The Globalization of Clinical Trials – Challenges, Opportunities and a Path Forward

JUSTIN MCCARTHY
Senior Vice President and Associate General Counsel, Pfizer Inc, USA
MARC WILENZICK
Assistant General Counsel, Pfizer Inc, USA
CARA CUENOT
Assistant General Counsel, Pfizer Inc, USA

I. INTRODUCTION

In recent years, pharmaceutical companies have expanded clinical research in emerging markets around the world and have increasingly involved populations that traditionally have had limited or no access to clinical trials (other than experimental treatments for communicable diseases). Trial sponsors can increasingly find well qualified investigators from Latin America, Eastern Europe, Asia and other non-European and non-North American regions. By identifying and involving such markets in their trials, industry can build a strong presence in formerly under-served areas, accelerate trial enrollment, and maintain or improve data quality and scientific standards.

There is much to gain through this global expansion of research – for instance, better access to promising new medicines for the treatment of “Western” diseases like certain cancers, diabetes and Alzheimer’s, that in fact recognize no geographic boundaries and cause universal suffering. In addition, proactively finding and funding more investigators, study sites, and trial staff in these emerging regions, together with efforts to work more closely with local communities, local scientists, and government officials, should continue to improve the quality of research and strengthen local medical infrastructure.

The global expansion of research is not without significant challenges, however, given ever-present discussions about informed consent of study subjects, and distrust of the motives of multinational companies in general. Medical journals and lay media frequently question the rationale for and the implications of the expansion of clinical research into emerging markets. This concern likely stems from a broader sense of mistrust of large companies in general and the for-profit pharmaceutical industry itself. A 2006-2007 survey showed that the pharmaceutical industry ranked in the lower third of public opinion in the U.S., ranking only slightly higher than the insurance industry, the federal government, the oil and gas industry, and tobacco companies. Sponsors must address these criticisms and concerns to build credibility and confidence in research done in emerging markets.

This article examines some of the factors that have contributed to the globalization of clinical research, the regulatory framework governing the conduct of multi-regional clinical studies, and some of the the risks and challenges posed by global trials,

particularly those trials conducted in emerging regions of the world. It also is intended to
describe practical steps that sponsors can and should undertake, with the counsel and
guidance of their in-house attorneys, to help ensure compliance with relevant legal and
ethical requirements, to minimize risks for their respective companies, and to restore the
trust and credibility that the pharmaceutical industry lacks. While this article is written
from the perspective of an industry sponsor, many of these issues apply to investigator
initiated research undertaken by Universities, and to government funded research
undertaken by the U.S. NIH and other agencies.

II. THE BUSINESS CASE FOR GLOBALIZATION INTO EMERGING MARKETS

Over the past five to ten years, patients from countries located in emerging regions
around the globe (i.e., countries outside of Western Europe, North America, Japan,
Australia, and New Zealand) have become more involved in clinical research. In 2007,
Tufts University’s Center for the Study of Drug Development predicted that leading
pharmaceutical companies would move up to 65% of their clinical trials from the
developing world into emerging regions in the next few years. More recent data suggest
this prediction might be right. As of February 2009, “there [were] now more Phase II-III
trials sites in the rest-of-the-world (ROW) than Europe (27.0% vs. 24.6),” with North
America and Europe losing about 6,500 sites. Last September, the E.U.’s European
Medicines Agency (EMEA) noted that approximately 70% of clinical subjects were
recruited in Europe and the U.S., while close to 30% of clinical subjects were recruited
from “other regions” -- countries located in Eastern Europe, Latin America and Asia
Pacific, and with some clinical subjects coming from Africa and the Middle East.

Questions about the motive for the globalization of clinical trials are frequent in the
literature. For instance, an expert noted in a New England Journal of Medicine article
that: “We don’t want to imagine that lower-income countries are the clinical trial mill for
higher-income countries.” At the same time, costs are a legitimate factor in deciding
where it makes sense to do a study.

The cost of developing a new medicine is, on average, in excess of USD $1.2 billion.
Equally concerning, very few medicines—just 2 out of 10—earn enough revenue for a
pharmaceutical company to recoup these substantial research and development costs.
As a result, conducting studies in a cost-effective manner is critical to every sponsor –
providing, of course, that it can be done without compromising quality or human subject
protections. By one estimate, the cost of conducting clinical studies in China and India is
one-third of the cost of conducting clinical studies in the U.S. As long as these studies
can be carried out in these countries with appropriate protection of human subjects and

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6 Pharmaceutical Research and Manufacturers of America (PhRMA) 2010 Annual Member Survey. “Amidst a Weak Economy, America’s Biopharmaceutical Companies’ Commitment to Research Remains Strong.” March (2010); also,
generation of quality data, cost is certainly a reasonable factor to consider in deciding on the placement of clinical trials.

Notwithstanding the potential for cost-savings, the overriding financial benefit of conducting global studies on the time it takes to complete the trial (i.e., last patient, last visit). On average, the length of time it takes to get approval to market a new medicine in the U.S. is about 52 months (compound synthesis to start of clinical testing) followed by about 90 months for the clinical testing and regulatory review, for a total time commitment of about 12 years.9 The challenges in enrolling patients for oncology trials illustrate this point. As of August 2009, there were about 6,500 cancer clinical trials listed on clinicaltrials.gov for adult cancer patients.10 According to a published analysis by VOI Consulting, only 3-5% of cancer patients in the U.S. enroll in clinical trials. 11 There are many reasons for this, but oftentimes the proposition of enrolling in a clinical trial is simply overwhelming for patients with a life-threatening illness.12 Consequently, many of these approximately 6,500 trials ultimately will be abandoned, and more than one in five trials sponsored by the National Cancer Institute will likely fail to enroll even a single subject.13

Even when trials do move forward, given the low clinical trial enrollment rate of cancer patients in the U.S., VOI estimated that it would take approximately 5.8 years to fully enroll all phase III cancer trials if only sites in the U.S. are utilized in the subject study.14 If, however, sites in both the U.S. and in emerging markets were utilized, VOI estimates that the enrollment time would be reduced to 1.9 years, representing an astounding time savings of 3.9 years.15 This time savings translates into quicker regulatory approvals, leading to swifter availability of treatments for patients suffering from life-threatening conditions and other medical issues.

Finally, another important factor that supports the increased globalization of clinical trials is the increasing need for representation of specific populations in clinical programs. In many instances, it is desirable to be able to assess clinical responses across different populations around the globe, as both genetic and cultural differences have the potential to impact the efficacy and safety of medications.

III. CHALLENGES ASSOCIATED WITH INTERNATIONAL RESEARCH

a. Ethical Challenges

While there are compelling reasons to include emerging markets in drug development, there are also challenges that need to be addressed. These challenges include ensuring that trial sponsors adhere to international standards of ethical conduct, comply with all

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applicable regulatory standards, and be sensitive to cultural norms in a particular region. Failure to properly adhere to ethical or regulatory requirements can lead to regulatory sanctions, adverse media attention or, in some cases, the risk of government enforcement or private litigation, particularly in the event of actual or alleged injury to subjects.

Many of the scientific and ethical challenges associated with including emerging markets in clinical trials have been described in the medical literature. Some of those challenges include, but are not limited to, the potential for the following:

- lack of transparency of clinical data results in emerging markets;
- lack of systematic regulatory oversight of multi-regional clinical research;
- lack of sufficient training for, and relatively inexperienced, clinical trial investigators in emerging markets;
- biases in the selection of subjects in multi-regional clinical trials (e.g., subjects enrolled in communities that are not intended to be major markets for the products being tested);
- lack of pharmacogenomic information for subjects in emerging markets (e.g., can study results be “generalizable” from one population to another due to genetic variances that may be prevalent in certain populations); and
- lack of consistency in research ethics committees (also known as institutional review boards in the U.S.) on a global basis.

In some situations, none of these challenges will exist, but where they do, solutions will “require input from stakeholders in academia, industry and regulatory agencies around the world” to ensure consistent or comparable approaches to informed consent, ethics committee review and favorable benefit-risk propositions for the trials.

Pfizer took a step toward bringing stakeholders together to address those issues with its multi-regional clinical trial initiative last year, involving stakeholders from large and small companies, research non-profits, bioethicists, clinical trial experts, researchers and academics. A publicly posted report of that initiative and some of the opportunities identified by the participants is available at http://www.pfizer.com/mrct. Collaborative meetings like this have potential to identify best practices and drive improvement to the complex scientific, technical and ethical challenges associated with global research.

b. Regulatory Challenges

Sponsors must ensure that their study complies with international standards of good clinical and pharmacovigilance practices, recognized ethical principles, such as the Belmont Report and/or the Declaration of Helsinki, as well as local laws, regulations and guidelines of each of the many jurisdictions in which the study is being conducted. Any deviation from international standards could cause the data to be rejected on quality grounds, especially for clinical trials conducted without large populations from the U.S.

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and E.U. This potential extends beyond the borders of the country in which the study is being conducted.

The EMEA, in a December 2008 Strategy Paper, expressed “growing concern both among regulators and in public debate about how well these [foreign] trials are conducted from an ethical and scientific/organisational standpoint (including Good Clinical Practices (GCP) compliance) and about the available framework for the supervision of these trials.”\textsuperscript{19} In light of these concerns, the E.U. requires that a set percentage (30% or so) of the clinical study population be from Europe, for approval of later stage (pivotal) trials for any E.U. marketing authorization. Similarly, the FDA has recently taken action to enhance scrutiny of GCP compliance with clinical trials conducted, announcing in August 2009 that it would step up its “efforts to prevent non-compliant investigators and others from participating in new product development;…procedures for debarment and disqualification have been enhanced to better protect participants in clinical studies and to ensure the safety and effectiveness of the medical products marketed to the American public.”\textsuperscript{20}

Within emerging markets, India, China and Brazil have all become increasingly important markets for clinical research. Larger pools of patients in these regions of the world tend to be eligible for enrollment in clinical trials because of their natural propensity to fall within the criteria set forth in a study’s protocol. For example, study protocols may hinge eligibility requirements on the fact that a patient is not on a current medication regimen due to the possibility of drug interactions that may skew or otherwise impact clinical trial results for the applicable study medication. Since many subjects in emerging markets often are not already being treated with existing medications (as opposed to U.S. and Western European counterparts) those patients may be more likely to qualify as subjects and want to participate in trials. This growing importance of India, China and Brazil in clinical research requires that sponsors have a thorough understanding of the regulatory frameworks applicable in each of these jurisdictions as well as an understanding of the potential challenges that might arise with respect thereto. Accordingly, the following sections, while certainly by no means exhaustive, are meant to provide a high-level overview of certain aspects of the clinical trial regulatory structures in each of India, China and Brazil.

\textbf{i. Regulatory Challenges: Clinical Trial Oversight -- India}

Over the last year, India has made attempts to improve the regulation of clinical trials conducted within India by introducing new regulatory requirements. In June 2009, it became mandatory for pharmaceutical companies and contract research organizations conducting trials in India to register their respective clinical trials with the Indian Council of Medical Research (ICMR) on a “Clinical Trial Registry.”\textsuperscript{21} The need for such a structure was highlighted by the revelation in 2006 that 49 infants had died as subjects of clinical trials conducted at the All India Institute of Medical Sciences.\textsuperscript{21} The Institute attributed the infants’ deaths to underlying illnesses and a large population being studied, but the revelation prompted a call for greater oversight.


The newly mandated registration includes information on the clinical trial, the source of funding, and details of the research ethics committee that will monitor the study. A Central Drug Authority bill has also been proposed, which, if put into effect, will enact new restrictions and tighten existing laws for clinical trials, and implement a central licensing mechanism for manufacturing approvals. The Central Drug Authority would give the Indian authorities the necessary enforcement power to take appropriate action against pharmaceutical companies and other sponsors of clinical trials that violate regulations or conduct a clinical trial without requisite approvals.

ii. Regulatory Challenges: Clinical Trial Oversight -- China

While China is an especially large market for studies, there are important distinctions in the Chinese regulatory framework that sponsors should understand when contemplating trials in the country. For instance, China requires that all clinical trials be conducted with a Clinical Trial Approval (CTA) issued by China’s State Food and Drug Administration (SFDA). The trials must be conducted within three years after the CTA is issued. In practice, a CTA is, however, generally not required for Phase IV trials. Further, under the framework set forth in the SFDA Drug Registration Rules, only drug manufacturers (foreign or domestic) are qualified to sponsor clinical trials. This renders the CTAs for investigator-sponsored clinical trials (especially those for pre-market studies) almost impossible to obtain. A sponsor can entrust a contract research organization (CRO) to carry out certain work and responsibilities in clinical trials. However, unlike the U.S., China does not have a regime in place that allows a study sponsor to transfer certain regulatory obligations in relation to the clinical trials to the CRO. Thus, the CRO would act merely as an agent of the sponsor, and the sponsor remains ultimately liable under applicable laws in relation to such entrusted responsibilities.

Although multinational drug manufacturers are permitted, upon approval by the SFDA, to conduct multi-center international clinical trials in China, such approval would usually be granted only for clinical trials relating to investigational drugs that already have been marketed outside of China or have entered Phase II or Phase III in global trials. In practice, the SFDA would not grant CTAs for the conduct of multi-center international trials in China on preventive biological products (e.g., vaccines) that have not been marketed outside of China.

iii. Regulatory Challenges: Clinical Trial Oversight -- Brazil

Beginning in 1988, with the passage of a resolution to regulate the conduct of clinical research, Brazil has developed a robust regulatory framework governing the conduct of clinical trials. Today, there are two primary regulatory bodies subordinate to the Ministry of Health with responsibility for the evaluation of clinical research studies in Brazil. These two bodies are known as the Agência Nacional de Vigilância Sanitária (National Health Surveillance Agency or ANVISA) and the Conselho Nacional de Saúde (National Health Council) through its Comissão Nacional de Ética em Pesquisa (National Ethics Commission for Clinical Research or CONEP). ANVISA, established by Law No. 9,782/99, is an autonomous agency linked to the Ministry of Health. CONEP, created by CNS Resolution No. 196/96, is responsible for the ethical aspects relating to the conduct of clinical trials in Brazil. Together, these regulatory bodies are responsible for the review, approval and oversight of clinical studies conducted by foreign sponsors in Brazil. The regulatory review and approval process can take up to eight months.

Complicating the already cumbersome research and development path in Brazil are certain unique regulatory requirements such as the need to provide study subjects unrestricted post-study access to the relevant investigational drug under study. To
illustrate, in *Kauã G.C. vs. State of Rio Grande do Sul*, the plaintiff, a minor with a rare disease, “mucopolysaccharidosis,” participated in a clinical trial involving “Aldurazyme” carried out by Genzyme do Brasil. After the trial, the subject was enrolled in the International Charitable Access Program to obtain access to the drug. Due to the high cost of the drug and cancellation of the access program, the plaintiff filed suit against the State of Rio Grande do Sul claiming that his constitutional right to health care mandated continued access to the study drug. The State of Rio Grande do Sul then filed a cross-claim against Genzyme arguing that Genzyme’s had the obligation to provide continued access to the drug.

In a 100-page decision issued in December 2008, the trial court required Genzyme to pay for the cost of the drug in light of Genzyme’s statement in the informed consent document that it would offer the continuation of treatment to those subjects who finished the study. Because the informed consent document did not contain a time limitation, the court held that Genzyme was responsible for the entire cost of the supply of the drug. In support of the decision, the court found that when a sponsor carries out a clinical trial it establishes a permanent link with the study subjects. The court also found that once the sponsor chooses to carry out a clinical trial, it undertakes responsibilities that supersede the State’s obligation to ensure access to healthcare. On December 2, 2009, the Rio Grande do Sul State Court of Justice, the highest court in the state judicial system, by majority vote affirmed the trial court decision in relevant part. This decision implicates both significant financial and ethical considerations for sponsors of clinical research in Brazil, producing a potentially chilling effect on the amount and type of research conducted in Brazil. Notably, the drug became commercially available in Brazil prior to the end of the study.

c. Litigation

The risk of private litigation, which is always present given the potential risk of subject injuries, is heightened when studies are conducted in emerging markets. Lawsuits can be filed locally, and, in some circumstances, plaintiffs have filed in the U.S. under the Alien Tort Claims Act (“ATCA”), despite jurisdictional limitations on such actions. An illustration of how such lawsuits can play out is the litigation that ensued following Pfizer’s clinical trial of Trovan in Nigeria.

In early 1996, northern Nigeria suffered severe outbreaks of bacterial meningitis, cholera, and measles. In response to this terrible public health crisis, private companies, NGOs, and government agencies donated various supplies and services to help victims of the epidemics. During a six-month period, the meningitis epidemic alone claimed approximately 12,000 lives, most of them children, and affected close to 110,000 people.

In response to the epidemics in northern Nigeria, Pfizer donated medicines for cholera and measles, and developed a protocol to conduct a clinical study of Trovan in children afflicted with meningitis. Pfizer submitted the proposed protocol to the U.S. FDA and Nigeria’s National Agency for Food, Drug Administration and Control (NAFDAC) seeking permission to conduct the study. The protocol for the study called for treating 100 children with Trovan and 100 children with ceftriaxone, then the “gold standard” treatment for meningitis. Trovan had shown to be highly effective in treating bacterial meningitis, and Pfizer was in the final stages of its clinical studies of Trovan, having tested Trovan successfully in over 5,000 people outside of Nigeria, primarily in the E.U.

After reviewing the protocol, all of the required Nigerian and U.S. governmental authorities approved the study.

Pfizer identified a hospital in Kano, Nigeria to host the study and a local paediatrician to be the principal investigator. The treatment phase of the study lasted three weeks. Parents who brought their children to the hospital were given the option of enrolling their children in the Pfizer study or receiving a common meningitis medication from an NGO working at the same hospital. Verbal informed consent was obtained from those parents who agreed to enroll their children in the study, as set forth in the study protocol.

Of the patients who received Trovan, 94.4% survived, compared to 93.8% with ceftriaxone, and 89% with the common meningitis medicine (chloramphenicol). The vast majority of the patients in the study were cured; a small number suffered from neurological deficits that are common results of meningitis. Five children died in the Trovan arm of the study, and six died in the ceftriaxone arm. Deaths were associated with every treatment available in Nigeria, and all clinical evidence points to the fact that the deaths occurring during the Trovan study were the result of meningitis and not the treatment provided. Years later, allegations regarding there had been proper informed consent and the ethics committee approval were made in media reports. Those reports led to litigation in 2002 and 2003, when a group of Nigerian minors sued Pfizer in federal courts in New York and Connecticut under the Alien Tort Claims Act, 28 U.S.C. § 1350, and various international laws, alleging that they had not given their informed consent to participating in the study and that they were harmed by the study medications. They also alleged that no ethics committee had approved the trial before the trial began.

The trial court dismissed the cases for failure to state a claim, lack of subject matter jurisdiction, and forum non conveniens, but in 2009 an appellate court reversed that decision, and Pfizer has now petitioned the U.S. Supreme Court to review the matter.

In 2007 the Kano State government and federal government of Nigeria filed criminal and civil actions against Pfizer in Nigeria, seeking $6.95 billion in damages for alleged failure to obtain governmental approval to conduct the trial. The Kano State cases were settled in 2009, without admission of any liability. Under the settlement, Pfizer will fund various health care projects and a claims process in Nigeria for a total amount of up to $75 million. The federal government cases were settled and dismissed several months later, with the company simply reimbursing the government for certain legal expenses.

The litigation associated with this study reveals the perils of conducting a clinical study with very sick children, in an economically deprived area of the world, and with an illiterate and vulnerable population. It is an unfortunate example of how government and public support for research can change abruptly, especially when fueled by media reports about alleged injustices.

IV. MINIMIZING RISKS ASSOCIATED WITH GLOBAL CLINICAL TRIALS

As the growth of study and site placement in emerging markets are likely to outpace study and site placement in the U.S. and Western Europe, sponsors need sound strategies for addressing ethical, regulatory, and legal challenges. The remainder of this article discusses some of the strategies companies should consider implementing as they expand their presence in emerging markets and describes, by way of illustration, some of the strategies utilized by Pfizer as part of its globalization strategy.

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a. **Standardization of Policies and Procedures**

A company’s own policies and procedures form the cornerstone of any strategy aimed at ensuring compliance with international rules, regulations and guidelines. Legal counsel, together with regulatory affairs, quality assurance and clinical operations, should examine company policies and procedures to make sure that such policies and procedures adequately and properly contemplate global trials. Particular attention should be paid to policies and procedures governing human subject protections, including informed consent, access to investigational therapies during and after clinical study, and ethical review and oversight.

At a minimum, a company’s standard operating procedures (SOPs) should require that all studies comply with the laws and regulations relevant in the jurisdiction in which the study is being conducted. In addition, the SOPs should reference and require compliance with internationally recognized guidelines and ethical principles, most notably International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), GCP, Council for International Organizations of Medical Sciences (CIOMs) and the Declaration of Helsinki.

The strongest position would be for a company to adopt a universal standard for all of its clinical research activities. Under such a standard, a company would essentially impose the highest standards of quality and compliance on all clinical research conducted by a company. This is the path that Pfizer has elected to pursue.

In 2003, Pfizer adopted a policy entitled “Global Clinical Trial Standards,” which states that Pfizer will conduct all of its research in accordance with the same standards, *regardless of where in the world the study is conducted.* This policy is posted on [http://Pfizer.com/development](http://Pfizer.com/development). The policy allows a Pfizer study team to implement additional controls, as required by local standards, to address unique human subject protection issues in any particular jurisdiction but requires global standards as well. Amongst other things, Pfizer’s policy requires independent ethical review by a local ethics committee. If, however, the country has a developing ethical review framework the company often will supplement the local ethical review with a parallel review from a more developed nation. If a country has specific requirements for the collection of tissue samples, Pfizer incorporates those requirements in addition to standard requirements in the local consent document.

Additionally, in the company’s Global Clinical Trial Standards policy, Pfizer has committed to making its medications available in each market where a clinical study is conducted with the medications by seeking applicable marketing approval. The commercial availability of a treatment upon completion of a study is not always straightforward, however. First, an investigational medication may, in fact, be abandoned during or after a trial for a variety of reasons, and so no new approval application would ever be filed anywhere. Second, it may take years after an early phase trial in one country is completed for other, later phase trials to result in even the first approval for the drug, meaning even a greater number of years before any application is made for approval. Finally, local pricing matters may be a major barrier, even if a new drug approval is obtained. There are no easy answers to these questions, but they should be considered as part of the study plan.

b. **Implementation of Training and Accreditation Programs**

A robust and comprehensive set of policies and procedures governing domestic and international research is an important foundation for global research activities. Beyond this, however, there are other steps a company can and should take to improve the quality
of international studies and minimize the risk of regulatory or ethical challenges. Enhanced training of investigators and others involved in research on GCP issues, human subject protections, and unique local requirements is critical in improving and assuring the ethical and scientific quality of clinical trials.

To this end, Pfizer initiated a series of partnerships with international and local professional groups to conduct training of potential clinical investigators on GCP requirements, standards, and oversight. In Korea, for example, Pfizer partnered with KONNECT to conduct a training program on GCP standards for investigators and study staff. In India, Pfizer developed a series of workshop and symposia, together with the Indian Council for Medical Research. A total of 11 workshops on GCP and study methodology and an ethics workshop were conducted in India. Similar training programs were run in Mexico, Africa, and Turkey. These programs were highly successful, and Pfizer plans to expand these training programs in these and other markets.

To support education of ethics committees, especially non-expert members of ethics committees that may lack a scientific background in the design and conduct of clinical trials, Pfizer asked the Clinical Trial Centre of the University of Hong Kong to create an ethics manual. Pfizer provided an unrestricted grant to the Clinical Trial Centre of the University of Hong Kong to support the creation of this manual with the Association for the Accreditation of Human Research Protection Programs (AAHRPP) and international experts in research ethics. The English version of the manual was finished in March 2010 and has been posted on http://Pfizer.com/development. Pfizer is distributing about 3,500 copies of this ethics manual to ethics committees, investigators, government agencies, and others. Translations of the manual into Spanish, Portuguese, and Mandarin are currently underway.

While these training programs are helpful and should continue, they also require the outlay of significant resources, and there is no centrally recognized training or certification body. A major advance for international research would be the development of an internationally recognized investigator training and certification program to build confidence and credibility in global trials. Industry stakeholders should come together to advance such an initiative. Until a central body or program is developed, however, companies should and will continue to run such training programs on an individual basis.

One avenue is to build upon established and recognized accreditation programs in other areas. For instance, AAHRPP has emerged as the “gold standard” accreditation body for the certification of institutional human research protection programs. Similarly, the Association of Clinical Research Professionals has a program for certifying clinical investigators and study staff24 that is well known in the U.S., but less so in emerging markets. With support from other stakeholders and governmental bodies, groups like these can expand their programs for training and certifying clinical investigators. An internationally recognized training and certification program for clinical investigators and study staff holds great promise and would be well worth the effort and resources required to establish such a program.

c. Multi-Regional Clinical Trial Project (MRCT Project)

Last year, Pfizer convened other stakeholders -- pharmaceutical and biotechnology companies (including Glaxo, Novartis, Merck, and Genzyme), clinical research organizations (CROs), non-industry sponsors of research (such as participants from the National Institutes of Health), researchers, and bioethicists -- to a summit meeting to

24 http://www.acrpnet.org/
discuss ways to enhance the planning and conduct of multi-regional clinical trials. The purpose of the summit was, and remains, an avenue to explore ways in which to improve human subject protection and data integrity for trials that are conducted on a multi-regional basis, with special emphasis paid to trials conducted in resource constrained regions of the world. Following the meeting, five working groups were formed to address some of the challenges identified by participants of the MRCT Project, including the conduct of ethics reviews, data and safety monitoring, site selection and investigator team expertise, professionalism of monitors, and transparency of clinical contract terms.

At a follow-up meeting held with Harvard University in January 2010, the groups discussed proposals that included, but were not limited to, the following: (1) study sponsors should/can encourage accreditation of human research protections programs globally by making funding available to research ethics committees to facilitate such accreditation; (2) developing a fellowship program to train promising new data monitoring committee members, in which fellows would serve on the data monitoring committee, along with more seasoned members, as a way of garnering experience/expertise; (3) exploring ways to develop an internationally recognized investigator training and certification program that would complement current accreditation programs for human subject protection programs; (4) encouraging professional certification of trial monitors; and (5) developing model terms for key provisions affecting research integrity, patient rights, and academic freedom. The report from the MRCT Project and some 25 in-progress recommendations are publicly available on [http://www.Pfizer.com/mrct](http://www.Pfizer.com/mrct).

d. Malaria Clinical Trial

One of Pfizer’s upcoming malaria trials is a powerful example of industry’s interest in developing new medicine that meet unmet medical needs, even though the research is costly and complicated and poses many of the risks described in this article.

Across Sub-Saharan Africa, malaria is a common cause of maternal and neonatal mortality and morbidity. Between 20-40% of pregnant women in the region have adverse pregnancy outcomes (i.e., stillbirth, spontaneous abortion, premature birth, low-birth weight, or neonatal death). Pfizer is developing a fixed-dose combination therapy to prevent the transmission of malaria and reduce adverse pregnancy outcomes. The study is being designed and run in collaboration with two partners, a non-governmental organization active in malaria research and an academic medical center with extensive expertise in tropical medicine.25

This important study will enroll 4,200 patients across 6-8 sites, each with a local, medically qualified principal investigator and a site study team of medical staff and field workers. The study will be overseen by an independent Data Monitoring Committee (DMC) consisting of well-known experts in malaria, including experts from Africa. Risks to patients are being minimized through these further additional steps:

a) The study protocol is being reviewed by a research ethics committee at a “Western” academic medical center and by institutional and state ethics committees in each of the countries where the study will be conducted.

b) As with every study, clinical investigators will obtain (and document) the patients’ informed consent. In this study, an additional step has been added to

25 Pfizer will be conducting the trial in collaboration with the Medicines for Malaria Venture (MMV) – a non-governmental organization primarily funded by the Gates Foundation and the London School of Hygiene and Tropical Medicine (LSHTM).
help ensure the comprehension of the consent process. The study team is developing a narrated speaking book to help convey information to illiterate participants as part of the informed consent process. Similar to some children’s books, these books have pre-recorded information with accompanying illustrations and text. The speaking book will contain information about malaria and its impact upon pregnancy, clinical trials generally, the study, and the subject’s rights and responsibilities in connection with the study.

c) Pfizer will train all the investigators on GCP and research ethics, including issues unique to vulnerable populations, the study protocol, as well as on bioethics and laboratory evaluations.

d) Pfizer will monitor 100% of the source documents – every data point collected for the trial will be verified by a monitor against source records.

If the study demonstrates that the experimental medicine is both safe and efficacious, the new combination therapy would be distributed throughout the public sector and in prenatal clinics upon applicable regulatory approval. If the study does not demonstrate this, the study may still yield important data and insights that will advance science in this area. Of course, Pfizer hopes that in any event the investigators and the subjects in the trial will come away from the trial knowing that the company took every precaution to respect local community values and patients’ rights.

V. CONCLUSION

Globalization of clinical trials is here and likely to continue as a norm for drug development. There are many business, regulatory and scientific reasons supporting this trend and it is incumbent upon research clinical trial sponsors to update and strengthen their internal policies and procedures to ensure that all research meets the same standards of quality and human subject protections. A strong step in this direction would be to adopt policies and procedures that apply a singular standard to all sponsored research, regardless of venue of the clinical study.

Sponsors and other stakeholders also have an affirmative responsibility to work with regulators, policy makers and local governments and institutions to build and strengthen the local infrastructure for clinical research, particularly in the areas of ethical oversight and the qualification of clinical investigators. Sponsors need to work with other stakeholders to develop an internationally recognized clinical investigator training and certification program to ensure that well qualified investigators are available to conduct studies in emerging markets. Such steps will strengthen the quality of, and confidence in, the research conducted in these emerging markets around the globe.

In the meantime, it is important that pharmaceutical companies and other sponsors of clinical research continue to place studies in emerging markets where there is a sound scientific and medical basis and support those studies with individual efforts to build infrastructure through training and education efforts as part of the study.

Justin McCarthy is a Senior Vice President and Associate General Counsel at Pfizer Inc and is the Chief Counsel for Pfizer’s Worldwide Research & Development division. He is responsible for coordinating legal support for the company’s research activities and
external collaborations across R&D and leads a clinical trial platform that supports Pfizer’s clinical trial activities across all of Pfizer’s business units. As part of this role, Justin is leading an industry-wide initiative focusing on improving public trust in industry-sponsored clinical trials and is a member of the SACHRP Subcommittee on Harmonization. Justin also has responsibility for Pfizer's global Privacy function.

In addition to counselling Pfizer on research policy and bioethics, Justin has led the design and implementation of a novel outside counsel program that attempts to fundamentally alter the relationship between inside and outside counsel by doing away with the billable hour and using a smaller alliance of firms with whom the company can form stronger relationships to provide more effective and efficient legal support to Pfizer. Justin joined Pfizer in 1993 based at corporate headquarters in New York, where he provided regulatory law support for all Pfizer businesses. In 1998, he relocated to Brussels where he provided legal support to Pfizer’s European Operations. He returned to the US in 2001 to support Pfizer’s expanded research and development operations after the merger with Warner-Lambert.

Prior to joining Pfizer in 1993, Justin was an associate in the Washington, D.C., law firm of Keller & Heckman, where he focused primarily on food and drug law. Justin holds a BS in Pharmacy from the University of Rhode Island and a JD from the Catholic University of America.

Marc Wilenzick is the Chief Compliance Counsel for R&D & Clinical Trials at Pfizer. He also serves as the lead regulatory and policy counsel for R&D. Prior to joining Pfizer, Marc was an attorney at the U.S. Food and Drug Administration. He holds a BA and a JD degree from the University of Texas at Austin.

Cara Cuenot is lead counsel for the BioCorrection Research Unit at Pfizer. She also helps to support R&D policy related matters. She holds a BS from the University of Vermont, a JD / MS from Syracuse University and her MBE from the School of Medicine at the University of Pennsylvania.