tamoxifen for prevention of breast cancer among high-risk women has been far less than predicted because of concerns about toxicity in otherwise healthy women. It is also often difficult to pull back from established interventions, such as postoperative breast irradiation following lumpectomy for older women with breast cancer. In 2004, the CALGB published results of a prospective, randomized controlled trial of postoperative breast radiation in women 70 years and older who received tamoxifen for early stage, estrogen receptor-positive breast cancer [20]. The data revealed no impact on overall survival for use of breast radiation; indeed, most of the deaths in this patient population were from causes unrelated to breast cancer. The data were updated in 2010 and confirmed the initial findings. Yet, a recent Surveillance, Epidemiology and End Results–Medicare analysis of radiation use in older women with breast cancer revealed no change in radiation use after publication of the clinical trial results [21].

LOOKING FORWARD

In more recent years, the pharmaceutical industry has largely replaced the publicly funded clinical trials infrastructure as the primary mechanism for development of new anticancer agents. Nevertheless, cooperative groups, Specialized Programs of Research Excellence, and other NCI- and foundation-funded research programs retain an important place in developing new treatments and improving the quality of cancer care. Through the collection of high-quality, clinically annotated biospecimens from patients enrolled in prospective clinical trials, the cooperative groups are well positioned to identify and validate prognostic and predictive biomarkers

that are necessary for the implementation of precision medicine. The CALGB, for example, has routinely collected leukemia specimens from patients with AML enrolled in CALGB protocols for more than 20 years. These specimens have enabled identification of many molecular subtypes of AML with varying prognosis and have facilitated development of targeted therapies in some disease subtypes. A 2001 report by CALGB identified internal tandem duplication of the *FLT3* gene as an adverse prognostic factor and *FLT3* as a potential target for treatment [22]. This observation led to the design of CALGB 10603, a prospective randomized controlled trial of adding a *FLT3* inhibitor to standard chemotherapy in patients with AML harboring the *FLT3* internal tandem duplication or mutation. The study, developed collaboratively with a pharmaceutical company sponsor, was conducted at sites in North and South America and Europe, using standardized and harmonized laboratory assays for *FLT3* mutations, to quickly screen and enroll the required number of patients with this rare subtype of AML.

The collection of tumor blocks from patients with colon cancer enrolled in CALGB adjuvant studies for stage II and III disease allowed the group to assess the prognostic importance of *Kras* [23] and *Braf* [24] mutation and to provide an independent validation data set for the OncoType Dx colon assay that was developed by a commercial firm [25]. Similarly, the collection of tumor blocks from patients with advanced NSCLC enrolled in a randomized phase II study of chemotherapy with celecoxib led to the hypothesis that high COX-2-expressing NSCLC has an adverse prognosis and that celecoxib might be beneficial when added to chemotherapy in patients with COX-2 overexpressing tumors [26].

Figure 2. Schematic representation of the National Clinical Trials Network.

Abbreviations: CCOPS, Community Clinical Oncology Programs; COG, Children's Oncology Group; DEA, Division of Extramural Activities; IRB, institutional review board; MB-CCOPs, Minority-based Community Clinical Oncology Programs; Mgt, management; NCI, National Cancer Institute; Ops, operations; Stats, statistics.

These hypotheses are now being studied prospectively in a randomized clinical trial, CALGB 30801 [27]. These and other studies demonstrate the ability of the cooperative groups to collect high-quality biospecimens from patients enrolled in clinical trials as well as to conduct clinical trials of targeted therapies in biomarker-selected populations. Indeed, the future of publicly funded clinical trials will likely depend on the ability of the system to adapt its infrastructure and procedures to achieve these goals of precision medicine. Going forward, the Alliance for Clinical Trials in Oncology has developed a pilot protocol to perform prospective molecular profiling on tumors from patients with certain advanced cancers with the goal of then matching those patients to prospective studies of targeted agents.

Despite its robust infrastructure and past achievements, the national cooperative group program has been criticized for its operational inefficiencies and slowness to adapt to new scientific opportunities. In 2009, the IOM issued a report that lauded the accomplishments of the NCI Cooperative Group Program but also delineated important deficiencies in the system [1]. The report noted system inefficiencies, such as prolonged startup times for trials and only a 50% rate of successful trial accrual. It was noted that the program has been ham-

pered by a 20% reduction in funding over the past decade and a cumbersome oversight infrastructure that reduces efficiency. The IOM report called for strengthening the publicly funded cancer clinical trials in the U.S., as well as for modifying the system so that it is scientifically nimble, efficient in trial launch and completion, and accessible to all members of the U.S. population.

These recommendations have prompted a reorganization of the cooperative group program, including the merger of several cooperative groups (Fig. 1). In addition, the NCI established an operational efficiency working group with a goal of reducing study activation time by 50% by placing strict timelines on the clinical trial development process [28]. The cooperative group program is now undergoing radical change as groups merge and re-organize to form the NCTN (Fig. 2). The goals of the NCTN are to provide an essential national infrastructure for publicly funded trials in cancer prevention, screening, diagnosis, and treatment; to provide a unified national platform for translational research; and to efficiently answer important clinical questions that are not well supported in a commercial environment. There are risks to replacing the cooperative group program, but there will be many rewards to

patients if the publicly funded cancer research enterprise can be transformed from a conventional clinical trials program into an engine for precision medicine and personalized cancer care.

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