decision making and may not be permitted to provide their individual consent. Moreover, the informed consent process may be challenged by the low literacy rates found among women in developing countries. Recruitment of married women also provides challenges as the protocol may require pregnancy testing or the agreement of the woman to adhere to family planning techniques. These procedures may be objectionable for either religious or cultural reasons and could threaten her position in the family. Despite the many obstacles, through the implementation of awareness programs aimed at men and women, the community can be sensitized and women can accept to participate.

CULTURAL DIFFERENCES

The challenges of working in the context of different cultures are considerable. Literacy rates in developing countries are relatively low, which impacts the informed consent process. Consent materials may need to be translated into local languages and visual and auditory techniques may need to be used to impart the necessary information. A clinical trial site in Mali has consent forms translated and recorded by the national translation service into local languages so that participants can listen to rather than read the content. Concepts such as randomization must be explained using locally relevant examples such as the likelihood of picking a particular peanut from a sack full of peanuts.

In pediatric trials, obtaining the appropriate signature on a consent form may also be difficult as children are often charged to family members while the natural parents are living elsewhere. Children may be ''adopted'' by distant family without seeking legal documentation from the local authorities. Multiple generations may share a single household, resulting in grandparents being considered as the primary decision makers. All of these particularities challenge the informed consent process compared with how it is conducted in industrialized countries, and sponsors often have to remain open-minded about what is acceptable.

Often, trials of vaccines already licensed for use in industrialized countries are performed under markedly different epidemiological and demographic conditions in developing to establish local efficacy. In this case, sponsors may wish to apply in the developing country venue the procedures and techniques that were successful elsewhere; this approach is variably successful. For example, whereas post-vaccination daily temperature monitoring by participants may be common practice in an industrialized or transitional country, in a poor developing country most people may not be accustomed or able to collect this information. Moreover, sponsors may request that case identification be made at organized health facilities because there can be greater certainty regarding the clinical findings. In contrast, locals may prefer to visit traditional healers because of lower cost, trustworthiness, or greater convenience. In this case, sponsors must rely on the local investigators' experience, and as a result, case identification methods between industrialized and developing country settings may differ.

SUSTAINABILITY OF STUDY-RELATED ACTIVITIES/STANDARD OF CARE

Populations that participate in research often benefit from the strengthening of local health services that occur as a byproduct in the area where the trial was conducted. In many cases, health care personnel are recruited, clinics refurbished, disease surveillance implemented, and participants educated in health matters. Since vaccine trials can last several years, the population becomes accustomed to this standard of care. When study activities have not been incorporated into routine health services, study participants come to rely on care from the study personnel and their utilization of the public health care system can be affected. As a result, it is important to discuss these issues with the community and the sponsor so that study material may be donated to the community at the end of the trial. In addition, local personnel, including governmental health care providers, should be used whenever possible so that these newly trained and sensitized personnel can remain at their usual post after the trial, thereby building sustainability. Thus, the community continues to benefit long after the trial has ended.

ISSUES RELATED TO TRIAL OVERSIGHT

As with any trial, there is a considerable amount of oversight from external groups, including ethical review committees and data and safety monitoring boards. Such oversight groups have certain challenges ahead of them that are specific to the developing country setting.

ETHICAL REVIEW COMMITTEES AND INSTITUTIONAL REVIEW BOARDS

In most cases, international vaccine trials are reviewed by local ethical review committees in the host country and external institutional review boards (IRBs) in the sponsor's country and in any collaborating countries. The ethical issues surrounding protocol review by multiple committees are addressed elsewhere; logistical aspects will be discussed here.

Since relatively few vaccine clinical trials have been conducted in most developing countries, ethical review committees have variable levels of experience and expertise. To demonstrate that they are following international norms, committees obtain an assurance such as the Federalwide Assurance (FWA), which is provided by the U.S. Department of Health and Human Services to indicate that the committee is in compliance with Code of Federal Regulations Title 45 Part 46. However, committees may not be acquainted with all of their assigned duties and sponsors, and investigators may find themselves requesting additional documentation or submitting unrequested annual reports. These requests may go beyond what the committee expects and may exceed the committee's resources. Nonetheless, these interactions should be considered part of capacity building as the committees gain expertise in the review of clinical vaccine trials.

Committees in developing countries may have a limited support staff, resulting in long turnaround times for review. In some cases, ad hoc committees may be convened, making subsequent reviews of protocols problematic, as the committee has to reconvene. Reviews by each collaborating institution can be difficult to coordinate, especially when they make conflicting requests. Nonetheless, any local requests regarding the study design must be agreed on by all participating institutions so that results may be interpretable across sites. Obtaining serial approvals (awaiting final approval from one committee before submitting for initial review by another committee) can take months or even years. To avoid long delays in obtaining final ethical approval, it is often most efficient to submit the protocol to all committees simultaneously, incorporate all requested