

# Guide for Investigators Conducting International Cancer Research Involving Developing Nations

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**International** medical collaborations, previously known as “medical missionary work,” have existed for centuries. As aptly described by Panosian and Coates,<sup>1</sup> historical motivations for this type of outreach included the desire to spread “religion as well as compassionate care.” The term “medical missionary” has endured over the years because of this history, and is therefore used in this commentary, but it is not intended to carry any paternalistic implications. Today, we see many programs (although one easily could argue that the supply is nowhere near close to meeting the demand), coordinated by individuals as well as by entire healthcare institutions and schools, that feature students, trainees, nurses, and physicians from developed areas of the world donating their time, expertise, and resources to medically underserved communities. These programs are mutually beneficial and enlightening.

Medical missionary-based efforts have witnessed a recent increase in activity related to oncology. Global partnerships in cancer prevention, detection, treatment, and research are expanding in both scope and volume. This growth has been fueled by strengthened recognition of the following issues:

- The worldwide cancer burden is rising,<sup>2,3</sup> and the increasing cancer mortality rates are disproportionately felt in medium- and low-income countries.<sup>4,5</sup> It is projected that cancer incidence and mortality rates will increase by 1% per year.
- Cancer burden varies by geography as well as cultural background, consistent with evidence that risk factors for selected cancers include some that are modifiable, such as those related to diet and lifestyle, or exposure to particular infectious or viral agents.
- Cancer burden varies by race/ethnicity, suggesting that the pathogenesis of some cancers may have hereditary components associated with ancestral background; international oncology research programs may therefore improve insights related to hereditary components of some cancers.
- Regardless of cancer etiology, outcome will be completely dependent on access to appropriate diagnosis and treatment.
- As westernized lifestyles and diet are increasingly adopted in underdeveloped countries, the cancer burden associated with the more industrialized societies (such as breast and colorectal cancer) is also becoming more prominent in the poorer countries, but with a notable and tragic lag in acquisition of early detection and treatment advances for these cancers. This results in even larger-magnitude disparities in cancer outcome between affluent and impoverished parts of the world.

Disparities in cancer screening, treatment and outcome between different populations have prompted many groups to provide support to developing countries via medical “missionary” services, as well as the conduct of cancer research and clinical trials. Launching cancer research programs in collaboration with developing countries has vital importance, but it requires patience, dedication, and attention to logistic details that do not necessarily arise in the course of oncology investigations based in the United States. This report is therefore designed to provide some guidance to United States-based cancer investigators who are interested in pursuing international research partnerships. The steps described are not necessarily sequential; several are interrelated and may be pursued on a concomitant basis.

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### **Step 1: Establishing Partnerships**

Once an investigator has generated his/her research questions, and it is clear that an international partnership will be meaningful, the next critical step is to identify the collaborating oncology team. This is not at all a trivial point, as healthcare resources are quite limited in developing countries, and oncology teams that can spare time as well as energy for research endeavors are particularly rare. Extensive time and money can be spent on the partial development of collaborations that never come to fruition. The investigator can more efficiently identify partnerships that are likely to be durable if he/she starts out by contacting other investigators within the home institution who have already established international exchange programs. Expanding on relationships that have already proven to be successful will strengthen the institution's comprehensive international program, and leads to a more efficient launching of the novel program. The investigator should look for ongoing student or trainee exchange programs at her/his institution. These programs and contacts might be within other medical departments, or they might even be coordinated by other schools affiliated with the home institution, such as the international section of the law school, business school, or humanities program.

If appropriate contacts are unavailable through the home institution, another strategy is to identify international contacts through the published literature. Lead authors from studies that were based in the country or region of interest could include potential collaborators who might welcome partnerships with international collaborators.

Academic professional societies, such as the American Society of Clinical Oncology ([www.asco.org](http://www.asco.org)), the Society of Surgical Oncology ([www.surgonc.org](http://www.surgonc.org)), and the American College of Surgeons ([www.facs.org](http://www.facs.org)) all have international components that can serve the dual purpose of initiating medical missionary as well as collaborative research programs.

### **Step 2: Travel Between the International Collaborative Sites**

#### **Travel by the United States-based investigator**

The principal investigator should certainly obtain his own/her own passport. It is useful (and for many countries mandatory) to obtain a travel visa for the country with which you are collaborating. Web-based businesses are available to coordinate the application process, but information about visa requirements and the application process can be obtained directly through the US Depart-

ment of State (<http://travel.state.gov/>). These visas will facilitate travel for multiple visits over a prespecified time interval. The application process usually requires payment of a fee, submission of the applicant's passport, additional applicant photographs, anticipated travel information, and contact information for references in the country that is being visited. In some countries, the visa is purchased at the time of arrival in the foreign country, but for other countries the process may take several weeks and should therefore be initiated well in advance of the first planned travel date. After application processing and approval, the passport will be returned to the applicant with the visa enclosed.

Safe travel to developing nations requires careful attention to infectious risks. Appropriate vaccinations or prophylaxis to protect against malaria, yellow fever, and/or other parasites/microbes are essential. Many universities will have specialized clinics established for preparing staff/employees for international travel. Alternatively, investigators can obtain relevant information from the World Health Organization (<http://www.who.int/ith/vaccines/en/>) or the Centers for Disease Control (<http://wwwn.cdc.gov/travel/default.aspx>).

The investigator must also address communication efforts and potential language barriers. If English is not the primary language of the collaborating country, then the investigator must plan for availability of translators. Even when English is the primary language, there may be regional dialects or languages that are more commonly used by the local community. Personal familiarity with these dialects is ideal, but if this is not feasible, then the investigator should attempt to be accompanied by a collaborator who can communicate more readily with the general population.

Travel within developing countries can also be problematic and should be addressed in advance of the planned visit. Taxi services will not necessarily be available, and reliable, knowledgeable drivers with safe automobiles should be identified and their services retained before arrival. The medical personnel with whom the investigator is collaborating may be able to coordinate these services, or the hotel may be able to assist.

#### **Bringing international collaborators to the United States**

Sponsorship for international research partners to visit the United States is quite valuable in cementing the research partnership. These visits allow the international collaborators to view the research methods and laboratory

facilities firsthand. They also provide opportunities for exchange of information and clinical experiences. For example, international collaborators may find it useful to attend meetings of the multidisciplinary tumor board, the clinical research quality assurance committee, or the protocol review committee. Observations from these meetings frequently provide ideas that can be modified for incorporation into the clinical practice of the international facility.

### **Step 3: Conduct of International Human Subjects Research**

Conduct of human subjects research involving international populations may require sensitivity to special issues related to the culture and resources of the partnering communities. For example, compensation to participants within the United States frequently takes the form of a modest financial payment or voucher to cover time, travel, and parking expenses. Participants in developing nations may have a preference for compensation in the form of meal(s), bottled water, and/or sanitary products, in addition to monetary compensation.

As in the United States, all human subjects research will require review and approval by an institutional review board (IRB) or its equivalent. The local IRB may require documentation of the international IRB approval before considering the protocol, or it may grant preliminary approval that is contingent on obtaining international approval. The international IRB-equivalent must have a Federal Wide Assurance number that documents its adherence to conventional rules of human research subjects protection. All registered Federal Wide Assurance numbers, as well as additional information regarding international human subjects research, can be obtained through the Office for Human Research Protections ([http://www.hhs.gov/ohrp/assurances/assurances\\_index.html](http://www.hhs.gov/ohrp/assurances/assurances_index.html)).

Another valuable resource to guide investigators conducting human subjects research is the Fogarty International Center (<http://www.fic.nih.gov/>). The Fogarty International Center is dedicated to “advancing the mission of the National Institutes of Health by supporting and facilitating global health research conducted by US and international investigators, building partnerships between health research institutions in the US and abroad, and training the next generation of scientists to address global health needs.” It therefore provides information regarding funding sources and the legalities of conducting international research.

### **Step 4: Specimen Acquisition and Transport**

Cancer research frequently involves the transport of tissue specimens from the patient source to the study laboratory, and international studies are fraught with potential risks that are necessarily appreciated when human studies research is conducted within a single American facility. The climate of some underdeveloped countries may involve extremes of temperature that can destroy precious and unique tissue specimens. The power supply of health-care and laboratory facilities may be unreliable, which can jeopardize long-term storage of accumulated tissue specimens. Commercial transport businesses and/or customs agencies may have restrictions on the transport of particular types of tissues or tissue storage agents (eg, dry ice). All of these potential barriers to the successful transport of research specimens should be sorted out before the actual research is underway.

Investigators seeking to conduct genotyping studies that involve DNA extraction may find that use of salivary sources are easier than reliance on blood specimens, and saliva collection kits (such as Oragene DNA kits, available via [http://www.dnagenotek.com/products\\_oragene.htm](http://www.dnagenotek.com/products_oragene.htm)) are readily available. Tissue specimens can be well preserved and easily transported when formalin-fixed and embedded in paraffin blocks. Laboratory resources within the collaborating international institution should be evaluated in advance, as many underdeveloped countries will have very limited supplies of the formalin preparations that are commonly used in the United States, or they may have a limited supply of the necessary tissue cassettes. The investigator from the United States must therefore budget for the expense of all supplies that are necessary for tissue acquisition. The manpower used to reserve, allocate, and store the relevant specimens may also be in limited supply, and support for these services should also be included in financial planning for the research. An absolutely critical point that cannot be overemphasized is the finding that research specimens from international patient populations (just as within the United States) can only be considered available for research if the primary, treating health-care facility has already accounted for all tissue necessary for diagnostic and treatment purposes.

Transport of intact, usable specimens can be further ensured by initial trial run transport of disposable, nonresearch specimens. For example, the investigator might collect an aliquot of his/her blood or saliva, use the planned transport mechanism, and then check for feasibility of the proposed studies on this specimen after it has reached the United States-based research or laboratory facility. A

tissue specimen that would otherwise have been discarded by the international collaborating facility could be used as a sample for testing the feasibility of transporting and studying a formalin-fixed, paraffin-embedded specimen. Specimens that are already sectioned and fixed onto microscope slides face the obvious risks associated with the fragility of glass preparations. In addition, if immunohistochemical studies are planned on these slides, the investigator must be sure that the glass slides are of the sturdy, heat-resistant composition that is commonly used in developed countries. The pathology laboratories in many underdeveloped countries may lack routine availability of immunohistochemistry services, and they therefore may not invest in slides that are appropriate for these types of studies. As noted previously, the expense and accommodation of these supplies is a burden that must be borne by the primary investigator.

The Centers for Disease Control can provide permits for research investigators to serve as “human couriers” in transporting tissue/biologic specimens (permits to “import or transfer etiological agents or vectors of human disease”), and applications can be obtained at <http://www.cdc.gov/od/eaipp/>. The advantages of obtaining this type of permit are that the investigator can personally accompany her/his research specimens during travel by commercial transit such as airlines, and these permits are accompanied by special labels that can be applied onto the specimen containers to minimize the risk of damage during the necessary inspection process related to international security programs. The investigator should carefully review the Centers for Disease Control regulations to determine whether his/her specimens would be eligible for and benefit from using this type of permit.

In summary, it is clear that international studies of cancer will increasingly involve collaboration with under-

developed countries. Hopefully these research partnerships will also strengthen communication and understanding between diverse populations. The success of these endeavors would also be expected to improve access to advances in cancer detection and treatment on a worldwide basis. Opportunities for cultural and academic exchange function in both directions; Western investigators and their trainees benefit greatly from their enlightenment regarding the costs and limits of healthcare resources worldwide, and the collaborating healthcare providers in underdeveloped countries can gain from the expertise and resources donated by their research collaborators. This summary is certainly not a comprehensive text on the conduct of international oncology research. Rather, the goal is to stress the value of this work and to provide some basic points of guidance regarding the successful initiation of this work.

## CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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