Approaches Vary for Clinical Trials in Developing Countries

In a hospital in Morocco, cancer patients must wait 2 or 3 days for a bed to open up. In a Guatemalan health center, two harried clinicians juggle all of the more than 400 new cases of leukemia each year. In some places in India, 60%–70% of cancer patients are turned away from hospitals because of a lack of medical resources.

“Clinical trials? Wouldn’t [providing] soap be a better place to start?” Ronald Barr, M.D., of McMaster University in Canada, said of conducting clinical trials in developing countries, only half joking. He remembers handing out blocks of soap to doctors in Kenya, who gave the precious bars to parents as an incentive not to abandon their sick children in hospitals. “There are huge fundamental challenges that need to be addressed before you can think about doing trials,” he added.

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Researchers at pharmaceutical companies and academic institutions and organizations are addressing these challenges head-on as interest grows in conducting clinical trials in developing regions, whether for humanitarian reasons, furthering scientific knowledge, or economic savings. However, opinions differ as to the types of trials needed and how such trials should be conducted.

There’s no question that research and development outside the United States. One major motivation for looking abroad is the lowered cost. Trials in countries such as China and India can cost about one-half to one-third that of running a trial in a developed country, estimates Robert Maguire, vice president and chief of operations for clinical research and development for Wyeth Pharmaceuticals.

Furthermore, such trials can save time—which could translate into saving money. Clinical studies in developed countries must compete with trials from other companies or institutions for trial participants in Europe and North America, so it may take a considerable amount of time to gather enough participants for a study. Also, some diseases do not have a high enough incidence rate within the United States to support a large-scale clinical trial, said Alan Goldhammer Ph.D., associate vice president for regulatory affairs for PhRMA. Some types of cancer, such as stomach cancer, occur at much higher rates in lower-income countries than high-income countries such as the United States.

In fact, most cancer cases actually occur in developing countries, notes Ian Magrath, M.D., president of the International Network for Cancer Treatment and Research (INCTR). “There’s a huge opportunity being missed, from a scientific perspective,” if researchers ignore cancer in low-income countries, he said. In addition, learning about the etiology and development of different kinds of cancers in different populations and in different environments may help researchers more thoroughly understand and then treat the disease, he said.

According to Magrath, most clinical trials being conducted in low-income countries are run or funded by pharmaceutical companies, as opposed to academic or nonprofit institutions like INCTR. He said he wishes that more clinical trials in low-income countries would focus on academic research, as opposed to pharmaceutical drug development. “It’s a great pity that there aren’t more academic studies going on,” he said. The motivation for academic studies would likely vary from that of pharmaceutical company clinical trials, so the types of studies and their design would probably differ.

Still, it’s an attractive market for pharmaceutical companies. Gary Stiles, M.D., executive vice president and chief medical officer of Wyeth Pharmaceuticals, estimates that his company currently focuses about 20% of its research and development studies in countries outside the developed countries of Europe and North America. However, within the next 2 years, the company plans to shift this percentage to up to...
40%, and other companies are following suit, he added. GlaxoSmithKline also intends to boost its drug trials conducted in countries outside the United States and Europe to 50% in the next 2 years, up from 29%.

**Problems With Designing Trials**

But exactly how such a presence should be carried out has been debated. Some researchers feel strongly that clinical trials that occur in less developed areas should not include drug development studies, or even randomized controlled trials. Others question whether the trials should be conducted at all when such basic medical necessities, like soap, are lacking.

Many trials of the past were designed to have experts from higher-income countries “parachute in and parachute out,” and they rarely returned good results, said Barr, who also works with the International Society for Pediatric Oncology (SIOP). Before any trials can be run, researchers must carefully consider the community and culture they will be working in; otherwise, they may run the risk of ethical quandaries, alienated participants, bad publicity, and poor results. “[Researchers] have to be in for the long haul,” said Barr. This means years of surveys, assessments, and follow-ups, not to mention building up needed infrastructure in the institutions carrying out the study—usually local institutions.

It may also mean finding alternative models of practice and protocols suited for developing countries and low-income areas. Methods and protocols that work in the United States may not translate to other countries, explained Scott Howard, M.D., of St. Jude Children’s Research Hospital in Memphis, Tenn.

Such research studies are most needed in less-developed countries, said Howard. Without the infrastructure, technology, and relative abundance of highly trained medical workers often found in high-income countries, the process of implementing clinical trials in developing countries must be tailored to the specific setting. Getting trial managers in low-resource settings to adhere to a standard protocol and treat each patient in the same way is a good starting point for many trials in low-income countries, said Howard.

At the same time, there is a lack of formal training and education, especially in conducting clinical trials, among researchers from developing countries, Magrath said. He estimates that only about one-third of oncologists in low-income countries have had “real research training.” There’s also a shortage
of other properly trained personnel needed for good clinical trials—nurses, lab technicians, data managers, clinical pharmacists, and biostatisticians. “They are rare beasts,” agreed Barr. Providing training for these medical workers is a main goal for organizations such as INTCR.

That lack of trained medical workers can translate into more work for those conducting the trial. For example, St. Jude Children’s Research Hospital takes in about 400 new cancer cases a year and employs 107 data managers and medical recorders, compared with a total of two medical workers struggling to manage the same number of patients at a hospital Howard works with in Guatemala. “They’re working so hard, just to look after [the patients], so finding the time to conduct clinical trials is very tough,” agreed Barr.

Creating Trials that Work

One of the most important components of conducting clinical trials in developing countries is the spirit of the adage, “first do no harm.” In that regard, some humanitarian organizations such as Oxfam question whether ethical standards that are stringently enforced in developed countries can be maintained in developing areas that often have weaker regulations and methods of enforcement.

Some researchers within the academic research community disagree on whether it’s ethical to give patients in lower-income countries treatments that are considered “second-class therapy” in high-income countries—a practice considered unethical in high-income countries, said Tim Eden, M.B.B.S., president of SIOP. Eden and St. Jude’s Howard agree that such studies are ethical; even if the outcomes are not comparable to those in high-income countries, lives are still saved if the outcomes are better than the baseline outcomes for that country, Howard said.

Raul Ribeiro, M.D., of St. Jude Children’s Research Hospital, believes that his hospital has been able to overcome some of these challenges and will be a success story for carrying out clinical trials in low-income countries. St. Jude “twins” with hospitals and communities in low-income countries to produce research, trials, and treatment options for children with leukemia. In these partnerships, St. Jude provides advice, ideas, and limited financial and technical support. The other hospitals provide the initiative and desire to carry out this work.

Ribeiro stressed that these hospitals seek out St. Jude, and not the other way around. Successful research programs like St. Jude’s also make sure that the thoughts and ideas of the partnering institutions are heard and encouraged every step of the way, added Eden, who works with the St. Jude program. “We ask: What do you think? How do you think this should be done?” he said. “[Researchers from high-income countries] must enable the local people; it’s not good telling them to do this and that,” he added.

St. Jude emphasizes that hospitals need to gain the support and trust of the local community for their trials, said Ribeiro. One way to do this is to show positive results. In clinical trials of childhood leukemia, the disease is relatively easy to treat and cure with minimal resources and infrastructure, which creates “a lot of positive energy in the community” for future trials, he explained. The personalized nature of twinning programs, as opposed to sponsorship from large companies or organizations, also allows trust to build, said Barr. Local doctors know the names and faces of the doctors from the hospital they are partnered with, so they are more willing to ask for advice.

Because of the time and effort invested by the researchers at St. Jude, some of the partner hospitals from low-income countries are at the point where they can start planning randomized controlled trials, said Ribeiro, and some have. Although they still have a long way to go, researchers remain hopeful. “It took developed nations more than 60 years to go from treating the first childhood cancer patients to where we are now … For low-income countries, it’s taken less than 10 years for the same change,” said Barr.

—Elana Hayasaka

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