Cooperative Group Cancer Clinical Trials: An NCIC Clinical Trials Group Perspective

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In the August 2011 *CUAJ* editorial, Dr. Klotz addresses randomized controlled trials (RCTs) and referred to their "decline and fall."[1] The editorial touches on diverse issues that include the conceptual importance of RCTs and their success at meeting stated objectives; it concludes by advising investigators to pursue small to medium-sized trials in collaboration with industry partners. Dr. Klotz also offers his perspective of the strategic objectives and operational processes of the NCIC Clinical Trials Group (NCIC CTG). We disagree with Dr. Klotz's views and would like to correct misperceptions related to the NCIC CTG. Dr. Klotz correctly identified that the clinical trials environment is undergoing major evolution; investigators should clearly understand these changes and their implications.

Results of RCTs form the basis of medical practice and policy determination under the paradigm of evidenced-based medicine.[2] Without these results, the quality of evidence is downgraded, there is less confidence in understanding the trade-offs associated with treatment benefits and risks and there is greater potential for inflicting harm or providing cost-inefficient care. Regulatory bodies, such as Health Canada and the U.S. Food and Drug Administration, generally require RCT results before approving new drugs. Evidence from RCTs, along with pharmacoeconomic data, forms the basis for new drug funding decisions.

There are multiple perceptions of today's RCTs. While the need for evidence from RCTs remains, there is debate about whether the "right types of trials" are being conducted to inform tomorrow's best incorporation of innovation,[3,4] policies at a population level,[5,6] and whether trials include sufficient leadership from the academic community.[7] The report from the Canadian Institutes of Health Research (CIHR) Strategy for Patient-Oriented Research (SPOR) lists six factors that contribute "*… to the gaps in the research-to-practice continuum.*"[8] At least four are associated with RCTs, including: "*Lack of clinical investigators, methodologists such as biostatisticians, clinical epidemiologists and health economists, and other needed experts; complicated coordination of large, multi-centre clinical trials because of requirements for multiple ethics reviews by each individual institution and the lack of standardized contracts; underfunding of patient-oriented research when compared to many other countries;*" and, "a *decentralized federation structure, making research coordination difficult…*"

Similar observations are recognized for cancer clinical trials. In a comprehensive review by the U.S. Institute of Medicine (IOM) of the National Cancer Institute's Clinical Trials Cooperative Group Program,[9] the authors state that "*Clinical trials that test the safety and therapeutic benefit of drugs and other treatments are essential for developing new and improved therapies for patients with cancer. However, the system for conducting cancer clinical trials in the United States is approaching a state of crisis.*" This report highlights the importance of a publically-funded trials system. While in no way minimizing the high degree of competency and creativity of scientists, including trialists, within the pharmaceutical and biotechnical sector, some research questions addressing health outcomes and cost-efficient care fall outside of industry's interest and can only be conducted by academic networks. These networks, like NCIC CTG, are connected at an international level so that results can be obtained in a more timely manner, are generalizable to a wider scope of patients, and so that trial costs are mutually leveraged.[10] Collaborations between academic networks and industry may produce trials of higher quality than possible by either entity alone, including addressing correlative translational research questions, quality of life and economic analyses. The Canadian Cancer Research Alliance considers this topic so important that, in 2010, it struck a Clinical Trials Working Group to address the observations that "*researchers, patients, policy makers, and funders across Canada as part of the development of the*

Pan-Canadian Cancer Research Strategy suggested that the ability to conduct cancer clinical trials in Canada was under growing threat. This was particularly the case for trials based on ideas developed by the academic sector (i.e. those from cooperative groups). It was also observed that pharmaceutical trials are increasingly moving to Eastern Europe or Asia where rapid accrual at lower costs is possible."[11]

The NCIC CTG has operated within this evolving environment since 1980. Our mission is to test interventions that will prevent cancer or improve the outcome of patients with cancer. Between 1980 and August 2011, the Group conducted, or is conducting, 252 trials within its Phase III Program (almost all are RCTs, total accrual is 63 166 patients) and 187 phase I-II trials within its Investigational New Drug (IND) Program (accrual is 5077 patients). As of September 2011, we are accruing to 45 trials and 96 others have ongoing follow-up to evaluate protocol endpoints. Accrual in 2011 is projected to surpass 3000 patients. The success of NCIC CTG is directly dependent on its funding from the Canadian Cancer Society Research Institute (CCSRI). In preparation for its 2009-2010 CCSRI Site Review, NCIC CTG underwent a strategic prioritization process that produced six strategic priorities, including to assess novel therapeutics, evaluate biological endpoints (including identifying biomarkers), conduct pragmatic phase III trials for their direct application to health care delivery policies, evaluate interventions that will prevent cancer, develop and evaluate new trial methodologies and facilitate training of the next generation of Canadian investigators. In 2010, an international panel assessed the Group's accomplishment and future directions and concluded: "*The NCIC Clinical Trials Group (CTG) is a world class clinical and translational research organization that has an impressive track record of conducting clinical trials that have changed medical practice, supported the global regulatory approval of new drugs, improved the survival and quality of life of cancer patients and provided new insights to the biology of cancer. The CTG plays a key role in training the next generation of clinical investigators. The group is clearly fulfilling the mission of the Canadian Cancer Society and merits its continued strong support.*"

Recently activated trials through the NCIC CTG test drug, radiation and surgically-related strategies. In one trial, a life-style modification strategy is evaluated. We have capitalized on outstanding developmental work of Canadian investigators to develop large scale RCTs. In Mammary.32, observational and pilot data have led to our leadership of a 3500 patient international trial testing the "re-purposing" of metformin as therapy for patients with breast cancer.[12-14] In Symptom Control.23, Canadian pilot data are used as a basis to test dexamethasone as an intervention to reduce the pain flare associated with radiation of bone metastases.[15,16] In Head and Neck.6, Canadian contributions to international meta-analyses generated the question to compare hyperfractionated radiation plus a monoclonal antibody with standard chemo-radiation treatment.[17,18] Canadian leadership, assessing exercise as a strategy not just for symptom benefit but also for its potential to reduce cancer recurrence, is being tested in Colon.21.[19] Within the Group's IND Program, a novel "umbrella" design has been incorporated to separately test two drugs in patients with one of 10 rare tumours and, in 2010, the Program began a phase I-II pediatric initiative.

While these positive activities exist, the Group faces the same challenges as previously described. Trials are now more complex because of the desire for increased scientific content, such as biologic correlative studies, and a complex regulatory environment. These complexities translate to higher costs. As Dr. Klotz describes, the fiscal climate of hospitals requires increased resources for research activities. Peer-review funding has not kept pace with these needs. The rapid gains of new knowledge of the molecular biology of cancer and possibilities for targeted treatments have created new opportunities for the private sector, including pharmaceutical, biotechnical and contract research organizations. For academia to have a leadership role within a partnering relationship with the private sector requires strategic positioning.

Within this context, NCIC CTG requires careful programmatic and project-specific business plans. Programmatic funding supports the platform for conducting a menu of trials; each trial requires a source of funding for trial-specific costs. These funds will come from peer-review grants and contracts with industry. The platform includes staff that is highly competent at trial development processes, data management and regulatory compliance. Systematic processes of prioritization are necessary. For instance, in 2008, the Group initiated a process to close all trials meeting protocol-stated endpoints unless a new set of objectives had undergone standard approval processes and a business plan developed. Since 2008, 267 trials have been closed through this mechanism, allowing resources at the NCIC CTG Central Office and investigative centres to be prioritized for new trials. Trials are followed closely for accrual metrics; we require 20% of the monthly targeted accrual be seen over months 13 to 18 following trial activation. Inability to meet this target is a strong predictor of accrual failure and to responsibly use resources, difficult decisions about trial continuation may be required.

The NCIC CTG's Genitourinary Committee has experienced the highs and lows associated with successful completion of landmark trials and the realities of the current environment. In 2010, the Prostate (PR).3 trial results were reported at the American Society of Clinical Oncology (ASCO)[20] and plenary session of the American Society of Therapeutic Radiology and Oncology.[21] These results confirm the role of radiation therapy for men with locally-advanced prostate and are regarded as practice-changing.[22] In 2011, the results

of PR.7 demonstrating the non-inferiority of intermittent as opposed to continuous androgen suppression therapy were presented at ASCO and recognized as one of the less that 1% of all abstracts categorized as "the Best of ASCO."[23] In contrast, three trials, Bladder.11, PR.11 and PR.12 were closed due to accrual failure. Because of this, and a need to clarify other methodologic issues, the currently-approved PR.15 trial comparing external beam radiation therapy with or without high-dose rate brachytherapy in men with intermediate-risk prostate cancer is planned to move forward first as a feasibility trial and will include success of accrual as one of its endpoints.

Dr. Klotz's advice to investigators to pursue small to medium-sized trials in association with industry requires clarification. Depending on trial specifics, this may be a very laudable objective. Small- to medium-size trials may provide important feasibility or other enabling data and signals of efficacy associated with a new therapy or biomarker. However, these trials are unlikely to influence practice policies. We believe that trial benefits should be measured by the concept of "research payback."[24,25] Under this paradigm, benefits are measured not only by publication and citation, but by evidence of adoption and benefits associated with adoption. For example, NCIC CTG's Bronchus (BR).10 trial was associated with a high-profile publication,[26] incorporated into evidenced-based practice guidelines[27] and has led to new practice patterns that are associated with improved survival at a population level.[28] Correlative studies associated with BR.10 have led to discovery of a potentially important biomarker that has possibilities for both commercialization and better patient outcomes.[29,30] If the time, efforts and costs associated with clinical trials are to be associated with important "payback", thoughtful planning, collaboration of multiple disciplines and perspectives, and meticulous conduct are required.

As evidenced by the thoughtful analyses provided in documents such as CIHR's SPOR statement and the U.S. IOM's review of the cancer cooperative group system, we are in a time where opportunities associated with new biologic discoveries have collided with a complex clinical trials environment. The NCIC CTG will continue to navigate these complexities, and places a high value and priority on developing and conducting trials that address the problems faced by all cancer patients, including those with malignancies involving the genitourinary system.

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