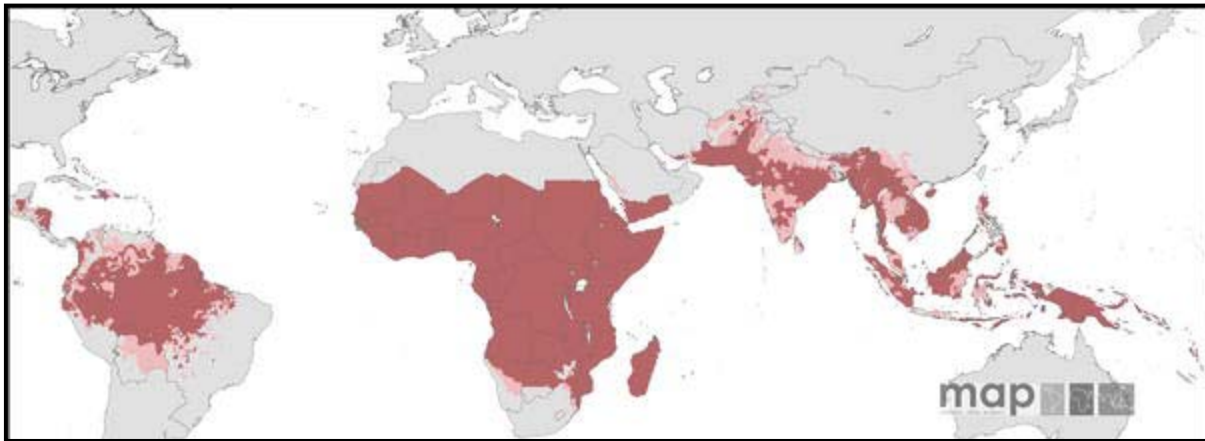


Malaria Treatment: Better than the Standard of Care

In 2008, more than 100 countries were endemic for malaria, almost half of which were in the African region as defined by the World Health Organization. About 3 billion people – 40% of the population worldwide -- are at risk of contracting the disease.¹

Malaria Risk Defined by Annual Parasite Incidence 2002-2006²



Note: Red marks stable risk; pink marks unstable risk; grey marks no risk.

Not only are people at risk; malaria is one of the top five killers worldwide:

- More than 500 million cases of malaria are reported annually
- Of those afflicted, about one million die
- 80 percent of deaths are children in sub-Saharan Africa³

Prevention and Treatment Save Lives

A variety of tools and methods exist to fight malaria. Some of the most commonly used prevention tools are the use of mosquito nets and indoor spraying of insecticides. Treatments include artemisinin-based combination therapy (ACT) and intermittent preventive treatment in pregnancy (IPT). A vaccine is also being pursued via an international collaborative initiative, but is still in the research stages and is not yet in use in the general population.

¹ World Health Organization, "World Malaria Report: 2008," 2008.

<http://www.who.int/malaria/wmr2008/>

² Guerra CA, Gikandi PW, Tatem AJ, Noor AM, Smith DL, et al. "The Limits and Intensity of *Plasmodium falciparum* Transmission: Implications for Malaria Control and Elimination Worldwide," *PLoS Medicine* Vol. 5, No. 2, e38 doi:10.1371/journal.pmed.0050038

³ "First Global Malaria Map in Decades Shows Reduced Risk," *ScienceDaily*, February 27, 2008. <http://www.sciencedaily.com/releases/2008/02/080225213650.htm>

Pfizer's Malaria Platform

Pfizer's Mobilize Against Malaria initiative, highlighted at the 2006 Clinton Global Initiative, is just one aspect of Pfizer's overarching commitment to combat malaria. With its 25-year history in malaria, Pfizer's investment is threefold: the research and development of new therapies, making Pfizer's portfolio of medicines available through innovative commercial partnerships, and supporting efforts to increase patient awareness of and access to effective use of antimalarials. Pfizer has conducted clinical research related to malaria in Africa, India and South America. The company is currently conducting studies in Burkina Faso, Cote D'Ivoire, Ghana, Kenya, Mali, Senegal, South Africa, Tanzania, Uganda, and Zambia.

Pfizer is also collaborating with the World Health Organization and the Special Programme for Research in Tropical Diseases (WHO/TDR) to target malaria and other neglected diseases by giving TDR access to Pfizer's library of medicinal compounds and also bringing scientists from developing countries into Pfizer's labs for training in drug discovery techniques. While this is early-stage research, with effective new treatments still years downstream, it certainly improves the chances of identifying compounds that may lead to new drugs. It is this kind of public-private research collaboration that is vital to tracking health challenges in developing countries.

Standard of Care

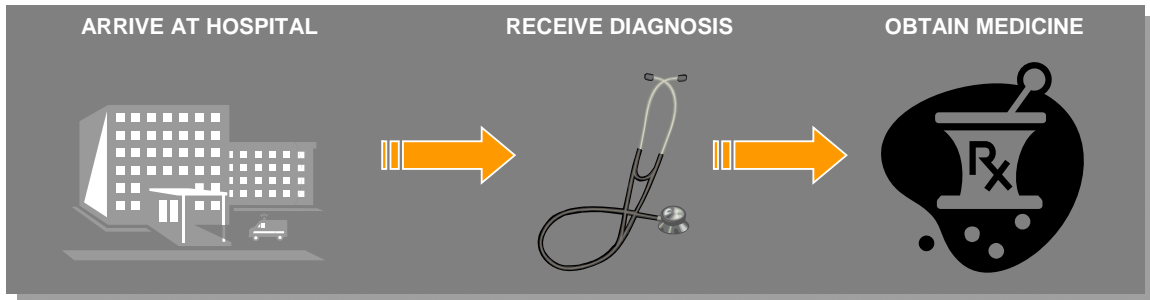
When practitioners are practicing medicine, they rely on a combination of knowledge of research, previous practices and their own experience. The combination of these skills and knowledge form a sort of baseline of appropriate treatment. The "standard of care" is what is recognized by reasonably prudent similarly professional health care providers as the acceptable level of care. Notably, standard of care does not necessarily mean "best" care, but instead refers to usual care which often includes a broad range of practitioner behavior.

For example, for any given disorder or disease, there are routine steps that should be taken by health care providers when caring for that particular patient. It does not necessarily mean every patient is treated in exactly the same way, but instead that all patients are treated using similar processes to determine how best to prevent, diagnose and/or treat each patient.

"Standard of care" services are generally understood to be those services that would be furnished even if the individual receiving those services were not a subject in a clinical trial."⁴

Clinical Trials and Standard of Care

During the course of a clinical trial in a resource-poor country, Pfizer understood the standard of care for treatment of malaria patients to be a fairly straightforward process:



With this process in mind, the clinical research study team designed a protocol that would closely mirror the standard of care for malaria patients in this locale. The protocol required the following steps:

1. Patient presents in emergency room with fever and/or other characteristics associated with malaria diagnosis
2. Consider patient for pre-study process by getting a blood smear to test for malaria
3. If positive, ask patient to consider enrolling in trial
4. Ask patient to read and if interested, sign an informed consent document
5. Begin study treatment

The described process replicated the usual standard of care for patients in that particular community who presented to a hospital or clinic with symptoms associated with malaria. The protocol had been approved by the local institutional review board, and reviewed by locally-practicing physicians, so it seemed unlikely the standard of care was not being observed.

However, after the trial began, the Pfizer study team heard anecdotally that it was taking several hours to move from step four to step five. Where typically a

⁴ FDA/Healthcare Regulation, "Medicare Reimbursement in Clinical Trials for "Standard of Care" in Flux," July 2007. Morgan Lewis Publications.

<http://morganlewis.com/index.cfm/fuseaction/publication.print/publicationID/ba377af6-483e-4cab-817b-7085914297d4/>

patient would receive malarial treatment within a few hours of confirmed diagnosis, it appeared that the informed consent process has the potential to delay the provision of therapy beyond that of typical medical care. While clinically a difference of two hours was inconsequential, it seemed to be outside the standard of care so deserved investigation.

Quality Controls and Standards of Excellence

The Pfizer study team investigated the study process further and uncovered something unexpected.

At the point where informed consent was sought, instead of patients and potential trial participants simply reading the forms and deciding whether or not to enroll, patients were leaving the clinic or hospital and travelling back to their villages to ask for input from community elders. Women, in particular, were leaving as they could not sign the informed consent form without input from a male relative. Patients were interested in the trial, as evidenced by their willingness to journey two or three hours roundtrip to obtain permission to sign the consent form. But in the process to obtain consent as required, the standard of care for malaria treatment seemed to be slipping.

Investigators' opinions about the protocol process were sought, but no concerns were communicated. The local doctors were comfortable that patients were receiving recommended treatments in a timely fashion.

However, instead of relying on the standard of care, as approved by the local IRB and the investigators involved, Pfizer decided it should revise the protocol to allow patients to be transported by van from the clinic to their villages and back to the clinic in order to expedite the informed consent process. Further, clinicians from the study site rode in the van with the patients to ensure they had medical oversight while out of the clinic. In this way, patients were still receiving culturally-appropriate care because the local needs for informed consent were being honored, but the standard of care was elevated to standard of excellence.

Discussion Questions

1. How should differences between local standards of care be reconciled with Western medical standards of excellence?
2. Who has the responsibility to assure standard of care is maintained in clinical trial research?
3. What steps can protocol writing teams take to assure local customs are considered in the medical investigation process?
4. Should trials always use the most effective, proven therapy, or is it permissible to use therapies used locally as the comparator in some clinical trials?
5. Who should decide whether the locally used treatment or another medically recognized treatment is appropriate to be the comparator drug?