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Global collaboration

Mastering scientific protocols is only half the battle when it comes to conducting a clinical study in another country, says **Andrew Fung**.

In 2010, I began work on a project to create a new type of malaria test. I wanted to diagnose the disease using saliva, with an inexpensive test that looked, felt and tasted like chewing gum, rather than through the conventional blood sample. I had first proposed the idea in an effort to impress at an interview for a postdoctoral position. To my great delight, it gained funding from the Grand Challenges Explorations programme of the Bill & Melinda Gates Foundation in Seattle, Washington. I was aiming to land a job designing medical devices, but ended up with a grant for a blue-skies idea.

Had I bitten off more than I could chew? I was a postdoc at the University of California, Los Angeles (UCLA), at the time, and Los Angeles has few malaria patients. How would I confirm the prevalence of the malaria-causing parasite's proteins in saliva? I would have to go overseas and, crucially, I would have to build a collaborative group of experts whose skills complemented my own.

Successfully managing this collaborative, international clinical study required not only the right team, but also careful planning, dealing with regulations and adapting to unexpected circumstances in a different culture. I learned that it takes more than a creative idea and bench experience to guide a project to its intended destination.

ASSEMBLE RESEARCH ALLIES

I had training in protein detection, an essential skill for analysing samples in the field, but needed help to run a clinical study in a malaria-endemic region. A friend and mentor — Theodore Moore, the clinical director of the Pediatric Blood and Marrow Transplant Program at UCLA — shared my interest in making new medical tools for developing communities. In 1989, as a senior medical student, Moore had started to volunteer for relief efforts around the world. He ended up training medical professionals in countries from southern Africa to the Middle East. I wanted Moore on the team because of his professional expertise and his sympathy for the cause.

I also needed access to malaria patients, and a partner to handle field operations. During Moore's medical missions in the Philippines, he had befriended just the right person: Daniel Horton, then administrator of the Palawan Baptist Hospital (PBH), which he had helped to establish. During his 36 years in rural Palawan, the province with the highest incidence of malaria in the Philippines, Horton had seen more malaria patients than he could remember. He knew how to improvise under unexpected conditions, and could help us to navigate the local culture. Moore and Horton had ▶

strengths in areas that were my weaknesses.

At our kick-off meeting, we agreed on the objectives and timeline of our work, drawing up an overall strategy and specific contingency plans. This is the best time to flag up foreseeable disruptions, address potential ethical problems and agree on how to share data and intellectual property. In our case, setting a general order of authorship before pouring effort into the collaborative melting pot gave us a smooth working relationship, free from surprise competition.

My advice is to make sure that the group meets in person before you start, especially if lead members haven't worked together before. Moore was familiar with the PBH and UCLA and coordinated all our efforts, but I didn't meet Horton or his team until we arrived in Palawan for the fieldwork. A pre-emptive visit to the hospital would have helped us to spot some lurking problems with site logistics and the availability of lab ware. Teleconferences should be saved for short communications and status updates.

ADAPT YOUR MATERIALS AND METHODS

When researchers are working internationally, experimental methods need to be adapted to the infrastructure of the host facility. For example, our original protocols recommended storing saliva at –80 °C. But ultra-low-temperature freezers weren't an option at the PBH, which has public electricity for just half the day, so we redesigned our approach to use a domestic freezer. Horton's researchers at the PBH also refitted their lab with a combination of electrical outlets at 120 volts and 220 volts so that we could use equipment from the United States in their hospital.

The climate affected our materials and processes. Reactions at room temperature have an entirely different behaviour in a tropical environment at 34 °C than in one where the normal temperature is around 25 °C. By using dry reagents stored in a desiccator, we kept protocols portable and stable. Because we would eventually transfer those protocols to Horton's team, we got other operators to reproduce our experiments in a few different labs, to anticipate possible hiccups.

"International partnerships are as much about people as they are about science."

Some basic materials may be difficult to find abroad. The hospital ended up stocking 40 litres of distilled water just for our chemicals, much more than they typically kept on hand. Will your reagents need a low-temperature supply chain? Team members who flew from Los Angeles carried perishable reagents in temperature-controlled boxes in checked baggage. At the PBH, we crushed ice to keep our working samples chilled using a domestic appliance for making halo-halo, a local fruit dessert.

Timing and logistics were crucial. Although my grant lasted for one year, the seasonal nature of malaria gave us only three months in which to collect samples. Early on, we ruled out shipping specimens from the Philippines to the United States for analysis, because of the high cost and legal barriers. That meant we had to transport chemicals and instruments overseas for fieldwork. Whether you choose to travel with these materials as passenger baggage or to ship them ahead as cargo, arranging their passage can be less than straightforward.

Customs carnets can be very convenient documents for arranging temporary import of scientific equipment: they act as merchandise passports, allowing simplified, tax-free customs procedures. Unfortunately, many countries, including the Philippines, do not accept carnets.

To find the best alternative, we sought guidance from a logistics officer for the International Medical Corps, a global organization for humanitarian relief based in Santa Monica, California. He made sure that we prepared meticulous packing lists and an official letter of intent designating our materials solely for academic research. By being detailed about what we were shipping and clear about our purpose, we could apply for authorization to import before we arranged for transit.

Because the PBH was not a licensed importer, we had to work with a door-to-door international forwarder and its clearing agent in Manila. The agent caught us off guard with a very high and unjustified quote for customs handling and brokerage. But with help from a friend who was chief customs officer in Manila, we ended up with a proper quote at a fraction of the original fee, and a personal escort through airport customs. Whatever import method you choose, you should make sure that you know what to expect at customs clearance in every country you have to go through. To avoid falling victim to price gouging, get quotes from more than one vendor. If anything seems grossly out of place, someone is probably not complying with local laws.

REGULATORY CHALLENGES

Logistics will get your boxes onto site, but the work that the scientists do there will be governed by myriad regulations. International collaborations involving clinical medical research require oversight from multiple institutional review boards (IRBs) charged with the protection of human subjects. Each review board has specific requirements for the protocol and consent forms.

To learn how to get through this often long and iterative process of approval most efficiently, Moore met with representatives from the IRBs of both UCLA and the PBH, as well as other experienced investigators. They explained best practice for international collaborations — cooperating with local government, upholding the institutions' integrity, writing protocols to prioritize patient safety — and aspects unique to UCLA. By working with the decision-makers from the start, we got protocols approved on the first pass.

Sometimes institutional approval isn't enough. Make sure to include local-government officials in your regulatory team, to head off authorities who may scrutinize your project for financial gain. As we prepared to enrol our first patients at the PBH, a member of a Philippines environmental and cultural heritage group told Horton that the study needed its permission to proceed, implying that a bribe of some sort was necessary. We felt our collective arm being twisted.

"In research, as in health, an ounce of prevention is worth a pound of cure."

Moore had already sent information about our study to Abraham Mitra, the governor of Palawan. When he and Horton sat down in Mitra's office and explained our circumstances, the governor was taken aback. "This is about malaria," he said. "What does it have to do with the environment?" A phone call was made and the problem evaporated. With written endorsement from the Provincial Health Office, we were clear of further regulatory obstacles. It never hurts to have friends inside the system.

WATCH OUT FOR UNEXPECTED TWISTS

In research, as in health, remember that an ounce of prevention is worth a pound of cure. Nevertheless, no amount of risk management — whether pertaining to technical uncertainty, complex logistics or impenetrable regulations — guarantees a smooth operation. We experienced some extra bumps first hand.

The oil company Pilipinas Shell Petroleum has operations in Palawan, and its social-development arm had partnered with the provincial government from 1999 onwards to launch a major anti-malaria campaign. Just before our study, their programme increased insecticide spraying, distributed bed nets and opened a new central clinic not far from the PBH. The timing of these interventions markedly reduced the number of malaria cases seen at the PBH, which could have jeopardized the project. We had to extend the enrolment period by several months to get enough people for our pilot study, and still ended up with fewer than we had expected.

International partnerships are as much about people as they are about science. They open unique avenues for discovery by empowering scientists to explore beyond their accustomed borders. So above all, enjoy the adventure. Granted, it is a risky enterprise, but one full of professional reward and personal satisfaction. ■

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