Urologic Oncology: Seminars and Original Investigations 37 (2019) 318–323

UROLOGIC ONCOLOGY

Seminars article

Mechanisms and funding opportunities in genitourinary cancer clinical research

Christopher W. Ryan, M.D.Executive Officer, SWOG*

Professor of Medicine, Knight Cancer Center, Oregon Health & Science University, Portland, OR

Received 2 November 2017; received in revised form 21 May 2018; accepted 26 May 2018

Abstract

Progress in the prevention, diagnosis, and treatment of genitourinary cancers is dependent on well-conducted clinical trials. The complexity and cost of clinical research continues to escalate, and success is dependent on adequate funding. Opportunities to fund such research include federal, industry, and private sources. The mechanisms whereby larger trials are conducted include contract research organizations, publically- and privately funded consortia, and the National Clinical Trials Network of the National Cancer Institute. The National Clinical Trials Network is the prime venue for investigators to conduct independent, phase III trials in the United States.

Keywords: Clinical trials; NCTN; Cooperative Groups; Urologic cancers; Funding

1. Background

Improvements in the care of patients with urologic malignancies are dependent on the testing and validation of new therapeutic agents and procedures in the context of prospective clinical trials. The complexity of conducting clinical research continues to evolve, and the cost of conducting clinical research has escalated in recent years. Increasing complexity of trial design and regulatory burden imposed by local and federal agencies translates into increasing effort at research sites and increasing staffing requirements [1]. Securing funding to conduct a clinical trial must be undertaken early in the development of any clinical trial. This article will review some of the mechanisms and funding opportunities available to conduct a clinical trial in urologic oncology, with a focus on the National Cancer Institute's (NCI) National Clinical Trials Network (NCTN).

2. Elements and costs of conducting clinical trials at sites

A number of steps are involved in the development, conduct, and completion of clinical trial, and costs are associated with each of these steps. Because of the many facets involved in clinical research, the scope of funding required to conduct a clinical trial at a participating site may not always be apparent to the investigator. Foresight is important, so that budgets can be appropriately structured very early in the trial design process.

The process of conducting a clinical trial at a research site is complex and is associated with many costs. The C-Change and the Coalition of Cancer Cooperative Groups have broken down the elements of conducting a clinical trial into what they have termed "The Seven Functional Steps" [2]:

(1) Protocol Selection
(2) Study and Site Feasibility Assessment
(3) Regulatory Submission
(4) Legal and Financial Review and Approval
(5) Site Activation
(6) Study Execution (Accrual and Follow-up)
(7) Study Closure

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

*Corresponding author. Tel.: +1-503-494-8487; fax: +1-503-494-6197.
E-mail address: ryanc@ohsu.edu

https://doi.org/10.1016/j.urolonc.2018.05.024
1078-1439/

Details of these procedures are beyond the scope of this article, but a working knowledge of each of these steps is necessary in considering the financial implications of conducting a trial at a study site. Each element has inherent time and financial costs that must be budgeted. Protocol selection by a site principal investigator or other member of the research team is undertaken to determine "fit" of a trial. A feasibility assessment including the practicalities, scientific interest, and budget needs is performed. Multiple levels of regulatory submission may be required depending on the study and the institution, including at least local and/or central institutional review board review, and possible local scientific review board, Food and Drug Administration Investigational New Drug (IND) application or Investigational Device Exemption, or other submissions. Financial review and contracting is followed by study start-up procedures and study drug procurement. Study conduct includes screening, enrollment, treatment, safety reporting, data submission, and follow-up procedures. After eventual study closure, document retention is a continued responsibility of the study site. Dedicated study personnel are required to conduct all of these tasks.

It should be obvious that the financial burden on a site to conduct clinical research can be significant if not appropriately budgeted for. All of the above factors must be taken into account by an investigator and his/her institution in determining a budget to conduct a clinical trial. Institutional overhead, which accounts for items such as rent, electricity, information technology, and other "indirect costs," will often add another layer that can add 20% to 40% to a study budget [3,4]. Negotiations are conducted between the sponsor and the site; for pharmaceutical company studies, reimbursement for actual workload can often be achieved and there may be one-time payment for the costs involved with activation at the site [2]. In the case of publically funded studies (i.e., Cooperative Groups), such payments are often fixed per patient accrual, and may fall below the costs of conducting the trial at the site (see below).

3. Routine costs of care vs. research costs

Many elements of clinical care of a research subject may be considered normal costs of routine patient care and may be billable to the subject's insurance, while others may be performed for research purposes only. Those tests, procedures, and treatments that are not considered routine costs of care require reimbursement to study sites and must be incorporated into the funding considerations for a trial. This matter is further complicated by local regulations and wide variance among insurance plans regarding coverage for interventions. Section 310.1 of Medicare's National Coverage Determinations provides guidance on the costs that Medicare will cover for Medicare beneficiaries participating in qualifying clinical trials and can provide a framework for determining which study procedures will require funding [5]. In general, Medicare defines routine costs in clinical trials to include conventional care items or services that are typically provided outside of a trial, as well as those items are services that are required solely for the provision of the investigational item or service, monitoring for its effects, or for prevention, diagnosis, or treatment of complications.

4. NCI Cooperative Groups and the NCTN

One forum available to investigators in the United States for conducting multi-institutional clinical research is the federally funded NCTN previously known as the Cooperative Group System.

The cancer Cooperative Groups represent a network of thousands of physicians, basic scientists, statisticians, allied health professionals, and clinical research associates who collaborate in the design, conduct, and publication of cancer clinical trials. These investigators are associated with academic and private hospitals, community practices, and private institutions.

The National Cancer Institute established the Chemotherapy National Service Center in the 1950s. Seventeen groups were funded to perform clinical trials with agents from the NCI's drug development program. Over the years, the Cooperative Group Program has evolved, eventually involving more than 3,100 institutions, 14,000 investigators, and enrolling over 20,000 patients annually [6]. This infrastructure has maintained its original mission to conduct large-scale, clinical treatment trials while also supporting research in cancer prevention, quality of life, special populations, and rare diseases.

A review by the Institute of Medicine in 2009 [7] recommended consolidation of the Cooperative Groups in order to improve efficiency, study prioritization, and optimize funding for NCI-sponsored research. In 2013, 9 adult cancer Cooperative Groups were consolidated into 4 groups (SWOG, Alliance for Clinical Trials in Oncology, ECOG-ACRIN Cancer Research Group, and NRG Oncology) composing what is now known as the NCI's National Clinical Trials Network. These groups are funded by separate grants to support Network Operations and Statistical and Data Management Centers. Together this funding provides for the basic infrastructure to support the conduct of clinical trials within each group. Reimbursement to participating sites for enrollment of patients is provided via the Network Operations grant.

The NCTN is coordinated by the Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment, and Diagnosis of the NCI. Through partnerships with pharmaceutical companies, CTEP holds IND applications for 140 agents [8] and makes these agents available for clinical trials conducted by the NCTN. Because funding of the Groups is via a cooperative agreement, it is an "assistance" mechanism whereby the NCI works closely with the Groups in partnership without assuming a dominant or directing role [6]. For a concept brought forth by a Group to be developed

into an active trial eligible for funding, CTEP must approve the concept, guided by peer review input from disease-specific Steering Committees made up of NCTN group disease committee representatives, NCI Community Oncology Research Program (NCORP) representatives (see below), statisticians, patient advocates, and NCI staff [9]. The Genitourinary Steering Committee is divided into Task Forces to review concepts and provide input each for prostate, bladder, and renal cancer.

Approximately 30 academic centers, mostly NCI-designated Cancer Centers, have been awarded Lead Academic Participating Site (LAPS) grants to support NCTN activities and research staff at those facilities. In order to receive this funding, an institution needs to demonstrate high levels of patient enrollment on NCTN trials as well as scientific contributions to the development of these trials [10]. Funding to LAPS institutions helps offset the cost of increased workload from high enrollment to NCTN trials. Per-patient reimbursement to LAPS institutions is higher than what is provided to other sites.

Community hospitals and networks are eligible for funding from the NCORP, which supports these institutions for their participation in NCTN studies [11]. The NCORP also funds the Cooperative Groups to conduct trials in cancer prevention, supportive care and symptom management, screening, and surveillance trials, as well as supporting quality of life, cancer care delivery, and health disparities research. NCORP is coordinated by the NCI Division of Cancer Prevention. The large network of community hospitals and physicians who participate in Cooperative Group activities has historically been a great strength of the program. Cooperative Group results can be interpreted with "real world" applicability due to wide participation by community hospitals and more generalizable eligibility criteria distinct from the highly dictated populations of patients enrolled in pharmaceutical trials.

The historic focus of the Cooperative Groups has been the conduct of large, phase III, practice-changing trials, although earlier phase trials are undertaken by the NCTN on a regular basis. These publically funded trials will often study questions not frequently addressed by pharmaceutical companies, such as comparative trials of marketed agents or drug combination studies with agents from different manufacturers [7]. Studies involving other modalities of treatment including surgery and radiation are not often prioritized by industry but can be addressed within the NCTN.

Federal funding for cancer research has remained flat for more than a decade [12]. Less than 3% of the NCI's budget was designated for the NCTN in 2016 [13]. Because of the ever increasing complexities of conducting clinical research, the funding available from the NCI is often inadequate to fully cover the costs of carrying out the trials, and a significant amount of costs are often borne by the investigators and institutions participating in these trials. Reimbursement to sites for patient accrual is fixed; however, compared to pharmaceutical sponsored trials, costs may be less due to standardization and minimization of study startup, data submission, and auditing procedures [2]. In some instances, extra funding is negotiated directly between the Group and the interested pharmaceutical company to provide additional site reimbursement. Additional funding is sometimes negotiated for additional services such as special data analysis, quality assurance monitoring, or research-specific clinical tests, that are of interest to the pharmaceutical company, for example, in anticipation of a Food and Drug Administration filing.

5. Example of NCTN urologic cancer research: SWOG

SWOG is one of the original US cancer Cooperative Groups and has enrolled over 200,000 patients since its founding in 1956. The advances in care resulting from its studies are estimated to have added 3.3 million years of life for cancer patients in the United States [14]. The SWOG Genitourinary Committee is an effective example of NCTN-funded urologic cancer research.

Investigators participating in the SWOG Genitourinary Committee bring forth ideas for new urologic cancer clinical trials. These are developed during discussions between key stakeholders, and feedback is gained during regular teleconferences and face-to-face semiannual meetings. Cognizant of the significant resources involved in developing and conducting a trial within the NCTN in a setting of finite resources available to do such, the Committee accepts trial proposals for formal review every 12 to 18 months and usually selects 2 to 3 of the highest priority studies to move forward in development with the full commitment of available resources. Trial concepts must be approved by SWOG group leadership prior to submission to CTEP for peer review including the Steering Committee process (see above).

The Genitourinary Committee of SWOG is well recognized for its successful conduct and reporting of important trials in urologic oncology. A key reason for its success is representation from specialists across disciplines, with active participation of Urologists and both Medical and Radiation Oncologists. Studies are multidisciplinary, including drug trials involving CTEP agents or sometimes directly secured from industry, surgical trials, and radiation trials. Translational medicine research is a component of most trials, and is funded by a variety of sources including federal (such as R01 or Biomarker, Imaging and Quality of Life Studies Funding Program) [15], foundation, or industry sources.

Numerous practice-changing studies have been conducted by the SWOG Genitourinary Committee. The Prostate Cancer Prevention Trial demonstrated that finasteride can significantly reduce the prevalence of prostate cancer [16]. SWOG 8507 established induction Bacillus Calmette-Guérin (BCG) followed by maintenance therapy as the standard of care for superficial bladder cancer [17]. SWOG 8949 demonstrated the benefit of cytoreductive

nephrectomy in improving survival in metastatic renal carcinoma [18].

6. Other federal funding for cancer clinical trials

The Specialized Programs of Research Excellence (SPORE) are administered by the NCI Translational Research Program, and provide funding for interdisciplinary translational cancer research. SPORE grants support both basic science and clinical investigators in collaborative cancer research centered around a specific organ site, focusing on rapid translation from the basic science lab into clinical settings. In 2016, there were 8 prostate, 2 genitourinary, and 1 renal SPORE funded by the program [19].

The NCI Experimental Therapeutics Clinical Trials Network supports the development and conduct of phase I and phase II trials through its participating sites, comprising 12 lead academic institutions, each overseeing a number of academic and community participating sites [20]. Investigators from non-network NCI-designated Cancer Centers may have the opportunity to conduct clinical trials through the network via its Early Drug Development Opportunity Program. The Experimental Therapeutics Clinical Trials Network is administered by CTEP, and investigators have access to investigational agents for which CTEP holds the IND.

The Department of Defense funds clinical prostate cancer research through the Prostate Cancer Clinical Trials Consortium. This research coalition of academic centers is composed of 11 participating clinical research sites as well as a number of affiliated sites. Studies are codeveloped between investigators, research sites, and industry [21]. The Prostate Cancer Clinical Trials Consortium is a joint public-private partnership in collaboration with the Prostate Cancer Foundation.

In 2017, the Department of Defense released funding opportunity announcement for a new Kidney Cancer Research Program [22]. This effort includes a Consortium Development Award to fund infrastructure for a consortium to conduct multi-institutional clinical trials in kidney cancer in the future.

7. Industry trials

The pharmaceutical industry plays an important role in funding clinical trials, and it is estimated that 70% of all U. S. clinical trial funding comes from corporate sponsors [23]. Between 2006 and 2014, the number of National Cancer Institute-funded trials decreased by 24% while the number of industry-funded trials increased by 43% [24]. The dependence of the pharmaceutical industry on U.S. academic investigators has declined significantly in the past 20 years, with increasing use of private-sector, contract-research organizations as well as overseas enrollment. While in decades past the pharmaceutical industry relied on outside academic investigators to design trials for Food and Drug Administration drug approval, today these trials are usually designed in-house by the company and outside investigators are brought in to join [23]. Experts may serve as advisors to the company in the trial design and serve as figurehead principal investigators, but it is rare for investigators to lead their independent study concepts through an industry-sponsored, phase III mechanism.

The Society of Urological Oncology Clinical Trials Consortium is a network of academic- and community-based urologic oncologists at over 180 sites in the United State and Canada who participate in urologic cancer trials [25]. Many of these trials are conducted in partnership with industry and allow companies developing urologic cancer therapies, diagnostics, biomarkers, and devices to access a network of specialists in the field.

While industrial sponsorship of cancer clinical trials has clearly been growing, it is mostly a phenomenon of drug studies, and urologic oncology studies of surgery and/or radiation often need to find other sources of funding. An analysis of published randomized clinical trials in oncology report that the majority of such trials evaluating drugs were funded by industry, while only 17% of surgical and radiotherapy trials were industry funded [26].

8. Investigator initiated trials

While the term “Investigator initiated trial” can be applied to any investigator-designed study regardless of funding source, the term is often used in reference to such trials funded by a pharmaceutical company which are investigator initiated and in which the investigator takes the role of sponsor. If the study requires an IND for the drug, this is held by the investigator, who usually “cross references” the company’s existing IND [27]. The company may supply the drug in question and/or financial support and may provide additional support such as placebo, laboratory testing, etc. There is no indemnification of the investigator [28]. The drug may be premarket or postmarket. Investigator initiated trials are often smaller in size than the large, randomized trials typical of a company-sponsored, registration trials. A company’s motivation in supporting such a trial may be to expand information around the drug and to establish data in settings outside of the drug’s primary use.

9. Private funding sources

Private foundations that may fund clinical trials include medical professional societies and disease-specific organizations. Academic institutions and their affiliated Cancer Centers may offer various competitive awards to fund clinical research projects.

Examples of relevant societies that solicit funding opportunities for clinical research include the American Urological Association [29] and the American Society of Clinical Oncology’s Conquer Cancer Foundation [30].

Private foundations that support disease-specific, genitourinary cancer research include the Prostate Cancer Foundation [31], Action to Cure Kidney Cancer [32], and the Bladder Cancer Advisory Network [33].

Crowdfunding

With the rise of social media and the decline of federal funding for clinical research, some have looked to online crowdfunding as a potential strategy to fund clinical trials. While still in its infancy, this strategy of direct appeal to a widespread audience has shown early signs of success. A brief report study crowdfunding for clinical trials noted a 62% (8/13) rate of such campaigns achieving their fundraising goals [34]. Most of these trials were for pilot or phase I trials and most had funding from other sources

Conclusion

The conduct of clinical research is inherently complex, with multiple layers of regulation and many steps involved in their design, approval, conduct, and analysis. For these reasons, an intimate knowledge of the clinical research process is necessary to budget appropriately and secure sufficient funding. Numerous private and federal avenues are available to fund smaller clinical trials. Industry and the NCTN are the main sponsors of large, phase III trials in the United States. Of these, the NCTN remains the prime venue for independent investigators to conduct such practice-changing studies.

References

[1] Vose JM, Levit LA, Hurley P, Lee C, Thompson MA, Stewart T, et al. Addressing administrative and regulatory burden in cancer clinical trials: summary of a Stakeholder Survey and workshop hosted by the American Society of Clinical Oncology and the Association of American Cancer Institutes. J Clin Oncol 2016;34:3796–802.

[2] C-Change, Coalition of Cancer Cooperative Groups. The Elements of Success: Conducting Cancer Clinical Trials: A Guide. 2007. http://c-changetogether.org/Websites/cchange/Images/Publications%20and%Reports/ClinicalTrialsSucess.pdf.

[3] Developing an investigator site budget for clinical trials. J Oncol Pract 2007;3:94–7.

[4] Editors. Determining suitable overhead rates to use for study budgets. Appl Clin Trials 2013;22:August 1, 2013.

[5] Centers for Medicare & Medicaid Services (CMS). 2007 National coverage determination (NCD) for routine costs in clinical trials (3101). https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=1&ver=2.

[6] National clinical trials network program guideline. National Cancer Institute Division of Cancer Treatment & Diagnosis (DCTD); 2012. https://ctep.cancer.gov/initiativesprograms/docs/NCTN_Program_-Guidelines.pdf.

[7] IOM (Institute of Medicine). A national cancer clinical trials system for the 21st century: reinvigorating the NCI Cooperative Group Program. Washington, DC: The National Academics Press; 2010.

[8] Adams J. Message from the CTEP associate director, cancer therapy evaluation program (CTEP). National Cancer Institute Division of Cancer Treatment & Diagnosis (DCTD); 2017. https://ctep.cancer.gov/DirectorsMessage/default.htm.

[9] National Clinical Trials Network (NCTN) Steering Committees. National Cancer Institute (NIH). 2016 https://www.cancer.gov/about-nci/organization/ccct/steering-committees/nctn.

[10] National Cancer Institute (NIH); 2015. https://www.cancer.gov/research/areas/clinical-trials/nctn.

[11] About NCORP. National Cancer Institute Community Oncology Research Program.https://ncorp.cancer.gov/about/.

[12] Federally Funded Cancer Research ASCO American Society of Clinical Oncology.https://www.asco.org/advocacy-policy/policies-positions-guidance/federally-funded-cancer-research.

[13] NCI Budget and Appropriations. 2017 National Cancer Institute (NIH); 2017. https://www.cancer.gov/about-nci/budget.

[14] Unger JM, LeBlanc M, Blanke CD. The effect of positive SWOG treatment trials on survival of patients with cancer in the US Population. JAMA Oncol 2017;3:1345–51.

[15] Biomarker, Imaging and Quality of Life Studies Funding Program (BIQSFP). National Cancer Institute (NIH).https://www.cancer.gov/about-nci/organization/ccct/funding/biqsfp.

[16] Thompson IM, Goodman PJ, Tangen CM, Lucia MS, Miller GJ, Ford LG, et al. The influence of finasteride on the development of prostate cancer. N Engl J Med 2003;349:215–24.

[17] Lamm DL, Blumenstein BA, Crissman JD, Montie JE, Gottesman JE, Lowe BA, et al. Maintenance bacillus Calmette-Guerin immunotherapy for recurrent TA, T1 and carcinoma in situ transitional cell carcinoma of the bladder: a randomized Southwest Oncology Group Study. J Urol 2000;163:1124–9.

[18] Flanigan RC, Mickisch G, Sylvester R, Tangen C, Van Poppel H, Crawford ED. Cytoreductive nephrectomy in patients with metastatic renal cancer: a combined analysis. J Urol 2004;171:1071–6.

[19] Specialized Programs of Research Excellence (SPOREs). 2017 National Cancer Institute (NIH); 2017. https://www.cancer.gov/about-nci/budget/fact-book/extramural-programs/spores.

[20] NCI Experimental Therapeutics Clinical Trials Network (ETCTN) Cancer Therapy Evaluation Program (CTEP). 2017 National Cancer Institute Division of Cancer Treatment & Diagnosis (DCTD); 2017. https://ctep.cancer.gov/initiativesPrograms/etctn.htm.

[21] Morris MJ, Basch EM, Wilding G, Hussain M, Carducci MA, Higano C, et al. Department of defense prostate cancer clinical trials consortium: a new instrument for prostate cancer clinical research. Clin Genitourin Cancer 2009;7:51–7.

[22] Program Funding Opportunities - FY17 Kidney Cancer Research Program (KCRP). 2017 CDMRP; 2017. http://cdmrp.army.mil/funding/kcrp.

[23] Bodenheimer T. Uneasy alliance—clinical investigators and the pharmaceutical industry. N Engl J Med 2000;342:1539–44.

[24] Ehrhardt S, Appel LJ, Meinert CL. Trends in National Institutes of Health Funding for clinical trials registered in ClinicalTrials.gov. JAMA 2015;314:2566–7.

[25] Shore ND, Dinney C, Uzzo R. The society of urologic oncology clinical trials consortium: a brief history and overview. Rev Urol 2017;19:122–4.

[26] Santini FC, Moraes FYd, Saad ED, Katz A. Relationship between type of therapeutic intervention and funding source in randomized clinical trials (RCTs) in oncology. J Clin Oncol 2014;32(15 suppl):6621.

[27] Investigational New Drug Applications Prepared and Submitted by Sponsor-Investigators Guidance for Industry US Department of Health and Human Services Food and Drug Administration (CDER) (CBER). 2015: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM446695.pdf.

[28] Suvarna V. Investigator initiated trials (IITs). Perspect Clin Res 2012;3:119–21.

[29] Funding Opportunities Overview. American Urological Association. http://www.auanet.org/research/funding-opportunities/funding-opportunities-overview.
[30] Grants & Awards. Conquer Cancer Foundation. https://www.conquer.org/grants-awards.
[31] Open RFAs. 2017 Prostate Cancer Foundation; 2017. https://www.pcf.org/c/open-rfas/.
[32] Direct Funding. 2017 Action to Cure Kidney Cancer; 2017. http://www.ackc.org/direct-funding/.
[33] Research Grants. 2017 Bladder Cancer Advocacy Network (BCAN); 2017. http://www.bcan.org/research-grants/.
[34] Sharma A, Khan JS, Devereaux PJ. Is crowdfunding a viable source of clinical trial research funding? Lancet 2015;386:338.