

FOR CANCER PATIENTS IN CANADA

Should Clinical Trials be Considered Part of “Standard of Care”?

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In 2010, an estimated 173,800 new cases of cancer (excluding about 75,500 non-melanoma skin cancers) occurred in Canada.¹ While major inroads have been made in cancer treatment with earlier diagnosis and treatment intervention, 40 per cent of women and 45 per cent of men (based on 2009 incidence rates) will develop cancer during their lifetime. One out of every four Canadians is still expected to die from this disease. Only continued clinical research focused on better methods of cancer treatment and prevention will improve these statistics.

In view of this, should clinical trials be offered as part of standard treatment for Canadians diagnosed with cancer? In order to answer this question we need to address several important issues.

1. How important is clinical cancer research?
2. What is Canada’s contribution to clinical cancer research?
3. What are the barriers to conducting clinical research? and,
4. What are the proposed solutions?

How Important is Clinical Cancer Research?

There is general agreement that in the last four decades the incremental steady improvements in cancer outcomes have largely resulted from carefully planned and executed clinical trials testing new treatments. The last two decades have seen major advances in knowledge of cancer cell biology. Put simply, we now have a better understanding of what turns a “normal” cell into a “cancer” cell and what allows these cancer cells to grow wildly, avoiding all the normal body checks and balances.

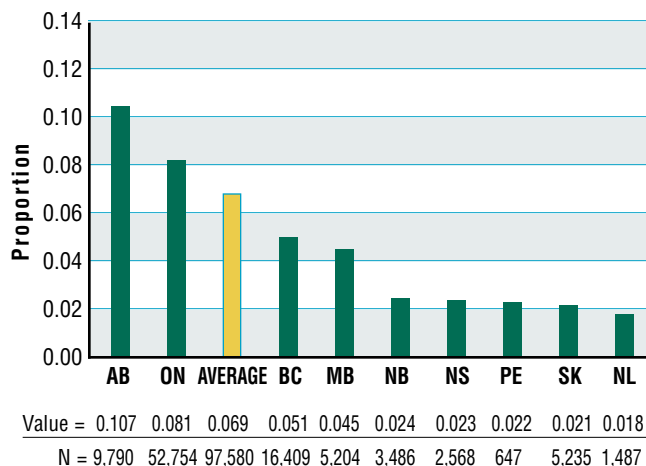
In the last decade, based on this knowledge, we have seen the emergence of a new generation of “targeted” cancer therapies. Targeted therapies are generally better tolerated than traditional cytotoxics and have expanded the concept of individually tailored cancer treatment as some of these drugs may be effective in patients whose cancers have a specific molecular target, but may not be effective in the absence of such a target. Clinical trials are important vehicles for evaluating these and other novel therapies that emerge from translational research activities. Moreover, institutions with

high participation rates in academic clinical trials have better patient outcomes than institutions with low participation rates.²

What is Canada’s Contribution to Cancer Clinical Research?

So, where does Canada stand in terms of participation in clinical cancer research? Accurate data are difficult to determine on the number of cancer patients enrolled in clinical trials and the types of trials in which they are enrolled. A widely quoted estimate is that three per cent of adult cancer patients are enrolled in clinical trials.³ In 2009, the percentage of patients enrolled in therapeutic clinical trials across Canada ranged from two per cent in the Atlantic Provinces to 11 per cent in Alberta, with a national average of seven per cent (Figure 1).⁴ With so few adult patients involved in cancer trials, progress in clinical research is slow. Additionally,

FIGURE 1
ADULT CLINICAL TRIAL PARTICIPATION RATIO—CASES SEEN BY PROVINCIAL CANCER CENTRES IN 2009⁴



Data Source: Provincial cancer agencies

individuals diagnosed with cancer may miss out on opportunities to access potentially effective new treatments. This is in stark contrast to clinical trial participation in the pediatric population. In 2009, pediatric clinical trial participation across Canada ranged from 15 per cent in Saskatchewan to 40 per cent in Ontario with a national average of 37 per cent.⁴ These high participation rates have been a key driver in improving survival in the pediatric population with five year overall survival rates for children, 0–18 years, now over 80 per cent.

Despite low participation rates, Canada has an outstanding international reputation for its contribution to cancer therapeutics development from first-in-human studies (Phase I trials) to randomized control trials aimed at changing clinical practice (Phase III). Indeed, when the mean impact factor (indicator of quality of scientific articles) of Canadian clinical cancer research publications was compared with that of other countries, Canada ranked first.⁵

Canadian researchers have made a significant contribution to clinical research. Academic research groups in Canada have conducted and published studies that have led to worldwide changes in clinical practice and standards of care for a number of different cancers, not only with regard

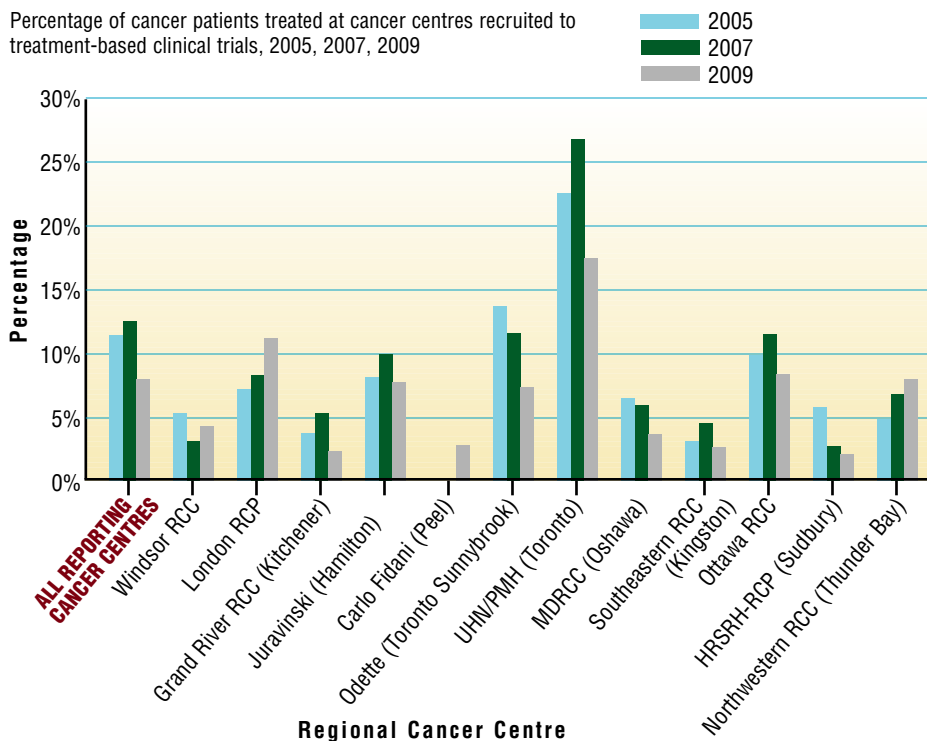
to survival⁶ but also palliative care, survivor support and symptom control.² These academic research groups include the NCIC Clinical Trials Group (NCIC-CTG), core funding from Canadian Cancer Society with institutional members from across the country; the Ontario Clinical Oncology Group (OCOG), core funding from Cancer Care Ontario (CCO) and Hamilton Health Sciences; and the Princess Margaret Hospital Phase II Consortium, core funding from the U.S. National Cancer Institute (NCI).

Numerous advantages pertaining to the conduct of clinical trials in Canada can be cited:

- Centres of Excellence—the number of high quality clinical sites as measured by level of good clinical practice (GCP),
- excellent training,
- experienced clinical trial and site management organizations,
- well-characterized patient populations,
- early-stage initiatives to create centralized research ethics boards, and
- a cost advantage for biotech/biomedical research and development.⁷

FIGURE 2
PERCENTAGE DISTRIBUTION OF TOTAL PATIENTS IN CLINICAL TRIALS, BY ONTARIO CANCER CENTRE⁸

Percentage of cancer patients treated at cancer centres recruited to treatment-based clinical trials, 2005, 2007, 2009



Report date: February, 2010

Date source: Clinical Trials Program (Ontario Institute for Cancer Research), Cancer Program Scheduling System (PMH)

Activity level Reporting

Prepared by: Cancer Care Ontario, Cancer Informatics

Yet the clinical trial landscape in Canada is changing—for the worse. In 2009, market research conducted by the Canadian Cancer Research Alliance revealed that cancer clinical trials in Canada were under growing threat.² This was particularly the case for trials based on ideas developed by the academic sector (i.e., those from cooperative groups). In 2010, CCO reported that cancer patient participation in clinical trials in Ontario from 2007 to 2009 had decreased 28 per cent, (from 5,469 patients enrolled in 2007 to 4,287 patients in 2009) citing a changing environment for supporting clinical trials (Figure 2).⁸

The NCIC-CTG shares similar concerns, according to Dr. Ralph Meyer, Director of the NCIC-CTG. While total patient enrollment in NCIC based clinical trials has remained relatively stable over the past five years, the costs (financial and human) of conducting clinical trials have escalated and there is greater complexity in activating clinical trials.

The Canadian Institute for Health Research (CIHR) has acknowledged that Canada is rapidly falling behind other industrial countries in terms of capacity to undertake patient-oriented research.⁹ Failing new action, Canada will rapidly lose its competitive advantage in developing novel therapies and evaluating them in patients.

What are the Barriers to Conducting Clinical Trials in Canada?

The barriers to conducting clinical trials in Canada appear to be multi-factorial and include:

- a relative lack of agency funding,
- a declining ability of hospitals/ cancer centres to support core clinical trial infrastructure,
- complex regulatory and administrative environments,
- increasingly complex studies, and
- emerging international competition

The lack of agency funding for clinician cancer research is perhaps the most serious barrier. The Canadian Institute for Health Research investment in patient oriented research represents only six per cent (\$60 million) of their annual budget which is markedly lower than comparative investments made by the U.S. NIH, the U.K. National Institute of Health Research and Australia's National Health and Medical Research Council.⁹

In 2007, \$398.5 million was spent on peer-reviewed cancer research, from 37 funding agencies in Canada. These statistics reflect a 5.4 percent increase in cancer research funding from federal government programs over a two year period (2005–2007) however, the proportion of funds dedicated to “clinical” cancer research is uncertain (Figure 4).² Approximately 45 per cent of research funding was allocated to biology, 11 per cent to

What are Clinical Trials?

Clinical trials are research studies done to evaluate whether a drug or treatment is both safe and effective for people. Each study tries to answer scientific questions and to find better ways to prevent, diagnose and treat cancer. Participating in a clinical trial can provide researchers with valuable information on new treatments; in some cases, it may also offer the chance for a cure or improvement in a patient's quality of life that is not provided by standard therapy. Clinical trials can range from testing new drugs for the first time in humans (Phase I) to testing the effectiveness of the drug in a certain tumour type, e.g., breast cancer (Phase II), to testing a new therapy compared to the standard of care (Phase III).

FIGURE 3
DISTRIBUTION OF 2007 CANCER RESEARCH INVESTMENT BY FUNDING SOURCE FOR EACH PROVINCE (\$398.5M)¹⁰

Funding source refers to source of dollars for each project and not to the funder sector of the funding organization.

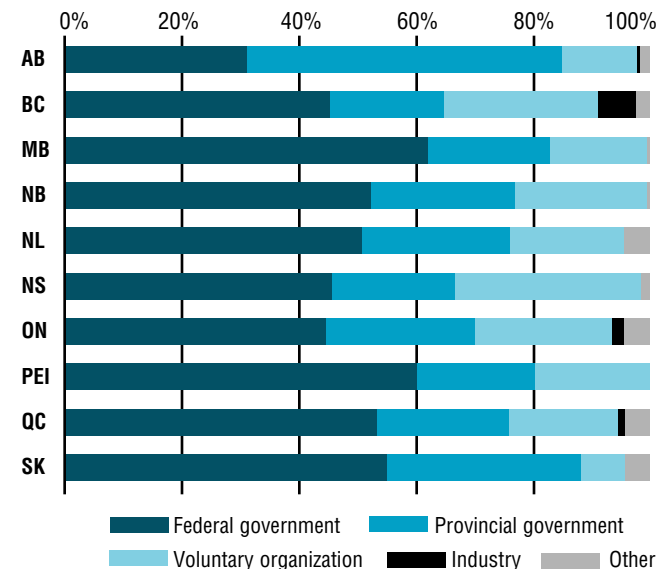
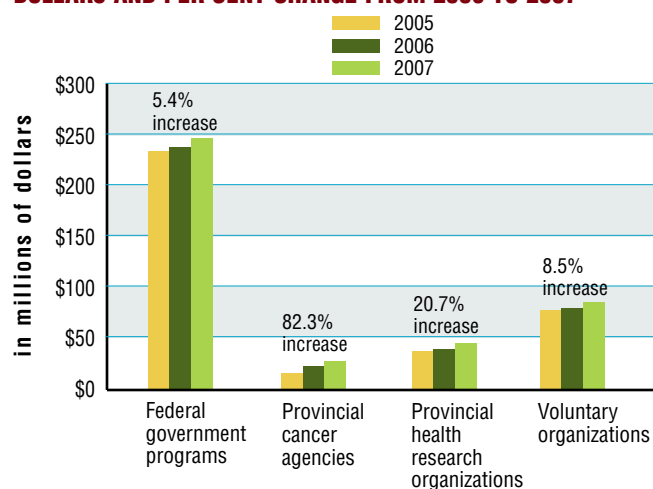


TABLE 1
2007 TOTAL CANCER RESEARCH INVESTMENT—BY PROVINCE OF PRINCIPAL INVESTIGATOR/PROJECT LEADER (PI/PL), IN DOLLARS PER CAPITAL INVESTMENT¹⁰

Province	Research Investments of PI/PL (\$)	Per Capita (\$)
Canada, total	398.5 M	12.10
Ontario	191.6 M	14.97
Quebec	97.5 M	12.68
British Columbia	48.2 M	11.18
Alberta	40.1 M	11.41
Manitoba	9.1 M	7.65
Nova Scotia	5.8 M	6.25
Saskatchewan	4.6 M	4.56
Newfoundland and Labrador	1.3 M	2.63
Prince Edward Island	0.2 M	1.24
New Brunswick	0.2 M	0.32

FIGURE 4
CANCER RESEARCH INVESTMENT BY FUNDER SECTOR IN DOLLARS AND PER CENT CHANGE FROM 2005 TO 2007²



etiology, two per cent to prevention, 11 per cent to early detection and diagnosis, 23 per cent to treatment, and the remaining 10 per cent to cancer control, survivorship and outcomes (Figure 5).² The per capita spending varied widely between provinces, ranging from \$0.32 million in New Brunswick to \$14.97 million in Ontario (Table 1 and Figure 3).¹⁰

The tight funding situation for clinical research in Canada has been compounded by a declining ability of hospitals and universities to support core clinical trial infrastructure. Universities have traditionally supported salaries and protected time for research while hospitals have allowed researchers the use of clinical laboratories and diagnostic tests. However, due to fiscal restraints, institutions have moved to a cost-recovery approach. Clinical researchers must find their own funding (through grants and per case funding) to support the infrastructure necessary for conducting clinical research in their institutions.

Emerging international competition poses yet another barrier. In 2007, the pharmaceutical industry spent \$1.3 billion dollars in research and development in Canada—\$600 million of which was spent on clinical trials.⁹ Recently however, there has been a strong shift with industry performing more clinical trials in developing countries in Eastern Europe, Latin America and South Asia.¹¹ These countries provide rapid access to large numbers of patients while conducting research that costs 30 per cent less than western nations. Consequently, Canada's participation rate in global pharmaceutical clinical trials decreased 12 per cent in 2007. With a 4.1 per cent share of global clinical trials, Canada ranked fourth behind France (4.3 per cent), Germany (5.7 per cent) and the U.S., which led with 49 per cent.¹²

It is not just shrinking pharmaceutical interest that concerns clinical investigators, it is also the impact on academic clinical trials developed and conducted by cooperative groups and investigators. From coast to coast, individual Canadian researchers and clinicians have also raised concerns that our nation's clinical trial capacity is eroding in the face of a variety of pressures and barriers. As noted by David Dilts, in a recent editorial on clinical cancer research in the U.S., the current trends are disturbing.¹³ While studies by pharmaceutical companies are important, it is essential that academic and cooperative groups continue to flourish.

“Any improvements in cancer care come from clinical trials.”

—Ezekiel J. Emanuel, MD, PhD, Chair, Department of Clinical Bioethics, U.S. National Institutes of Health³

Losing the competitive edge has far-reaching implications in our ability to lead the work of translating new discoveries into clinical applications.³ Clinical trials developed and conducted by Canadian academic investigators could answer the clinical and translational questions that are based on the most promising discoveries from Canadian laboratory researchers. Such trials could address the greatest concerns for the health and well-being of Canadians, in a manner most relevant to the Canadian healthcare system. Thus, the threat to cancer trials, at a time of great opportunity for the translation of research discoveries to clinical testing, is a critical national issue.

The increasing complexity of clinical trials has also had a significant impact on clinical cancer research centres across the country. The NCIC-CTG has seen a two-to-three fold increase in staffing demands necessitated in part by the increase in ethics and regulatory compliance required for conducting clinical studies. The timeline for conducting a trial – the time from activation of the trial to the first patient

enrolled in the trial – has also increased significantly.

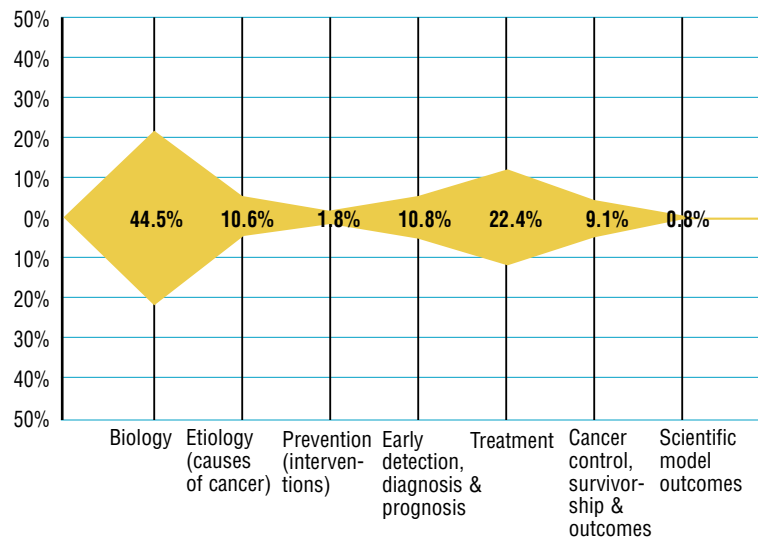
So what can we do to ensure the future “health” of clinical cancer research in Canada?

What are the Proposed Solutions?

A number of initiatives aimed at promoting the “health” of our research community and preventing further erosion of resources have recently been launched in Canada.

In February 2010, the Canadian Institute of Health Research (CIHR) proposed a 10-year plan to change health care including a strategy for patient-oriented research (SPOR) in Canada.⁹ It was proposed that Canada increase its investments and better coordinate its efforts in patient-oriented research to improve the quality, accessibility and cost-effectiveness of health care. The success of such a plan would require support not only from the federal, provincial and territorial governments but also from major stakeholders including research institutions (universities, hospitals, community centres), and clinician scientists as well as private

FIGURE 5
DISTRIBUTION OF 2007 CANCER RESEARCH INVESTMENT BY CSO CATEGORY (\$402.4M)²



and charitable sectors. This strategy would consist of four major components:

1. Improvements to the research environment and infrastructure,
2. up of mechanisms to better train and mentor health professionals and non-clinicians,
3. strengthening organizational, regulatory and financial support for multi-site studies, and
4. supporting best practices in health care.

Members of the Association of Canadian Academic Health-care Organizations (ACAHO) strongly supported the patient-oriented clinical research initiative.¹⁵ To advance the initiative, the Association proposed that the federal government incrementally invest \$10 million that would allow for the implementation of a series of pilot projects that if successful, would move to a broader series of projects across the country. But would this be enough? Comparatively, the National Cancer Research Network funding for cancer research alone in the U.K. is close to four times this amount per year. The U.K. investment in clinical research infrastructure for all diseases (NIH) is hundreds of millions per year.⁹ An investment of 10 million dollars in Canada for all diseases is unlikely to have any real impact.

In May 2010, with support from the Canadian Partnership Against Cancer, the Canadian Cancer Research Alliance launched the Pan-Canadian Cancer Research Strategy (PCCRS).³ This strategy provides a vision for Canadian cancer research achievements over the next five years. Priorities for enhanced funding and collaboration include cancer prevention, basic discovery research (i.e., genomics, cancer initiating cells, new agent discovery, biomarkers), clinical trials, health services/economics and tumour-specific partnered initiatives (e.g., collaboration with Canadian Breast Cancer Research Alliance).

These priorities have resulted in the identification of 24 key action items to be implemented between 2010 and 2012. The plan for clinical trials is to clearly outline the issues facing trials in Canada and make recommendations on how these issues can be resolved. The report will examine jurisdictions with healthy and growing cancer trial enterprises, consider how to engage the pharmaceutical industry and identify ways to maximize patient-oriented clinical research. In addition, the Pan-Canadian Cancer Research Strategy will aim to create an optimal cancer research system - one in which there is a balance of research funding across the three main categories: project grants, infrastructure and research personnel.

Regional initiatives have also been launched to enhance patient enrollment in cancer clinical trials in Canada. In 2004, the Ontario Institute of Cancer Research (OICR) set a goal to double Ontario patient recruitment into cancer clinical trials, within three years, in 28 participating cancer centres throughout the province. With a three year budget of \$12.9 million clinical trials recruitment increased from 8.9 per cent in 2004 to 12.4 per cent in 2007 (Figure 2).⁸ The suc-

“If Canada is not successful in rewarding innovation, innovation will be developed elsewhere.”¹⁴

—Russell Williams, President of Rx&D Canada

cess of this program however was based on a business model predicated on self-sustaining fiscal resources from enhanced patient recruitment to pharmaceutical trials. Increasing regulatory requirements and lack of ongoing infrastructure support resulted in a drop in clinical trial enrollment to 8.5 per cent in 2009, a lower figure than before the program went into effect.

In contrast, the National Cancer Research Network (NCRN) was established in the U.K. by the Department of Health in 2001 to provide the National Health Service with the infrastructure to support prospective trials of cancer treatments and support research undertaken by cancer charities. The initial goal was to double the trial enrollment of cancer patients by 2004. With an annual investment of \$20 million per year, overall accrual to clinical trials rose from a baseline of less than four per cent of new cases to 14 per cent by 2006. By 2010, recruitment of cancer patients to Cancer Network studies had quadrupled since 2001—from one in 26 patients to around one in six.^{16,17} Unlike the OICR infrastructure program, the Department of Health funding continued beyond the initial three year commitment.¹⁸

In 2001, stakeholder consultations with researchers, study sponsors, clinical trials sites and regional ethics boards identified inefficiencies in the research ethics review process as a major barrier to the establishment of multi-centre cancer clinical trials in Ontario. In 2003, the Ontario Cancer Research Network responded by establishing the Ontario Cancer Research Ethics Board (OCREB).¹⁹ The board now has 22 member-centres, representing the majority of the province's hospitals that conduct cancer trials in Ontario. This overarching ethics board markedly reduces the duplication and workload for researchers, sponsors and local ethic boards throughout Ontario. Similar specialized multi-institutional research ethics boards operate in Alberta and British Columbia.

Recommendations

If we believe, as a society, that finding a cure for cancer is important then federal and provincial governments, health care organizations, hospitals, universities and foundations must acknowledge and support clinical cancer research. The success of programs such as the Pan Canadian Cancer Research Strategy, and the CIHR Strategy for Patient-Oriented Research, along with other clinical cancer

initiatives, will depend on the following commitments.

- 1 A long term financial commitment by government(s) and healthcare organizations to provide stable funding and a system of support for clinical cancer researchers. Funding support could be modeled after the U.K.'s National Cancer Research Network program that has successfully supported clinical cancer researchers and consistently increased patient participation in clinical trials throughout the U.K. over the past ten years.
- 2 Adequate infrastructure support within cancer based healthcare organizations that facilitate patient participation in clinical trials. This would require sustainable resources for patient recruitment, clinical research associates, data managers and oncology nurses.
- 3 Measurable indicators that include real time assessment and implementation of what is working well and elimination of what is not.
- 4 Improved efficiencies in the activation and conduct of clinical trials in order to remain competitive in international markets, to ensure that Canadians have continued access to novel cancer drugs and treatments. This would require the development of a seamless national approach to contract negotiations, research ethics approval, regulatory monitoring and budget negotiations.

All of this could be made possible if each Canadian affected by cancer were offered a clinical trial as a "standard" treatment option. We, the general public, can do our part by accepting the importance of cancer clinical research and endorsing this change in medical practice. No longer would individuals who participate in clinical trials have to feel like "guinea pigs". Rather, by understanding that participation in clinical cancer trials assures consistent standards and reliable quality of care, concerns about participating in research would evaporate. Participation in a study may lead not only to better outcomes for the patient but may also make a significant contribution to the discovery of new and better cancer treatments. Importantly, cancer control would be immeasurably accelerated.

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