Clinical Trials for Pulmonary Hypertension in the Developing World

Pulmonary Vascular Disease: The Global Perspective

Bhagavathula K. S. Sastry, DM; Michael D. McGoon, MD, FCCP; and J. Simon R. Gibbs, MD

More clinical trials in pulmonary hypertension (PH) are being conducted in developing countries now compared with the past. This is a welcome development, considering the rarity of the disease, with its limited treatment options and poor prognosis. Conducting clinical trials in the developing world potentially decreases the time and costs of drug development and provides access to new drugs to an underserved population. However, the range of PH presentations, standards of care, and socioeconomic environments among developing countries is different from that of developed countries. Eagerness to complete clinical trials universally should not compromise accepted ethical practices. Patients from developing countries may be particularly vulnerable because of illiteracy and poverty and may not truly understand the informed consent process and clinical trials. Investigators, ethics committees, and regulators must ensure that potential participants are not exploited. Drug trials should be done only in those communities in which the drug would be made accessible if proven effective. Studies have to be designed taking safety, accessibility, and generalizability into consideration. Selecting appropriate investigators and institutions, supporting them with proper training, and providing infrastructure and facilities would promote uniform standards of clinical research across the globe. Coordination and cooperation among regulatory bodies of different countries is an urgent necessity that would facilitate the globalization of clinical research. If done appropriately, the potential benefit for the worldwide population of patients with PH would be substantial.

Abbreviations: CHD = congenital heart disease; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension

The globalization of clinical research has been recognized recently as a phenomenon of growing importance, which requires careful scrutiny of its impact on medical practice, economics, and ethics. Improvements in technology and communication have permitted the exportation of many aspects of clinical research efforts into new parts of the world for the first time. The expansion of research in historically disenfranchised societies may be viewed as a laudable humanitarian effort. The actual driving forces behind this trend are generally more utilitarian than simple good will and include, most notably, the financial advantages realized by pursuing drug and device development in locales where the cost of doing so is less. Furthermore, by incorporating larger study populations in countries with fewer regulatory hurdles, additional cost savings can accrue. Although not necessarily intrinsically wrong, the goal of promoting rapid development of medical advances globally nevertheless carries with it the potential for unintended adverse consequences, which must be identified and confronted.

Pulmonary hypertension (PH) is a rare, chronic, and frequently lethal condition. Clinical research within the arena of PH is emblematic of both the advantages and challenges of global medical research. Current treatment of PH is largely the product of clinical
research that has been carried out in the United States, Western Europe, and Australia. Early studies could be completed quite expeditiously because of the absence of prior effective treatment or competing protocols. The population of patients with pulmonary arterial hypertension (PAH) in the developed world is now too small to enable multiple clinical trials having different objectives to enroll simultaneously and to proceed swiftly. A logical remedy to this obstacle would be to broaden the scope of study geographically to include more patients with PAH and/or to study patients with other forms of PH. Thus, recent clinical drug studies have frequently used a multinational design. This article examines some of the real and hypothetic consequences of this trend, especially as they apply to developing countries.

**Distribution and Types of PH**

Consideration of issues and dilemmas posed by global clinical research in the field of PH must include the causes of PH in different parts of the world and the gaps in knowledge about how different types of PH should be managed. From a global perspective, the exact incidence and prevalence of PH are unknown. In published reports from across the world, the case mix was variable, as were the methods of case ascertainment. Peacock et al calculated an annual incidence of 7 cases per million and a prevalence of 26 to 52 cases per million. The incidence of PAH in Israel is estimated to be 1.4 new cases per year per million population. From the national registry maintained in France, Humbert et al have reported estimates of minimum prevalence and incidence of PAH to be 15 and 2.4 cases per year per million adults, respectively. In the United Kingdom, 24.9 patients per million population receive PAH licensed drug therapies.

The incidence and prevalence of PH in developing countries will likely be impossible to establish in the foreseeable future. An estimated 20 to 25 million people or more suffer from PH of different causes in the developing world. It is often underrecognized, and the present health-care systems do not allow prevalence to be measured with any certainty.

Although all types of PH are present in the developing world, possibly affecting more patients than in industrialized nations, certain types are more prevalent in developing countries than in developed countries (Table 1). Paucity of resources to diagnose and treat surgically correctible shunt lesions early in life, for example, leads to a higher prevalence of Eisenmenger syndrome. In India, an estimated 130,000 to 270,000 infants with congenital heart disease (CHD) are added to the total pool every year. Another 37,000 cases are diagnosed during childhood. Currently, only 2% to 3% of infants born with CHD receive timely attention and undergo correction. The majority of the remaining CHD population either fails to survive beyond infancy or early childhood or develops irreversible PH.

Although the incidences of rheumatic fever and rheumatic heart disease have progressively decreased, they nevertheless remain common in developing nations. Some patients with rheumatic valvular heart disease continue to have persistent PH even after correction of the valvular lesions.

An estimated 33 million patients are living in the world with HIV/AIDS, most of them in underdeveloped or developing countries. About 0.5% of HIV-infected patients develop PH. Schistosomiasis is highly prevalent in Brazil and certain other developing countries. It is estimated that > 200 million individuals are infected with schistosomiasis throughout the world; in one study from Brazil, 30% of PAH was due to schistosomiasis. An estimated 30 million people suffer from hemoglobinopathies worldwide, with a higher prevalence in developing countries. Nearly 10% of this patient population develops PAH. In contrast to substrates of PH that are more commonly observed in developing regions, PH due to left ventricular diastolic dysfunction, which occurs later in life, is seen more often in the Western world.

### Table 1—Pulmonary Hypertension More Often Seen in the Developing World

<table>
<thead>
<tr>
<th>Pulmonary vascular disease associated with infections</th>
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<tbody>
<tr>
<td>Helminthes</td>
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<tr>
<td>Schistosomiasis</td>
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<td>Filariais</td>
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<td>Clonorchiasis</td>
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<td>Viruses</td>
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<td>HIV</td>
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<td>Human herpesvirus 8</td>
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<tr>
<td>Pulmonary vascular disease associated with hemolytic anemia</td>
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<tr>
<td>Sickle cell anemia</td>
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<tr>
<td>Thalassemia</td>
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<tr>
<td>Hereditary spherocytosis</td>
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<tr>
<td>Pulmonary vascular disease associated with high altitude</td>
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<tr>
<td>Pulmonary vascular disease associated with cardiac disease</td>
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<tr>
<td>Left-to-right shunts</td>
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<tr>
<td>Valvular heart disease</td>
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<tr>
<td>Endomyocardial fibrosis</td>
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<tr>
<td>Pulmonary vascular disease associated with environmental toxins</td>
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<tr>
<td>Cocaine</td>
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<tr>
<td>Methamphetamine</td>
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<tr>
<td>Contaminated rapeseed cooking oil</td>
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<tr>
<td>L-tryptophan</td>
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<tr>
<td>Tobacco leaves cured by mineral oil</td>
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<tr>
<td>Bush tea from <em>Crotalaria spectabilis</em></td>
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<tr>
<td>Pollution caused by domestic burning of wood</td>
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DIFFERENCES IN PATIENT MANAGEMENT

Differences in the types of PH most often confronted in developing countries are matched by differences in management. The typical patient who presents in a developing country such as India or China often has advanced disease and poor prognosis.\textsuperscript{18,19}

The basic evaluation of PH to determine the cause and severity of the disease may remain incomplete because of a lack of resources, awareness, or expertise. Cardiac catheterization, which is crucial in the diagnostic evaluation of PH, is not performed routinely in some countries. Most cardiac catheterization laboratories do not have facilities for vasoreactivity testing or access to inhaled nitric oxide. In the absence of a complete workup to rule out different causes, the final diagnosis may be incorrect. Generally, no specialized centers, clinics, or referral programs for PH patients exist in developing countries.

Most of the recent advances for treatment of the disease have not reached the patients of the developing world. Furthermore, the poorer general standard of care in less developed countries affects the outcomes of treating any disease, including PH. This may affect the outcomes of clinical trials because phase 3 trials in developed countries are now frequently being carried out in patients pretreated with at least one disease-targeted therapy, whereas patients in developing countries are often untreated. Reasons for suboptimal care include poor awareness of the disease and its treatment options, limitations of health infrastructure and resources, and the extremely high costs of most of the newly introduced drugs for management of the disease.\textsuperscript{20} In addition, in some areas, treatment may be compounded by the use of traditional remedies of uncertain efficacy.

Prostanoids and endothelin receptor blockers are not available in many developing countries, whereas some countries like India have many generics of sildenafil with potential variations in their efficacy. Importantly, there are few data regarding the use of any of these medications in many of the PH types most prevalent in these areas. That the use of these drugs cannot simply be extended to other forms of PH safely and effectively without clinical trials is exemplified by the early termination of a sickle cell disease trial because of an increase in vasoocclusive crises in patients receiving sildenafil compared with placebo.\textsuperscript{21}

PRESENT-DAY SCENARIO

At the time of this writing, 210 clinical trials in PH are being conducted all over the world. Of these, more studies are being carried out in the developed world than in developing countries, and the majority of these are sponsored and conducted by universities and other funding organizations rather than by the pharmaceutic industry. Relatively more industry-sponsored clinical trials are performed in the developing world than those sponsored by the universities. The magnitude of the problem is driven home by the fact that, in the United States, with a population of about 300 million, 133 clinical trials are being conducted, whereas in India and China together, with a population of 2,500 million people, only 13 clinical trials are in progress.\textsuperscript{22} Given the limited access of many people to good medical care and diagnostic facilities, the lack of clinical research training of health-care professionals, and the lack of essential clinical trials infrastructure, this is hardly surprising. Nevertheless, the situation is changing, with a gradual increase in industry-sponsored clinical trials being conducted in the developing world.\textsuperscript{23}

ETHICS

One purpose of clinical research is to find solutions to medical problems that are common across the globe, so doing clinical research in developing countries has a strong ethical justification. An argument can be advanced that clinical drug research in developing countries provides a first step toward making more advanced pharmacologic interventions available in these medically underprivileged nations. Appropriately, however, the question arises at the outset as to whether ethical concerns exist about conducting PAH research in countries with different standards of care.\textsuperscript{24,25} Are these concerns introduced by different economic or health-care systems or standards of living? Although the goal of disseminating more effective treatment would seem in itself to have a strong ethical motivation, the potential for abridgment of other ethical tenets is considerable. Guidelines, which have evolved to ensure ethical behavior in certain countries, are predicated on the universality of their application and cannot be considered appropriate for one population and not for another.

A fundamental principle is that regardless of where research is performed, study participants must not be exploited. The proposition that medical resources are relatively scarce in developing countries is precisely what places patients in those countries at risk for ethical compromise. Desperation to obtain any treatment of a lethal disease may lead to overzealousness in promoting research that is not ethically robust. For example, informed consent, the mainstay of protection of the rights of human research subjects, risks being glossed over in the effort to facilitate the completion of a research endeavor. Even when consent forms are constructed conscientiously, lack of education and medical sophistication may impede the explanation
of fundamental concepts such as randomization, placebo or other controls, standardized follow-up, and risk of treatment with a study drug. Patients and inexperienced investigators may overlook the nuances of selection criteria in such a way that the risk of participation is higher than in other cultural environments. Subjects may even misinterpret involvement in a study as treatment itself, especially in the context of limited alternative therapies.

Participation in a clinical trial must be purely voluntary, competent, and informed, with consent understood and uninfluenced by other considerations, as stated in the 1947 Nuremburg Code. But in actual practice, this seldom occurs, particularly if no alternative treatment is available. The decisions of patients, especially those who are impoverished, are often influenced by the economic context and system of medical coverage and care. The economic incentives and the possibility of obtaining continuous and personalized medical care, which would be otherwise unavailable, make informed consent difficult. In certain countries, financial incentives for participating in a clinical trial may be more than a potential study subject’s regular wages. Consequently, ethical considerations arise with respect to remuneration of the study subjects, the investigators, or both. Compensations for participation in a study have many potential consequences in poorer countries because it creates an incentive that may minimize consideration of the risks and disadvantages of participating. Hence, economic incentive must not be the sole reason for the patient's participation in the clinical trial. There should not be any monetary payment to the patient except to cover the expenses incurred by his or her participation. Similarly, payment to the investigators and their institutions should be transparent and should be commensurate with the costs of performing the study.

Clearly, investigators and institutional review boards from developing countries should ensure that participants understand as much as possible before they consent to participate in a clinical trial. It is often difficult to read and comprehend all the information given in the informed consent form, even for an educated person. Introduction of audiovisual methods to explain the clinical research may be more suitable to the less literate patients of developing countries.

Ethical issues related to study design also require careful consideration. Although placebo-controlled trials have higher scientific integrity, as more drugs for treatment of PAH are approved for clinical application, the use of placebo control in treatment-naive patients has become ethically unacceptable. If placing an otherwise untreated patient at risk for assignment to a placebo arm is inappropriate in developed countries, then it must also be unethical elsewhere, even if alternative therapy is unavailable. Although it may be argued that potential study participants would obtain access to a new drug, this introduces an element of inducement that may supersede considerations of risk or other disadvantages. Not performing clinical trials for these reasons, however, would effectively disallow access to the new drugs for these populations.

In many countries, the spotlight of public concern has focused on transparency about conflict of interest. The perception of investigator bias jeopardizes the integrity and acceptance of study results. Conflicting allegiances, which may taint a study, would adversely affect human safety.

**Regulations**

The ethical foundations of medical research principles are based on prohibiting one group, nation, or culture from inflicting harm on another in the name of scientific advancement. These principles should be applied uniformly across the world. This requires either standardization of safeguards or agreement that regulations that apply to research in locations with established rules should apply equally in countries in which clinical research is being newly introduced.

The fact that studying the effect of a drug on human subjects may be expedited in countries with less rigorous regulatory oversight is a prima facie example of an ethical violation by which patients are exploited. Because clinical drug studies in PAH are currently expanding into a worldwide arena, regulations are increasingly necessary to ensure that ethical research meets the standards of the Declaration of Helsinki, the Nuremburg Code, the guidelines of the International Committee of Medical Journal Editors, and the principles of the International Conference of Harmonization–Good Clinical Practices. These documents recognize the need for careful attention to the global application of proper conduct of clinical trials. Although such efforts provide general guidance, the degree to which they are embraced and applied in different locales and in studies for different diseases may vary greatly. A need exists for a clinical trials partnership between developed and developing countries to promote collaborative research and to answer major questions in PH worldwide within a strict ethical and regulatory framework. Such a partnership would embrace academia, industry, bioethics committees, regulatory agencies, statisticians, and funding bodies with a common purpose.

The competence of the investigators and the quality of data are not peculiar to any particular country but are specific to the individual sites or the investigators. Selection of an investigator and the site is of primary...
importance with regard to the quality of data. Investigators must have sufficient clinical experience in PH and diagnostic facilities to enroll appropriate patients, manage them safely, and measure end points accurately. Investigators from developing countries, their ethics committees, and, where possible, patients should be involved in the process of clinical investigation, from the design of the clinical trial to publication in a peer-reviewed journal. They should have access to the complete prepublication clinical data. Scientific meetings conducted with the involvement of independent experts would ensure uniform standards, better quality data, and patient safety.

It is the responsibility of the institutional review boards and the regulators to ensure that the standards described above are followed. Regulatory authorities should ensure that all conflicts of interest of the investigators are declared and their independence from the sponsor is protected. To have uniform standards in clinical trials, coordination and cooperation among regulatory bodies of different countries is an urgent necessity. End points that may lead to drug licensing are not agreed on between the United States and Europe.

SAFETY

It is important to reflect on whether PAH studies are monitored with similar rigor in all countries. Is a different level of risk of participation in a study of a PAH drug allowable in different countries? One study of IV medication in a developing country was terminated early because of the high frequency of complications related to the delivery system and difficulty with its management by the subjects and the participating institutions. In retrospect, the pursuit of the study in an environment that was not suitable for optimal management of a complex therapeutic system may have been ill advised, particularly because even placebo-controlled patients received a chronic IV catheter. This serves as an example of studies that may be inappropriate because of an ethically questionable design (although placebo control may have been scientifically “ideal”) that was not used in the pivotal studies decades earlier of IV prostacyclin analogs in the United States. The shortcomings of the design were compounded by a health-care system and study population that were not capable of ensuring safe drug administration through access to care and patient education.

A major concern is that investigators in different countries may not have the same level of standards in terms of clinical and technical skill, as well as knowledge and skill in the conduct of clinical trials. Clearly, there must be a learning period, but this should be based on mentorship and ongoing collaboration rather than on learning from adverse consequences.

Because the standard of care influences the clinical outcomes and safety of study subjects, it is incumbent upon the sponsor to ensure that participants from developing countries get a level of care that is reasonably comparable to that available in developed countries. Within a country, the standard of care varies from institution to institution, and some institutions in developing countries are able to provide the same standard of care as that available in developed countries. Conducting clinical trials in such limited institutions and reimbursing the total cost of the care may solve this problem to some extent.

ACCESS TO MEDICAL CARE

The extent to which patients have access to appropriate medical care in various regions of the world necessarily impacts clinical studies. The issue can be framed by the following question: Is it appropriate to carry out a clinical study in a nation in which, if a drug intervention were found to be efficacious, the vast majority of the population would not have access to the drug? If the answer is “No,” then it would seem that the study was done in that nation as a “proving ground” for the use of the drug in more privileged nations. Because the use of one population as experimental subjects to benefit another population is antithetical to medical research ethics, mechanisms should be encouraged by which effective interventions are made available by reasonable means to all appropriate patients in all regions where drug studies are carried out. Such a principle should apply equally to developed as well as to developing nations and would mandate that even in countries such as the United States, drug prices not exceed the means of needful patients. As per the Declaration of Helsinki, the study sponsor and regulatory authorities should ensure that the best proven therapy is available and accessible to the community in which the trial is conducted. This is especially important in PH, for which the treatment options continue to be suboptimal and expensive.

GENERALIZABILITY

A final concern is whether the results of PAH studies performed in one country are applicable to clinical practice or regulatory decisions in another country. Independent of whether the results of a study in one country should be employed in another country (as mentioned above), the question is whether the results in one country can be extrapolated or applied to the medical care of patients in another country. How
should the potential for racial, genetic, and cultural influences on PAH study results be accounted for? In the absence of a clear answer to this question, extreme caution is recommended.

CONCLUSION

Globalization of clinical trials in PAH is underway and will prove challenging. The potential worldwide benefits for the PAH population are substantial, provided that trials are performed in centers in any country that maintain high ethical and scientific standards. Thus, the development of clinical trials for PH in countries with limited clinical and research capabilities requires establishing clinical trial centers and supporting them with the training of health-care professionals and the provision of infrastructure and facilities for a specialist PH service with clinical research. Such trials must also address the treatment in which the trials are conducted, using agents that are practical and affordable in their health-care systems. Clinical trials should be performed only when the sponsor and regulatory authorities ensure that the drugs under study would be available for these populations at an affordable cost, if they are proven effective.

Ethical considerations are not the monopoly of any particular country or region; globalization of clinical trials has to take place without any prejudice. Appropriate selection of dedicated and skilled investigators and institutions should minimize the likelihood of unethical practices tainting clinical trials.

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