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REVIEW ARTICLE

Improving Cancer Outcomes Through International Collaboration in Academic Cancer Treatment Trials

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ABSTRACT

Purpose
The need for international collaboration in cancer clinical trials has grown stronger as we have made progress both in cancer treatment and screening. We sought to identify those efforts already underway which facilitate such collaboration, as well as barriers to greater collaboration.

Methods
We reviewed the collective experiences of many cooperative groups, governmental organizations, nongovernmental organizations, and academic investigators in their work to build international collaboration in cancer clinical trials across multiple disease sites.

Results
More than a decade of work has led to effective global harmonization for many of the elements critical to cancer clinical trials. Many barriers remain, but effective international collaboration in academic cancer treatment trials should become the norm, rather than the exception.

Conclusion
Our ability to strengthen international collaborations will result in maximization of our resources and patients, permitting us to change practice by establishing more effective therapeutic strategies. Regulatory, logistical, and financial hurdles, however, often hamper the conduct of joint trials. We must work together as a global community to overcome these barriers so that we may continue to improve cancer treatment for patients around the world.

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INTRODUCTION

As improvements in cancer treatment have led to increased survival, the need for expanded collaboration on treatment trials has correspondingly increased. First, new active treatments which prolong survival in turn often require larger sample sizes to detect potential benefit from experimental regimens or to determine the similar efficacy of a less toxic regimen. Second, developments in molecular biology have allowed the use of molecular markers to define patient cohorts based on tumor biology.[1] As a result, we must cast a wider net to enroll the necessary number of patients with the appropriate molecular classification within a reasonable timeframe. Third, the success of effective screening and earlier diagnosis has decreased the incidence of advanced-stage disease for certain cancers in developed countries. Fourth, targeted therapy may offer effective treatment for relatively rare tumor types or rare subtypes of common cancers. Fifth, the integration of the plethora of new cancer treatment agents into existing treatment regimens will require the rapid conduct of phase III trials so that results are relevant to current clinical practice. Finally, the completion of larger trials across multiple countries will assure the broad applicability of research findings worldwide as well as facilitate the uptake of improvements in cancer treatment into standard practice. The following discussion focuses on efforts made to facilitate global collaboration, as well as some of the barriers to such collaboration. Both clinical investigators and policy makers need to be aware of these issues.

FACILITATING INTERNATIONAL COLLABORATION IN CLINICAL TRIALS

Exchange of Information on Clinical Trials

The importance of a central registry for clinical trials was underscored by the WHO with the

creation of the WHO International Clinical Trials Registry Platform in 2005.[2] Registries contributing to this global trials registry include the US National Library of Medicine registry, called Clinical Trials.gov, and the National Cancer Institute (NCI) registry of United States and international cancer clinical trials.[3,4] The European Commission is considering the establishment of a public database for all clinical trials conducted in the European Union.

Harmonization of Staging, Classification, and End Points Definition

Consensus on standards for disease classification, staging, and trial end points is required to make international collaboration in clinical trials successful. At present, the International Union Against Cancer works in conjunction with the American Joint Committee on Cancer and the International Federation of Obstetrics and Gynecology to maintain and update the current cancer staging system.[5] The WHO and the International Agency for Research on Cancer have led efforts toward standardization of pathologic diagnoses through publication of the International Classification of Diseases for Oncology, as well as various monographs on specific cancer sites.[6] More recently, efforts to harmonize molecular staging of cancer have been led by the hematologic oncology and pediatric oncology communities.[1,7-12]

Regulatory authorities in Europe, Japan, and the United States established the International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use in 1990.[13] The International Conference on Harmonisation issued a common technical document in 2000; it continues to work on harmonization for drug development and registration. As part of implementation of these efforts, the US Code of Federal Regulations now makes clear that foreign clinical data can be the sole basis for granting marketing approval to a new drug by the US Food and Drug Administration.[14] Several agents, including bevacizumab for metastatic breast cancer, temozolamide in conjunction with radiation for newly diagnosed gliomas, and letrozole for early, hormone receptor–positive breast cancer in postmenopausal women, were approved for marketing in the United States and Europe based only on data from clinical trials conducted outside those jurisdictions.[15-17]

The NCI, the National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG), and the European Organisation for Research and Treatment of Cancer (EORTC) have undertaken to harmonize adverse event reporting and data capture for cancer clinical trials. These harmonization efforts have included the development of common nomenclature and scoring for treatment-related toxicity and adverse events.[18-20]

Objective assessment of tumor response in both solid and hematologic tumors has recently been the subject of several international efforts. The Response Evaluation Criteria in Solid Tumors Working Group (with membership from NCI, EORTC, NCIC-CTG, supplemented with input from the nine NCI-sponsored clinical trials groups, pharmaceutical industry, and regulators) published criteria for response assessment in 2000, which was updated in 2008.[21,22] These criteria have been endorsed by regulatory bodies such as the US Food and Drug Administration and the European Medicines Agency. The NCI and EORTC are currently revisiting the 1999 recommendations regarding use of [18F]-fluorordexoyglucose and positron emission tomography for use in evaluating tumor response.[23] Similarly, recommendations for standard response criteria for lymphomas and acute myeloid leukemia have been published.[24,25]

The Breast Cancer Intergroup of North America has recognized the need for harmonization of clinical end points in trials of adjuvant treatment for breast cancer. They have proposed "standardized definitions for efficacy end points."[26,27]

Other harmonization efforts have included the development of standard protocol language for surgical procedures, the details of chemotherapy administration, and supportive care measures. The International Atomic Energy Agency is working to develop harmonization for radiation treatment planning and dosing in cancer treatment trials.

Challenges to International Collaboration

In the face of these efforts to increase participation in clinical trials and to facilitate international collaboration, national and regional regulatory authorities have heightened the level of oversight and regulation required for clinical trials in recent years. Therefore, when trials are conducted in multiple jurisdictions, an increasingly complex array of differing regulations apply. For example, in 2001, the European Union issued a directive concerning clinical trials of medicinal products to ensure compliance with the International Conference on Harmonisation Good Clinical Practice guidance.[28] This directive affects the conduct of almost all phase I, II, and III trials assessing a drug or drugs. The requirements of the European Union Clinical Trials Directive, which were developed for industry-sponsored studies, have hampered the opening of clinical studies with academic sponsors that often do not have the resources available to meet the expanded regulatory obligations.[29] In addition, the European Union Clinical Trials Directive has also slowed collaboration between European investigators and those outside the European Union. Implementation of this directive has varied from country to country within the European Union, adding to the level of complexity and staff requirements.[30]

The US Department of Health and Human Services Office of Human Research Protection has mandated that all research sites outside of the United States that participate in research funded by the US government must file documentation certifying that each research site observes the Declaration of Helsinki on Ethical Principles for the Conduct of Research on Human Subjects and has an independent ethics committee.[31] Sites participating in trials sponsored by the NCI must also undergo regular on-site audits.[32]

Both the systems and forms for reporting study-related adverse events can vary from country to country, although most cooperative groups and academic institutions do use the harmonized criteria for categorizing and grading adverse events. In addition, companies often differ in their requirements for reporting adverse events, as well as their interpretation of each country's regulatory requirements.

INDEMNITY INSURANCE

In many countries, independent ethics committees/institutional review boards may require indemnity or clinical trial insurance for institutions for non-negligent harm resulting from clinical research, as well as insurance coverage for patients for untoward events. In the European Union, such insurance is required by the European Union Clinical Trials Directive. Insurance availability often varies by country.

TUMOR AND SPECIMEN COLLECTION

The growing interest in establishing the molecular determinants of outcome and of predictors of therapeutic benefit has led to the frequent incorporation of translational biologic questions in randomized trials. Both exploratory and validation studies may have implications for intellectual property issues relating to correlative biology.

To address these translational questions, collection of tumor and other specimens from each patient enrolled is thus becoming increasingly commonplace. Shipment of specimens across international borders may require permission from a national oversight body or may be forbidden altogether. In some cases, it may be necessary to set up parallel specimen banks and core laboratories in each country or region. If multiple specimen banks and core laboratories are established, however, the trial will need to institute quality assurance procedures to ensure that all specimen banking and analyses are performed using the same techniques.

As correlative science techniques have evolved, so has the need for harmonization of tissue collection, processing, and testing. The NCI has recently published guidelines for tissue acquisition, as has the EORTC.[33] The North American cooperative groups and the Breast International Group have formulated breast cancer–specific guidelines, which they have agreed to incorporate in future studies.[34]

IMAGING FOR STAGING, TREATMENT PLANNING, AND EVALUATION OF RESPONSE

As cancer imaging has grown more sophisticated, the need for quality assurance and quality control of imaging studies has also grown. Therefore, international collaboration in cancer clinical trials often requires the development of guidelines for imaging studies, plans for routine central review of some or all studies, and consideration of a virtual imaging bank in which digitized imaging studies from patients on clinical trials can be collected and reviewed. The NCI, working in collaboration with cooperative groups with expertise in image acquisition, the American College of Radiology Imaging Network, the Quality Assurance Review Center, and the Cancer and Leukemia Group B imaging core laboratory at Ohio State University, developed a virtual imaging evaluation workspace in 2007. The consortium has established an imaging core service and repository with capability of acquiring and storing image objects on a worldwide basis. In addition, the same collaborators plan to develop standard operating procedures for assessment of imaging end points in cancer as well as evaluation of new imaging markers.

RADIATION THERAPY

As a critical modality for cancer treatment, radiation in clinical trials must undergo similar processes for quality assurance and quality control as other modalities of treatment. The NCI supports quality assurance for radiation dosimetry in NCI-sponsored trials through the Radiological Physics Center, quality assurance for radiation delivery methods through the Radiation Therapy Oncology Group and the Quality Assurance Review Center, and, more recently, quality assurance for advanced-technology radiation therapy (eg, three-dimensional conformal radiation therapy, intensity modulation therapy) through the Advanced Technology Consortium.[35-39] These quality assurance activities have been routinely implemented for NCI-sponsored cancer trials in North America, as well as for select academic and pharmaceutical trials in Europe and Japan. Globally, however, quality assurance requirements, such as facility questionnaires, facility credentialing, external reference dosimetry audits, and phantom measurements, vary from group to group, both in content and evaluation criteria. This variation hampers collaboration and makes comparisons and meta-analyses difficult. In addition, both radiotherapy technology and the tools for quality assurance are constantly evolving. Close engagement between clinical trialists and manufacturers is required to integrate new digital formats smoothly and ensure that a common framework for data interpretation can achieve a uniform level of quality.

FINANCIAL AND LOGISTICAL SUPPORT

The ability to conduct cancer clinical trials efficiently requires ongoing support for infrastructure, both centrally and at participating institutions. Building the infrastructure for a specific trial is much less efficient than building and maintaining infrastructure for an ongoing series of trials. The central and institutional costs for cancer treatment trials are summarized in Tables 1 and 2. Support for these costs may come from a variety of sources, including government, industry, charity, and local academic institutional contributions. Government support has varied from country to country and region to region. The NCI began to support the infrastructure for cancer clinical trials in 1956. In 2007 the NCI's budget for the US-based nine clinical trials cooperative groups, which together enroll about 25,000 patients per year to trials, was approximately $145 million. Over the past 10 years, the United Kingdom has formalized and provided centralized funding for standing clinical trials networks throughout the country, initially for oncology, and now for medical research of all types. The United Kingdom provides infrastructure support to all clinical sites participating in approved phase II and III trials and large cohort studies through the National Cancer Research Network. Publicly funded charities such as Cancer Research UK and government agencies, such as the Medical Research Council, provide support for both early- and late-phase

Table 1. Central Costs for Cancer Treatment Trials

Protocol design and development, including support for meetings and conference calls
Preparation of applications to central regulatory authorities and central ethics authorities, as applicable
Collection/monitoring of institutional and investigator regulatory compliance
Verification of patient eligibility and management of treatment assignment
Clinical trial insurance
Patient random assignment
Database development
Data collection and management
Drug supply and distribution
Statistical design and analysis
Tumor, specimen and imaging banking
Quality assurance/quality control
Onsite monitoring and audits of participating sites
Pharmacovigilance

Table 2. Institutional Costs for Cancer Treatment Trials

Ethics review and local competent authority review of proposed trials, open trials, adverse events, amendments
Time of local investigators, research nurses, pharmacists, and data managers
Time and resources for related studies (pathology, imaging) over and above that which is standard of care
Research pharmacy
Quality control efforts

clinical trials through research grants to clinical investigators and trials units.[40,41] The estimated yearly budget for academic cancer clinical trials in the United Kingdom, including support for network infrastructure is about £55 million. The Ireland–Northern Ireland National Cancer Institute Cancer Consortium, with financial support from the Republic of Ireland, the United Kingdom government, and the NCI, established a clinical trials network covering the Republic of Ireland and Northern Ireland.[42] In France, the Ministry of Health and INCa (Institut National du Cancer) have established support for clinical trials through competitive requests for applications as well as support for data management centers, including those of specialized networks. The governments of Japan and Korea have undertaken steps to support infrastructure for and encourage academic clinical trials in cancer. A similar effort is underway in the Middle East. The government of Australia, through Cancer Australia, has recently undertaken support and expansion of existing trials networks, which had previously been funded through a variety of means including fundraising and charitable donations, peer-reviewed grants for individual trials, and infrastructure support for some groups by the New South Wales Cancer Institute. Funds raised by charity (the Canadian Cancer Society) have been used for many years to support the core activity of the NCIC-CTG. Professional medical societies in China, India, Japan, Korea, and other countries have undertaken to start cooperative groups to run clinical trials for cancer patients. Local institutions also have generously contributed their own funds, as well as funds raised through charitable appeals, to help support the infrastructure for clinical trials, such as the costs listed in Tables 1 and 2.

We note that limitation of funding has hindered clinical trial research in many instances. In the United States, for example, the per-patient cost to support research nurses, data managers, and physician time for a hypothetical phase III cancer treatment trial has been estimated at $6,000 (US$) in 2003.[43] NCI funds are only sufficient to underwrite a per-patient payment of $2,000 (US$). Clinical trials groups outside the United States that lack substantive support from charity, industry, or government often must decline participation in promising phase III studies unless separate industry funding is available.

PHARMACEUTICAL INDUSTRY INVOLVEMENT IN INTERNATIONAL TRIALS

Pharmaceutical companies may run international trials on their own, or in conjunction with established clinical trials cooperative groups. Effective collaboration between industry and clinical trials groups has resulted in the successful completion of many important cancer trials. Not surprisingly, however, there may well be tensions between the objectives of the pharmaceutical company, which generally wants to support trials that provide data appropriate for a licensing application, and those of the cooperative group, which wants to evaluate the additive benefit of that new agent to standard treatment. In some cases, the cooperative group may also want to combine or compare agents from two different companies. In addition, in many instances, a trial addressing a question of great importance to oncologists and patients may be of no interest to the pharmaceutical industry. An international consortium of academic breast cancer trialists have recently proposed a model template for successful partnership between academia and industry.[44]

Pharmaceutical support for trials may include the supply and/or distribution of experimental drugs, per-patient payments to participating institutions, and support of central activities, such as investigator education, laboratory assays, statistical analysis, data management, quality control/quality assurance, and audits. The provision of study drug and financing across international boundaries may be complicated due to the variation in licensing arrangements across the globe. Recently, the Chief Executive Officer Roundtable on Cancer, working in partnership with the NCI and academic institutions in the United States, developed a set of common contract clauses designed to shorten the length of time required for legal agreements.[45]

CURRENT REPORT CARD ON GLOBAL COLLABORATION

How should we characterize the current state of global collaboration in cancer treatment trials? Ideally, clinical trials groups for each cancer site should have a regular mechanism for the exchange of ideas about current science and proposed trials. Such a structure would facilitate the design and conduct of complementary trials, avoid unnecessary duplication, and stimulate collaboration on meta-analyses of similar studies. Where appropriate, groups can work together on the design and management of joint global trials.

Regional international networks have been established for decades both in Europe and in North America. For example, leading European oncologists set up the EORTC in 1962. Today, EORTC's top 35 accruing institutions are located in 11 European countries, as well as Turkey and Egypt. Similarly, cancer researchers in Canada and the United States have worked together for many years through such collaborative groups as the National Surgical Adjuvant Breast and Bowel Project, the Radiation Therapy Oncology Group, and the Children's Oncology Group. The NCIC-CTG has worked closely with investigators in the United States, Europe, and Australia. Global networks for cancer treatment trials in the developing world have been set up by both the International Network for Cancer Treatment and Research and the International Atomic Energy Agency. In addition, many groups of trialists have established ongoing collaborations to perform meta-analyses based on data from individual patients accrued to clinical trials. A partial list of recent key cancer treatment trials made possible through effective international collaboration is presented in Appendix Table A1 (online only).

Effective interchange between clinical trials groups has most often been accomplished under the umbrella of international intergroup committees. A list of the activities which we would expect from an effective international intergroup is presented in Table 3. One of the best examples of effective intergroup activities is in breast cancer. Globally, the Breast International Group and the International Breast Cancer Study Group bring together 41 member groups from Europe,

Table 3. Expectations for Functional Global Intergroup Committees

Required participation by member groups in at least some intergroup trials
Required participation by groups in intergroup activities
Dues to support intergroup infrastructure and meetings
Attendance at meetings and conference calls
Regular face-to-face meetings, conference calls, and trial-specific workshops
Routine exchange of information about active and planned studies
Joint development of concepts for new trials
Development of joint trials as appropriate and feasible, ideally to include:
Single protocol with country-specific appendices
Common case report forms
Single data base
Development of complementary trials as appropriate and feasible
Routine engagement with industry as an intergroup
Individual-patient date meta-analyses as appropriate

Canada, Latin America, Australia/New Zealand, and Asia, in addition to those from North America. The Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization trial (NCT 00490139), sponsored by NCI, the Breast Intergroup, and GlaxoSmithKline is an example of a worldwide trial made possible through international collaboration and industry partnership.[46]

In brain cancer, the EORTC, NCIC-CTG, the Trans-Tasman Radiation Oncology Group (based in Australia and New Zealand), and the United States–based Radiation Therapy Oncology Group and North Central Cancer Treatment Group have developed a joint disease strategy for high-grade gliomas. This work follows up on the joint international temozolamide trial previously mentioned.

In gynecologic cancer, the Gynecologic Cancer Intergroup, formed in 1997, brings together 16 cooperative groups that conduct cancer treatment trials for women with gynecologic cancer. Under the auspices of the Gynecologic Cancer Intergroup, cooperative groups from Australia/New Zealand, Italy, the United Kingdom, and the United States quickly completed accrual of 4,000 women to Gynecologic Oncology group 182/International Collaboration in Ovarian Neoplasia 5, the largest ovarian cancer treatment trial to date.[47]

In addition, there are numerous instances of academic and industry-led trials conducted across the developing and developed worlds. To date, however, global integration of academic cancer treatment trials remains the exception, rather than the norm.

CONCLUSION

The scientific imperative for international collaboration in cancer treatment trials is clear. Our ability to establish international collaborations will result in maximization of our resources and patients, permitting us to complete definitive trials in a timely manner. Regulatory, logistical, and financial hurdles, however, often hamper the conduct of joint trials. The advantages and disadvantages of such international collaboration are listed in Table 4. Ongoing efforts on the part of cancer investigators, cooperative groups, national research institutions, national governments, competent authorities, ethics committees, and pharmaceutical companies are needed to strengthen global collaboration so that we may identify effective treatments for our patients more quickly. In addition, integration of investigators and cooperative groups in China, India, Japan, Korea, Latin America, and other countries in Asia, Africa, the Middle East, and Europe into the existing intergroups and clinical trials networks will make our trials more representative of cancer patients from around the globe and the results from our trials more broadly applicable to those patients.

Table 4. Advantages and Disadvantages of International Collaboration in Cancer Treatment Trials

Advantages	Faster accrual from more sites for patients with common cancers and with all stages of disease
	Faster accrual for patients with uncommon and rare tumors, specific molecular defects, and less common histologic subtypes
	Broader applicability of research results
	Fewer duplicative trials
	More complementary trials
	More rapid dissemination of innovations in cancer treatment
Disadvantages	Differing regulations between countries
	Differing levels of infrastructure support for cancer clinical trials between countries
	Differing processes and schedules for scientific review by funding bodies between countries
	Longer lead time for concept and trial development
	Differing licensing arrangements for specific drugs between countries
	Contractual issues with pharmaceutical companies in different countries
	Drug distribution issues in different countries

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