

# Prior Agreements in International Clinical Trials: Ensuring the Benefits of Research to Developing Countries

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When biomedical research is conducted in the developing world, the disparity in power between rich and poor nations manifests itself in two ways. In most cases, the industrialized world sets the agenda and carries out the research. The involvement of developing countries is limited (a gradual change, however, is evident), and only in a few instances do they function as full and equal partners.<sup>1</sup> Moreover, although it assumes very few research burdens, the industrialized world receives the great majority—and in some cases, all—of the research benefits because, unlike the developing world, it can afford to buy a proven intervention. The burdens of research, in contrast, are borne by developing countries whose poorest inhabitants serve as research subjects but rarely share in its benefits. Many interventions are well beyond the economic reach of both research subjects and their governments.<sup>2</sup>

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† This Article was originally prepared by the author as a commissioned paper for the National Bioethics Advisory Commission (NBAC). Substantial portions were adopted by NBAC and appear in either an identical or similar form in its report, *Ethical and Policy Issues in International Collaborative Research: Clinical Trials in the Developing World*. The views expressed herein are those of the author and may not reflect those of NBAC. Prior to its acceptance for publication in the *Yale Journal of Health Policy, Law, and Ethics*, this Article was the subject of a presentation at the Columbia University Seminar on Human Rights in December 2001. An edited version of this Article will appear in a volume tentatively entitled *Looking Beyond the State: Non-State Actors and Human Rights*, to be edited by the organizers of the Columbia University Seminar.

<sup>1</sup> 1 NAT'L BIOETHICS ADVISORY COMM'N, ETHICAL AND POLICY ISSUES IN INTERNATIONAL RESEARCH: CLINICAL TRIALS IN DEVELOPING COUNTRIES 3 (2001) [hereinafter 1 NBAC]; NUFFIELD COUNCIL ON BIOETHICS, THE ETHICS OF RESEARCH RELATED TO HEALTHCARE IN DEVELOPING COUNTRIES 24-30 (2002).

<sup>2</sup> This discussion is grounded in distributive justice, an ethical principle that seeks a fair and equitable distribution of social benefits and burdens. In the research context, distributive justice demands that no one group or class of persons assumes the risks and inconveniences of research if that group or class is unlikely to benefit from the fruits of that research. This concept extends to international collaborative research, which involves an arrangement between researchers and sponsors from industrialized and developing countries and their local institutions, but not necessarily the countries themselves, (although the Ministry of

Under these circumstances, for the research to be ethical, research benefits must be fairly and equitably apportioned to the host community,<sup>3</sup> a term which may be difficult to define in a particular research setting. One of the greatest challenges facing international research ethics is crafting practical and economically feasible solutions to help ensure that citizens of developing countries are not exploited for the benefit of the industrialized world. Data from a survey conducted for the benefit of the United States National Bioethics Advisory Commission (NBAC) indicate that, to some extent, post-trial availability of research benefits is a consideration in research hosted by developing countries.<sup>4</sup> Nevertheless, forty-eight percent of researchers in developing countries and thirty-three percent of U.S. researchers who responded believed that the interventions tested in their research were unlikely to become available to most host community residents in the foreseeable future.<sup>5</sup>

This Article examines the use of prior agreements in international clinical trials<sup>6</sup> to ensure provision of drugs and other research benefits to developing countries where research is conducted. Post-trial access to the

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Health usually must grant approval for the research). See 1 ANNA MASTROIANNI ET AL., *WOMEN AND HEALTH RESEARCH: ETHICAL AND LEGAL ISSUES OF INCLUDING WOMEN IN CLINICAL STUDIES* 78 (Anna Mastroianni et al. eds., 1994) (“[J]ustice is to be construed as a universal requirement, not confined within the borders of any one nation.”). As Ruth Macklin writes:

To meet the requirements of distributive justice in international research ... [b]eneficiaries of the research outcomes must include people in the developing countries where research is conducted, as well as the developed country that sponsors the research. These conditions make it clear that it is not only the benefits and burdens accruing to the research participants, but also the potentially beneficial outcomes of the research that count in determining equity.

Ruth Macklin, *Justice in International Research*, in *BEYOND CONSENT: SEEKING JUSTICE IN RESEARCH* 132 (Jeffrey P. Kahn et al. eds., 1998). See also 1 MASTROIANNI ET AL., *supra* (noting that in its discussion of distributive justice, the report issued by the Institute of Medicine states that “[b]eneficiaries of the research outcomes must include people in the developing countries where the research is conducted, as well as in the [developed country that sponsors the research]”); Solomon R. Benatar, *Distributive Justice and Clinical Trials in the Third World*, 22 *THEORETICAL MED.* 169, 169-76 (2001); D.R. Cooley, *Distributive Justice and Clinical Trials in the Third World*, 22 *THEORETICAL MED.* 151, 151-67 (2001).

<sup>3</sup> “Host community,” “host population,” and “host country” are terms that are often used interchangeably.

<sup>4</sup> NANCY KASS & ADNAN A. HYDER, *ATTITUDES AND EXPERIENCES OF U.S. AND DEVELOPING COUNTRY INVESTIGATORS REGARDING U.S. HUMAN SUBJECTS REGULATIONS B-141* (2000). This background paper was prepared for NBAC and is available in Volume II of its report, *Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries*.

<sup>5</sup> KASS & HYDER, *supra* note 4, at B-141.

<sup>6</sup> Primarily Phase III clinical trials that directly demonstrate the effectiveness of a new intervention to a statistically and clinically significant degree were examined. Determining when this type of clinical trial has occurred is no simple matter.

benefits of research is an issue that has not yet had the benefit of careful study and public discussion. Other than the World Health Organization (WHO), which for years has been using prior agreements in its collaborations with industry to promote development of health-related products, agreements for making research benefits available to host countries after a study is completed have only recently begun to surface in international clinical trials. Consequently, the number of agreements in place today is limited.

Two closely related assumptions guide the discussion. First, to be ethically acceptable, clinical research conducted or sponsored by an industrialized country<sup>7</sup> in a developing country should be responsive to the health needs and priorities of the population on which it is carried out.<sup>8</sup> In other words, research should aim to improve the health of the population from which subjects are drawn. Second, there is an ethical obligation to ensure that the developing country, and not just the individual research participants, benefits from the research.<sup>9</sup> This obligation can be characterized as a means of applying or implementing the first premise. Unless there is a reasonable likelihood that developing countries will partake in the fruits of research in a timely manner, research cannot be responsive to the needs of the subject population or be expected to improve its health.<sup>10</sup> However, there may be instances where provision of research benefits other than (or in addition to) effective interventions is warranted.<sup>11</sup>

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<sup>7</sup> The term “industrialized country” can include a government agency, pharmaceutical company, university, non-governmental organization (NGO), or any other entity or organization, public or private, and the individuals who represent them.

<sup>8</sup> COUNCIL FOR INT’L ORGS. OF MED. SCIS., INTERNATIONAL ETHICAL GUIDELINES FOR BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS Guideline 10 (2002) [hereinafter CIOMS] (“Before undertaking research in a population or community with limited resources, the sponsor and the investigator must make every effort to ensure that . . . the research is responsive to the health needs and the priorities of the population or community in which it is to be carried out. . .”).

<sup>9</sup> WORLD MED. ASS’N, WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI: ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS Principle 19 (adopted 1964, revised 2000) [hereinafter WMA] (“Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.”); Robert A. Crouch & John D. Arras, *AZT Trials and Tribulations*, HASTINGS CENTER REP., Nov. 1998, at 26, 26; Leonard H. Glantz et al., *Research in Developing Countries: Taking ‘Benefit’ Seriously*, HASTINGS CENTER REP., Nov. 1998, at 38, 40.

<sup>10</sup> CIOMS, *supra* note 8, Guideline 10 (“Before undertaking research in a population or community with limited resources, the sponsor and the investigator must make every effort to ensure that . . . any intervention or product developed, or knowledge generated, will be made reasonably available for the benefit of that population or community.”).

<sup>11</sup> See *infra* Part I.

The Article is divided into three parts. Part I explains what prior agreements are and how they are being used in international clinical trials. Part II urges the use of prior agreements to help overcome some of the barriers to making effective interventions available in developing countries. It also refutes current arguments against the use of prior agreements. Part III discusses the various types of prior agreements currently in use and offers concluding observations.

### I. HOW PRIOR AGREEMENTS CAN BE USED TO MAKE RESEARCH BENEFITS AVAILABLE

“Prior agreements,” also known as “community benefit agreements,” generally refer to arrangements made before research begins that lay out a realistic plan for making effective interventions or other research benefits available to the host community after a study is completed. The use of the term “agreement” generally does not have any legal connotation in the international research context, and while some of these agreements may be legally binding instruments, others are not. In the area of Human Immunodeficiency Virus (HIV) vaccine trials, for example, “[p]revious experience indicates that manufacturers usually agree verbally to explore alternatives to make products available, but they rarely do so in writing.”<sup>12</sup>

It is difficult to formulate general rules regarding the nature and scope of prior agreements. Every study conducted is unique, and the needs and circumstances of developing countries vary so greatly and often change and evolve over time. The parties to these agreements usually include some combination of producers, research sponsors, and potential users of effective interventions or other research benefits. Industry, academia, and organizations of various kinds are frequently producers and sponsors, while non-profit health organizations and governments of developing countries are most likely to be users.

The role of researchers in the prior agreement process warrants some discussion. Since researchers are not directly responsible for providing effective interventions to host communities (they neither control research funds nor set policy), in some, if not many, instances, they are not parties to these agreements. Researchers from both industrialized and developing countries still play an important role, however, in ensuring that issues pertaining to post-trial obligations are fully considered as part of protocol development and review. It is also essential that, throughout a study and for some time afterward, researchers maintain an ongoing dialogue about

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<sup>12</sup> Jose Esparza, *AIDS Vaccine Research in Asia: Needs and Opportunities, Report from a UNAIDS/WHO/NIID Meeting, Tokyo, 28-30 October 1998*, 13 AIDS 1, 10 (1999).

these issues with national and community health officials as well as with sponsors of both the study and / or post-trial benefits. Their commitment to research as well as their knowledge and expertise about the health problem they are studying place researchers in a unique position to advocate for the use of an intervention in the host community after a study is completed. The Nuffield Council on Bioethics, in its recent report, *The Ethics of Research Related to Healthcare in Developing Countries*, notes:

[T]he researcher should present findings in such a way that healthcare policy-makers can understand their implications and, at the least, the findings can be used for advocacy purposes with respect to the future provision of the intervention....[T]hey can draw attention to problems which have been neglected, or conditions whose impact has been underestimated, and demonstrate that there are feasible solutions.<sup>15</sup>

Important questions related to representation of the study population in the negotiation process also need to be addressed. Who should serve as the representative and how is that determined? What authority does that party have to serve in that capacity? How is the acceptability of a prior agreement to the study population to be determined? In one sense, as advocates for the use of a study intervention in the host community after a trial is completed, researchers serve as representatives for the study population. Yet, in almost all cases, the study population will also be represented by a governmental unit (or units) of some kind, which has given permission for the study to be conducted. Generally, it will be a ministry of health at the national level; often, a local governmental body will be involved as well. However, unless these governmental units are both willing and able to take action, effective interventions are unlikely to be made widely available in a host community. Because of resource scarcity, priority setting by developing countries is extremely difficult, and without external funding, many countries would be unable to make interventions available after a study is completed.

In at least two ways, prior agreements can provide research benefits to populations from which study participants are drawn. One way is to stipulate that an intervention, if proven effective, will be made available to the host community at a cost it can afford. This could be accomplished by providing the intervention to the class of individuals represented by the trial participants for a specified period of time at a specified cost. Exactly what this would entail in a given situation depends upon a number of factors, particularly the health problem that an intervention is intended to

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<sup>15</sup> NUFFIELD COUNCIL ON BIOETHICS, *supra* note 1, at 122.

address. Alternatively, if a country's need for a particular drug can be adequately quantified and the shelf life of the drug and other factors render it appropriate to do so, the country could make bulk purchases of the drug at a subsidized price.

Prior agreements can also provide derivative benefits—research benefits other than the studied intervention. The first meeting of the Global Forum for Bioethics in Research in 1999<sup>14</sup> reached the consensus that researchers, sponsors, and host governments should seek arrangements that emphasize derivative benefits such as technology transfer and capacity building, rather than simply making effective interventions available.<sup>15</sup> Similarly, the Nepal Health Research Council's recently published research ethics guidelines state that sponsors “should consider means in which the research capability of Nepal can be strengthened. . . .”<sup>16</sup>

Derivative benefits can come in many forms. With technology transfer, a pharmaceutical company could agree to grant host governments a free or low-cost license to produce a drug in exchange for a commitment from those governments to manufacture and distribute the drug to their constituents. Capacity building asks researchers and sponsors to help develop a host country's capacity for designing and conducting clinical trials, for scientific and ethical review of proposed research, and for implementing research results after a trial is completed. These efforts, which find support in documents such as the Council for International Organizations of Medical Sciences (CIOMS) *International Guidelines for Biomedical Research Involving Human Subjects*<sup>17</sup> and the Joint United Nations Programme on HIV / AIDS (UNAIDS) *Guidance Document, Ethical*

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<sup>14</sup> Karen Hofman, *The Global Forum for Bioethics in Research: Report of a Meeting, November 1999*, 28 J. L., MED. & ETHICS 174, 174 (2000) (“Held in Bethesda (Maryland) on November 7-10, 1999, the intent was to bring together individuals involved in medical research in low- and middle-income nations to share views with each other and with organisations that support clinical research.”).

<sup>15</sup> *Id.* at 175.

<sup>16</sup> NEPAL HEALTH RESEARCH COUNCIL, NATIONAL ETHICAL GUIDELINES FOR HEALTH RESEARCH IN NEPAL §7(d), at 9 (2002).

<sup>17</sup> CIOMS, *supra* note 8, Guideline 20 (“In externally sponsored collaborative research, sponsors and investigators have an ethical obligation to ensure that biomedical research projects for which they are responsible in such countries contribute effectively to national or local capacity to design and conduct biomedical research, and to provide scientific and ethical review and monitoring of such research. Capacity-building may include, but is not limited to . . . establishing and strengthening independent and competent ethical review processes / committees, strengthening research capacity, developing technologies appropriate to health-care and biomedical research, training of research and health-care staff, [and] educating the community from which research subjects will be drawn.”).

*Considerations in HIV Preventive Vaccine Research*,<sup>18</sup> are aimed at lessening the mismatch in developing countries between the high burden of disease and the lack of technical capacity to make use of existing knowledge or to generate new knowledge to address health problems. Another derivative benefit is the provision of various forms of health care. For instance, post-trial maintenance of a primary care clinic established in conjunction with a study might be extremely beneficial to a host community. A final example of a derivative benefit is a commitment from researchers to continue working with a developing country (after a trial) to solve particular health problems.

One advantage of derivative benefits is that significant aid can still be provided to a host community when research is not expected to produce an effective intervention for a number of years—for “only rarely does a single research study lead to the discovery of a new intervention that can be introduced promptly into routine care”<sup>19</sup>—or when an experimental intervention proves ineffective. This, in turn, may help lessen the perception that the industrialized country is exploiting the developing country. In addition, where research sponsors are either unable or unwilling to make effective interventions available, capacity building may provide a realistic, less costly alternative.

The benefits that are actually negotiated will depend upon a number of factors. As mentioned, the health problem addressed by a research protocol is one such factor. Will there be a need for the intervention once the study is completed? Can the health problem be cured or is it a chronic or terminal condition? What will be the cost of the intervention or other benefit? The nature and number of sponsors responsible for providing the intervention is also relevant. Is the sponsor, for example, a non-governmental organization (NGO) or a pharmaceutical company?

Likewise, the conditions in a host country as well as its capabilities will influence the agreement. One of the most important considerations in every case is the host country’s health care system. In poorer countries, provision of an effective intervention would probably be appropriate in most instances. The suitability of providing derivative benefits will depend upon the nature of the benefit and the economic and technological state

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<sup>18</sup> JOINT UNITED NATIONS PROGRAMME ON HIV / AIDS, *ETHICAL CONSIDERATIONS IN HIV PREVENTIVE VACCINE RESEARCH: UNAIDS GUIDANCE DOCUMENT* Guidance Point 3 (2000) [hereinafter UNAIDS] (“Strategies should be implemented to build capacity in host countries and communities so that they can practise meaningful self-determination in vaccine development, can ensure the scientific and ethical conduct of vaccine development, and can function as equal partners with sponsors and others in a collaborative process.”).

<sup>19</sup> NUFFIELD COUNCIL ON BIOETHICS, *supra* note 1, at 121.

of a developing country. For example, technology transfer makes sense for countries with strong local pharmaceutical industries (or countries that are developing them), while building research capacity or obtaining researcher commitments would be appropriate for many, if not all, developing countries.

Whether it suffices to provide derivative benefits instead of an intervention that has proven to be effective is a question that is, in itself, extremely controversial. Some contend that it is ethical to conduct research on a population that will not receive any direct benefit from that research so long as that population is compensated in some other important way, such as by increasing the host community's ability to conduct research or constructing a water sanitation plant in a community that lacks clean water. Others argue that the fruits of the research must accrue directly to the population from which research subjects are drawn.

#### A. *The Ethics of Conducting Research in Developing Countries*

As mentioned, biomedical research conducted in developing countries by industrialized countries must be responsive to the health needs and priorities of the host community to be ethically acceptable. This fundamental principle of international research ethics is well documented in prominent international guidelines such as the CIOMS *Guidelines*<sup>20</sup> and the World Medical Association (WMA) *Declaration of Helsinki*.<sup>21</sup> It also forms the cornerstone of the NBAC report, *Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries*.<sup>22</sup> The implementation of this principle, however, is much more difficult. As former National Institutes of Health Director Harold Varmus and former Surgeon General David Satcher noted, “[o]ne of the great challenges in medical research is to conduct clinical trials in developing countries that will lead to therapies that benefit the citizens of these countries.”<sup>23</sup>

Some have argued that, to be ethically acceptable, research must “offer the potential of actual benefit to the inhabitants”<sup>24</sup> of a developing country by providing host communities affordable access to an effective intervention. It is not enough that the tested intervention is provided to trial participants. Without guaranteeing affordable access to the population from which participants are drawn, the developing country

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<sup>20</sup> CIOMS, *supra* note 8.

<sup>21</sup> WMA, *supra* note 9.

<sup>22</sup> 1 NBAC, *supra* note 1, at 8.

<sup>23</sup> Harold Varmus & David Satcher, *Ethical Complexities of Conducting Research in Developing Countries*, 337 NEW ENG. J. MED. 1003, 1003 (1997).

<sup>24</sup> Glantz et al., *supra* note 9, at 39.

receives little benefit. If the knowledge gained from research is used primarily for the benefit of the industrialized world, the research may rightly be characterized as exploitative and therefore unethical.<sup>25</sup> Exploitation, as the term is used herein, refers to exploitation “in execution, or in the final analysis,” not intent. Even if researchers and sponsors are well intentioned, “their research may nevertheless violate ethical canons if its positive fruits are not made reasonably available to former research subjects and other inhabitants of the host country.”<sup>26</sup>

The argument that research must benefit the host community can be taken even further. Leonard Glantz and his colleagues argue that it is not enough to make an effective intervention available to a host community by removing financial barriers to access if there is no means of getting the intervention to the population that needs it: “Where the health care infrastructure is so undeveloped that it would be impossible to deliver the intervention even if it were free, research would be unjustified in the absence of a plan to improve the country’s health care delivery capabilities.”<sup>27</sup> Consistent with this argument, the CIOMS *Guidelines* declare that “[e]xternal sponsors are ethically obligated to ensure the availability of ... [health care] services that are a necessary part of the commitment of a sponsor to make a beneficial intervention or product developed ... reasonably available to the population or community concerned.”<sup>28</sup>

Although there are many explanations for conducting research in developing countries, there are generally two sound reasons for doing so. One is that no known effective intervention exists for a serious health problem in a developing country. Research is the best method for developing solutions to such health problems. The other reason arises from the reality of health economics in developing countries. Developing countries often lack the resources to purchase existing interventions. Many of them may not be able to provide even the most rudimentary health care. Under these circumstances, there are many experimental interventions that should be tested precisely because they offer the promise of an affordable, albeit perhaps imperfect alternative. The question of affordability is extremely important in both scenarios. In either case, if the intervention will be too expensive, its effectiveness is irrelevant. Because

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<sup>25</sup> Crouch & Arras, *supra* note 9, at 26; Carlos Del Rio, *Is Ethical Research Feasible in Developed and Developing Countries?*, 12 *BIOETHICS* 328, 330 (1998); Glantz et al., *supra* note 9, at 39.

<sup>26</sup> Crouch & Arras, *supra* note 9, at 30.

<sup>27</sup> Glantz et al., *supra* note 9, at 41.

<sup>28</sup> CIOMS, *supra* note 8, Guideline 21.

such research will not benefit the host country, it should not be done.<sup>29</sup>

## II. WHY PRIOR AGREEMENTS SHOULD BE USED IN INTERNATIONAL CLINICAL TRIALS: A RESPONSE TO CRITICISMS OF PRIOR AGREEMENTS

Most stakeholders in the research enterprise would probably agree that, at least in principle, the use of prior agreements is ethically desirable and should be encouraged in international clinical trials. Prior agreements can help researchers, sponsors, ethics review committees, host governments, and other parties involved focus on whether the host community will truly benefit from the proposed research. On a practical level, however, a variety of individuals and organizations, primarily researchers, research sponsors (both public and private), host governments, and ethicists object to requiring prior agreements as a condition for research approval. These criticisms, discussed below, have most often arisen in the context of general discussions about such agreements rather than in specific instances where the use of an agreement was at issue.

### *A. Prior Agreements Delay or Prevent Research*

One criticism of requiring prior agreements as a condition for research approval is that it will only delay or prevent new drug research in developing countries.<sup>30</sup> Sponsors may be reluctant to commit financially to providing effective interventions, which in turn might affect their willingness to support research in developing countries. One response is that, even if this is true, host populations lose nothing because the research benefits would not be available to them anyway.<sup>31</sup> In addition, prohibiting research protects the host community against exploitation by the industrialized world.

Moreover, the use of prior agreements and the advancement of research beneficial to developing countries are not mutually exclusive goals. First, to assume that all, or even most, effective interventions will simply be distributed to developing countries free of charge is erroneous. While it is true that a few countries cannot afford to buy interventions even

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<sup>29</sup> Leonard H. Glantz, Testimony Before the National Bioethics Advisory Commission 150, 152-55 (Jan. 13, 2000), *available at* <http://www.georgetown.edu/research/nrcbl/nbac/transcripts/index.html#jan00>.

<sup>30</sup> Glantz et al., *supra* note 9, at 41; Reidar K. Lie, *Justice and International Research*, in *BIOMEDICAL RESEARCH ETHICS: UPDATING INTERNATIONAL GUIDELINES* 27, 29 (Robert J. Levine et al. eds., 2000).

<sup>31</sup> Glantz et al., *supra* note 9, at 41.

at a subsidized cost, others can buy interventions as long as they are not expected to do so at industrialized-world prices.<sup>32</sup> Still others can be licensed to produce the tested interventions.

Second, while in many instances, research sponsors will play a primary role in providing effective interventions, this will not always be the case. Normally, public agencies that sponsor research are too constrained financially to make interventions available post-trial. However, when such an obligation arises, public agencies become responsible for locating another funding source for the intervention, such as an organization involved in promoting health or development. Similar creative funding arrangements may provide incentives for private industry to research diseases occurring primarily in the developing world. By distributing financial burdens more widely, the actual or perceived barrier to research imposed by prior agreements can be reduced. Much-needed research can move forward while, at the same time, developing countries are protected from exploitation.

### *B. There Are Formidable Financial, Logistical, and Other Obstacles to Prior Agreements*

A second criticism is that, in practice, many aspects of prior agreements can be extremely problematic.<sup>33</sup> Affordability, distribution, and appropriate product use must all be considered prior to conducting

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<sup>32</sup> The pharmaceutical industry routinely claims that high drug prices are required to finance the high cost of research and development as well as to compensate for research failures and the large number of drugs that are never profitable. NUFFIELD COUNCIL ON BIOETHICS, *supra* note 1, at 32; PHARMACEUTICAL RESEARCH & MFRS. ASS'N OF AM., 2002 PHARMACEUTICAL INDUSTRY PROFILE 20-23 (2002). However, the prices that industry insists upon go well beyond what others believe to be necessary to prevent innovation from suffering. For example, certain experts argue that industry devotes much larger shares of each revenue dollar to marketing and paying CEO salaries and shareholder dividends than to research and development. *See, e.g.*, DONALD DRAKE & MARIAN UHLMAN, *MAKING MEDICINE, MAKING MONEY* (1993); Alan Sager & Deborah Socolar, *Affordable Medications for Americans: Problems, Causes, and Solutions*, Paper presented to the Prescription Drug Task Force, United States House of Representatives, July 27, 1999, at 14-17, *available at* [http://www.nysenior.org/News/reports/affordable\\_medicines.pdf](http://www.nysenior.org/News/reports/affordable_medicines.pdf). Also, the United States government has played a significant role in the research and development of drugs from which industry ultimately profits, including several antiretroviral drugs used to treat AIDS. *See* Patrick Bond, *Globalization, Pharmaceutical Pricing, and South African Health Policy: Managing Confrontation with U.S. Firms and Politicians*, 29 INT'L J. HEALTH SERVICES 765, 767-69 (1999); Mary T. Griffin, *AIDS Drugs and the Pharmaceutical Industry: A Need To Reform*, 17 AM. J.L. & MED. 363, 397 (1991); Margaret Duckett, *Compulsory Licensing and Parallel Importing: Background Paper, International Council of AIDS Service Organizations* § 5, at <http://www.icaso.org/icaso/docs/compulsoryenglish.htm> (July 1999).

<sup>33</sup> Lie, *supra* note 30, at 29.

research. The UNAIDS *Guidance Document* identifies specific issues that need to be addressed to ensure availability of an effective intervention, including “payments, royalties, subsidies, technology and intellectual property, as well as distribution costs, channels, and modalities, including vaccination strategies, target populations, and number of doses.”<sup>34</sup>

In certain cases, a host community may be hard to define. How and by whom should that determination be made? Do the people of the host country constitute the community? What if the research participants represent populations that are not confined by national borders? What about research participants from earlier trials that have some bearing on product development? Does the obligation to provide the benefit extend to these populations? Difficulties could also arise with respect to provision of the intervention. Who should be responsible for providing it? What does making the intervention “available” mean in a particular situation? Does it mean for some designated period of time or for as long as the intervention is needed? Will the intervention be provided free of charge or will there be some nominal cost? If the latter, how will that cost be determined? If there is agreement on these terms, parties still face equally difficult and important concerns, such as implementation, treatment monitoring and compliance, and general medical care for the community that will receive the research benefit. Feasible plans must be developed and incorporated into the prior agreement.

It is easy for critics to dismiss the use of prior agreements because there are as yet no answers to some of these difficult issues. However, the difficulties inherent in the negotiation and implementation of prior agreements do not outweigh the ethical imperative to secure them. The resolution of critical health problems always requires grappling with complex and challenging issues, and the concerted efforts and talents of multiple partners from diverse environments and disciplines are often needed. Collaborative efforts are routinely employed to address drug funding and / or distribution problems in developing countries in a non-research context, such as a NGO purchase or a donation by a pharmaceutical company. With a NGO purchase, it must be determined whether a product will be distributed free of charge or, if not, what the charge will be to a host country. With both NGO purchases and company donations, decisions must be made regarding how and to whom drugs will be distributed. These same types of problems can be resolved for international clinical trials.

Negotiating prior agreements also requires parties to focus on

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<sup>34</sup> UNAIDS, *supra* note 18, at 14.

expected research benefits in a detailed and concrete way that helps minimize delays in availability. There may be cases where those reviewing a protocol, such as an institutional review board (IRB) / ethics review committee or a country's ministry of health, know (or should know) that an intervention will not be widely available in the host community after the trial is completed. For example, an experimental drug might require refrigeration, but a prospective host community may lack such storage capability. Developing a plan for funding and distribution would bring that fact to light. If the problem cannot realistically be overcome, parties would need to reevaluate whether the trial can be conducted ethically. Whether or not such availability issues prove insurmountable, there is no reason to believe that they cannot be addressed before research begins, or that they are somehow easier to address after a study is finished.

If obstacles to availability can be overcome, parties need to reach an understanding on how a host community will actually benefit from proposed research. A host country's entire population need not benefit immediately, but sufficient numbers should benefit over a reasonable period of time so that a meaningful contribution to the overall welfare of the developing country or countries is evident. Debates over the CIOMS *Guidelines* definition of "reasonable availability" have yet to produce a precise resolution, so arriving at a definition that would satisfy everyone remains a formidable challenge. There are, for example, questions about the scope and content of "reasonable availability" as well as "about the exactitude and stringency of the required prior assurances."<sup>35</sup> The development of an internationally acceptable standard is, however, a highly desirable goal that is of utmost importance to conducting ethical research in developing countries and should continue to be a subject of discussion. Ideally, such a standard should be broad enough to afford the flexibility needed for a variety of cultural and moral contexts without departing from the ethical principle that it embraces. The CIOMS *Guidelines* acknowledge that "the issue of 'reasonable availability' is complex and will need to be determined on a case-by-case basis"<sup>36</sup> and suggest several relevant considerations.<sup>37</sup>

In the meantime, the use of prior agreements would permit case-by-

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<sup>35</sup> Crouch & Arras, *supra* note 9, at 30.

<sup>36</sup> CIOMS, *supra* note 8, Commentary on Guideline 10.

<sup>37</sup> *Id.* (suggesting factors such as "the length of time for which the intervention or product developed, or other agreed benefit, will be made available to research subjects, or to the community or population concerned; the severity of a subject's medical condition; the effect of withdrawing the study drug (e.g., death of a subject); the cost to the subject or health service; and the question of undue inducement if an intervention is provided free of charge").

case determinations without first reaching a consensus on the difficult and divisive issue of reasonable availability. Prior agreements may even facilitate agreement by providing specific examples of successful or unsuccessful benefit-sharing arrangements.

*C. It Is Not the Prevailing International Standard*

A third criticism of requiring prior agreements in international clinical trials is that making effective interventions and other research benefits available to host communities is not the prevailing international standard. It is far from being universally accepted by researchers, sponsors, ethicists, public health officials, politicians, industry, and others with an interest in the research enterprise.<sup>38</sup>

One response to this argument is that ethics is not about “what is,” but rather, “what ought to be.”<sup>39</sup> An ethical obligation to make effective interventions available to host communities can be traced as far back as the *Belmont Report*, which was issued in 1979 by the United States National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. In its discussion of the principle of justice and the distribution of the burdens and benefits of research, the National Commission touches indirectly upon the issue of making effective interventions available to those populations upon which they were tested. It states:

[W]henever research supported by public funds leads to the development of therapeutic devices and procedures, justice demands that these not provide advantages only to those who can afford them and that such research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research.<sup>40</sup>

The following international documents lend additional support for an obligation to make effective interventions and other research benefits

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<sup>38</sup> Lie, *supra* note 30, at 29.

<sup>39</sup> Solomon R. Benatar, *Justice and International Research: A Response to Reidar K. Lie*, in *BIOMEDICAL RESEARCH ETHICS: UPDATING INTERNATIONAL GUIDELINES* 41, 47 (Robert J. Levine et al. eds., 2000); Ruth Macklin, *After Helsinki: Unresolved Issues in International Research*, 11 *KENNEDY INST. OF ETHICS J.* 17, 20 (2001).

<sup>40</sup> NAT'L COMM'N FOR THE PROT. OF HUMAN SUBJECTS OF BIOMED. & BEHAVIORAL RESEARCH, *THE BELMONT REPORT: ETHICAL PRINCIPLES AND GUIDELINES IN THE PROTECTION OF HUMAN SUBJECTS* 5 (1979).

available to host communities: the CIOMS *Guidelines*,<sup>41</sup> the *Declaration of Helsinki*,<sup>42</sup> the UNAIDS *Guidance Document*,<sup>43</sup> the WHO *Operational Guidelines for Ethics Committees that Review Biomedical Research*,<sup>44</sup> and the Ethics Committee of the Human Genome Organisation *Statement on Benefit-Sharing*.<sup>45</sup> They all demand resolution of product-availability and benefit-sharing issues before research begins. A number of them impose an affirmative obligation to provide effective interventions to a host community.<sup>46</sup>

The UNAIDS *Guidance Document* was the first of its kind to focus explicitly on resolving drug access problems as part of international clinical trials. Not only does it insist on addressing availability before research begins, but also, it identifies in general terms the parties who should be

<sup>41</sup> CIOMS, *supra* note 8, Guideline 10 (“Before undertaking research in a population or community with limited resources, the sponsor and the investigator must make every effort to ensure that ... any intervention or product developed, or knowledge generated, will be made reasonably available for the benefit of that population or community.”).

<sup>42</sup> WMA, *supra* note 9, Principle 19. The latest revision of the *Declaration of Helsinki* contains a new provision concerning the need for the accrual of some potential benefit to host countries.

<sup>43</sup> UNAIDS, *supra* note 18, Guidance Point 2 (“Any HIV preventive vaccine demonstrated to be safe and effective ... should be made available as soon as possible to all participants in the trials in which it was tested, as well as to other populations at high risk of HIV infection. Plans should be developed at the initial stages of HIV vaccine development to ensure such availability.”).

<sup>44</sup> WORLD HEALTH ORG., OPERATIONAL GUIDELINES FOR ETHICS COMMITTEES THAT REVIEW BIOMEDICAL RESEARCH (2000). The WHO *Operational Guidelines*, which “establish an international standard for ensuring quality in ethical review,” *id.* at 1, recommend that “a description of the availability and affordability of any successful study product to the concerned communities following the research” be considered as an element of review by ethics committees. *Id.* ¶ 6.2.6.6.

<sup>45</sup> HUMAN GENOME ORG. ETHICS COMM., STATEMENT ON BENEFIT-SHARING (2000). The Human Genome Organisation (HUGO) is the international organization of scientists involved in the Human Genome Project, the global initiative to map and sequence the human genome. The HUGO Ethics Committee endorses the equitable distribution of the benefits of genetic research. Its *Statement on Benefit-Sharing*, which provides that “all humanity” share in the benefits of genetic research, suggests that there be prior discussion with individuals and communities about benefit-sharing and, more specifically, about “affordability and accessibility of eventual therapy, and preventive and diagnostic products of research.” *Id.* § G. The most far-reaching provision in the *Statement* calls for for-profit entities engaging in genetic research to donate a percentage of their annual net profit (e.g., 1%-3%) “to the health care infrastructure or for vaccines, tests, drugs, and treatments, or, to local, national, and international humanitarian efforts.” *Id.*

<sup>46</sup> CIOMS, *supra* note 8; NAT’L CONSENSUS CONFERENCE, GUIDELINES FOR THE CONDUCT OF HEALTH RESEARCH INVOLVING HUMAN SUBJECTS IN UGANDA (1997); NAT’L HEALTH COUNCIL, RESOLUTION NO. 251 (1997) [hereinafter NHC RESOLUTION NO. 251]; NAT’L HEALTH COUNCIL, RESOLUTION NO. 196/96 ON RESEARCH INVOLVING HUMAN SUBJECTS (1996) [hereinafter NHC RESOLUTION NO. 196/96]; UNAIDS, *supra* note 18; WMA, *supra* note 9.

part of that process and the relevant issues to consider. Guidance Point Two states:

Any HIV preventive vaccine demonstrated to be safe and effective ... should be made available as soon as possible to all participants in the trials in which it was tested, as well as to other populations at high risk of HIV infection. Plans should be developed at the initial stages of HIV vaccine development to ensure such availability.<sup>47</sup>

Parties “should include representatives from relevant stakeholders in the host country, such as representatives from the executive branch, health ministry, local health authorities, and relevant scientific and ethical groups.”<sup>48</sup> Including host country representatives greatly improves the chances that the values and culture of that country will be taken into account. Others parties should include “representatives from the communities from which participants are drawn, people living with HIV / AIDS, and NGOs representing affected communities” as well as “international organizations, donor governments and bilateral agencies, representatives from wider affected communities, international and regional NGOs, and the private sector.”<sup>49</sup>

In recent years, various provisions relating to post-trial benefits have begun to appear in the ethics guidelines of several industrialized and developing countries, including the United Kingdom,<sup>50</sup> Canada,<sup>51</sup> Nepal,<sup>52</sup> Uganda,<sup>53</sup> and Brazil.<sup>54</sup> The guidelines promulgated by the United Kingdom,<sup>55</sup> Canada,<sup>56</sup> and Nepal<sup>57</sup> simply demand resolution of access

<sup>47</sup> UNAIDS, *supra* note 18, at 13.

<sup>48</sup> *Id.* at 14.

<sup>49</sup> *Id.*

<sup>50</sup> MED. RESEARCH COUNCIL OF THE U.K., MEDICAL RESEARCH COUNCIL INTERIM GUIDELINES FOR RESEARCH INVOLVING HUMAN PARTICIPANTS IN DEVELOPING SOCIETIES: ETHICAL GUIDELINES OF MRC-SPONSORED STUDIES (1999) [hereinafter MRC-UK].

<sup>51</sup> MED. RESEARCH COUNCIL OF CAN. ET AL., CANADIAN TRI-COUNCIL POLICY STATEMENT, ETHICAL CONDUCT FOR RESEARCH INVOLVING HUMANS (1998) [hereinafter MRC-CA].

<sup>52</sup> NEPAL HEALTH RESEARCH COUNCIL, *supra* note 16.

<sup>53</sup> NAT'L CONSENSUS CONFERENCE, *supra* note 46.

<sup>54</sup> NHC RESOLUTION NO. 251, *supra* note 46; NHC RESOLUTION NO. 196/96, *supra* note 46.

<sup>55</sup> MRC-UK, *supra* note 50, Specific Consideration 9 (“In anticipation of any beneficial results of therapeutic research, there should normally be discussion in advance with relevant parties in the developing society ... about subsequent availability of the relevant product to local inhabitants.”).

<sup>56</sup> MRC-CA, *supra* note 51, Commentary to art. 7.2 (stating that the Research Ethics Board should examine “the issue of continuing access after the trial”).

<sup>57</sup> NEPAL HEALTH RESEARCH COUNCIL, *supra* note 16, app. III. The model checklist developed for use by ethics review boards includes consideration of the “possibility of [the]

issues before research begins without imposing any affirmative obligation to make interventions available once a trial is completed. In contrast, Uganda<sup>58</sup> and Brazil<sup>59</sup> require more than just advanced discussions. In many cases, ethics guidelines do not carry the force of law or no mechanisms exist for effective enforcement. Nevertheless, in the future, one might reasonably expect to see increasing numbers of international and national research ethics guidelines embrace product-availability and benefit-sharing obligations.

Indeed, there is increasing recognition of the need to make moral progress in international research. Unlike before, there are efforts to refine vague benefit-sharing provisions such as “reasonable availability,”<sup>60</sup> “reasonable likelihood,”<sup>61</sup> and “a reasonable effort.”<sup>62</sup> Accordingly, we must rethink our ethical obligations and interpret them in ways that are appropriate to the ever-changing environment in which clinical research is conducted in developing countries. Today, private industry, rather than government, sponsors and conducts the lion’s share of international research.<sup>63</sup> Coupled with the global imbalance of power and disparities in

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intervention (vaccine, drug, or supplementation) being available to the participants population if found effective.” *Id.*

<sup>58</sup> NAT’L CONSENSUS CONFERENCE, *supra* note 46, § V(D)(4). Uganda imposes an obligation to provide interventions to research participants as well as to the host community, but distinguishes the obligations owed to these two groups. It mandates:

The investigator must provide assurances that, if the investigational product is found to be beneficial, the investigator will make every effort to ensure its provision, without charge, to participants in the trial following the conclusion of the trial. In addition, the investigator shall make a reasonable effort to secure the product’s availability to the local community in which the research occurred.

*Id.*

<sup>59</sup> NHC RESOLUTION NO. 251, *supra* note 46; NHC RESOLUTION NO. 196/96, *supra* note 46. Research should “guarantee the individuals and communities where the research was undertaken a return on the benefits obtained in the research.” NHC RESOLUTION NO. 196/96, *supra* note 46, § III.3(n). Research participants must be ensured “the benefits resulting from the research project, in terms of social return, access to procedures, products or research agents.” *Id.* § III.3(p). Still further, “in case of research conducted abroad or with external cooperation” evidence “of commitments and advantages to the research subjects and to Brazil, which will result from the implementation of the research” must be submitted to the ethics review committee. *Id.* § III.3(s). Finally, as part of the research protocol, “[a]ccess to the medicine being tested must be assured by the sponsor or by the institution, researcher, or promoter, if there is no sponsor, in the event its superiority to the conventional treatment is proven.” NHC RESOLUTION NO. 251, *supra* note 46, § IV.1(m).

<sup>60</sup> CIOMS, *supra* note 8.

<sup>61</sup> WMA, *supra* note 9.

<sup>62</sup> NAT’L CONSENSUS CONFERENCE, *supra* note 46, § V(D)(4).

<sup>63</sup> Richard A. Rettig, *The Industrialization of Clinical Research*, HEALTH AFF., May-Apr. 2000, at 129, 131.

access to health care, the ethical obligation to engage in post-trial benefit-sharing should extend beyond the publicly supported research envisioned by the National Commission over twenty years ago. Although it is not the prevailing international standard, the obligation to make effective interventions available to host communities after a trial is over is still an ethical standard to which we ought to aspire for all clinical research conducted in the developing world. Approving protocols based on this standard forces researchers and sponsors to be realistic about their reasons for conducting research in a developing country.

#### *D. Researchers Cannot Realistically Influence Health Policy*

A fourth criticism is that requiring prior agreements as a condition of research approval “would go far beyond the influence one can reasonably expect of researchers concerning changes in a country’s health policy.”<sup>64</sup> In other words, how often would a developing country’s policy change as a result of research so that effective interventions will get to the people that need it?<sup>65</sup>

The answer to this question is “sometimes.” One example from the Nuffield Council report that illustrates the limited influence of researchers to make effective interventions available is the iodination of salt to combat goiter in Nigeria. In that case, it took the Nigerian Ministry of Health fifteen years to act.<sup>66</sup> However, another example from the Nuffield Council report involving the use of nevirapine to reduce mother-to-child transmission of HIV in Uganda is indicative of a study that successfully influenced national health policy.<sup>67</sup>

<sup>64</sup> Lie, *supra* note 30, at 29.

<sup>65</sup> Alfred Sommer, Testimony Before the National Bioethics Advisory Commission 155, 162-68 (Sept. 16, 1999), *available at* <http://www.georgetown.edu/research/nrcbl/nbac/transcripts/index.html#sep99>.

<sup>66</sup> NUFFIELD COUNCIL ON BIOETHICS, *supra* note 1, at 123. According to a Nigerian researcher at Harvard University:

In 1975 a group of scientists led by the Chairman of the Nigeria Medical Research Council presented research data to the Nigerian Department of Health which revealed the high prevalence of goitre in the country. Attention was drawn to the impact of iodine deficiency not only in causing goitre but also by reducing the intellectual capacity of children born to iodine-deficient mothers. The group urged the government to introduce iodination into the two salt factories in which the government had investments. UNICEF had offered to cover the cost of modifying the equipment to accommodate the iodination process.

*Id.*

<sup>67</sup> *Id.* at 124. In this study, nevirapine was administered to HIV-infected pregnant women at the onset of labor and to the babies within forty-eight to seventy-two hours after delivery. The study showed that in the experimental arm, there was a fifty percent reduction in

The problem, in most instances, is not the inability of researchers to influence national health policy (or that developing countries are forced into prior agreements that they do not want). Rather, it is that access to effective interventions, which goes far beyond affordability, is an issue that researchers, sponsors, IRBs, ethics review committees, and / or host governments have either failed to address altogether or neglected to address in sufficiently explicit and realistic terms. As Solomon Benatar pointed out, “research considerations cannot be divorced from considerations of health, and health cannot be divorced from the economic and political considerations that affect health.”<sup>68</sup> These and other related issues, such as the financing, delivery, and appropriate use of interventions, must be considered during discussions on post-trial benefits. Also, although researchers play an important advocacy role in the prior agreement process, making effective interventions available cannot be the sole province of researchers. It is crucial to involve sponsors, host governments, host communities, international aid agencies, and other interested parties.

There may be circumstances under which one or more of these parties will not make a firm commitment until after research clarifies an intervention’s prospect of benefit, safety concerns, and the effectiveness of alternatives. Testifying before NBAC, one international health researcher noted:

[I]n a ... vaccine study in an[] African country . . . the Health Ministry resented the requirement that some commitment be made up front feeling that that was a patronizing requirement and that they would be able to make a commitment when they saw the results of the study and could do an appropriate analysis of cost and benefit. And that gets to some of the perceived paternalism and rigidity of the current guidelines.<sup>69</sup>

Moreover, the results of a trial may strengthen the position of the host country in negotiating with sponsors, manufacturers, and private philanthropies.

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transmission of HIV-infection from mother to child at fourteen to sixteen weeks compared to the control group, which received only zidovudine (AZT). Laura A. Guay et al., *Intrapartum and Neonatal Single-Dose Nevirapine Compared with Zidovudine for Prevention of Mother-to-Child Transmission of HIV-1 in Kampala, Uganda: HIVNET 012 Randomised Trial*, 354 LANCET 785 (1999).

<sup>68</sup> Benatar, *supra* note 39, at 41.

<sup>69</sup> Jack Killen, Testimony Before the National Bioethics Advisory Commission 115, 120 (Sept. 16, 1999), *available at* <http://www.georgetown.edu/research/nrcbl/nbac/transcripts/index.html#sep99>.

In the complex and uncertain environment in which research is conducted in developing countries, a commitment to a continuing process of discussion and negotiation about post-trial benefits, undertaken by the parties before research begins, is the first step. During their initial discussions about proposed research, developing countries should make known to researchers their positions concerning availability of the intervention or other benefits after the study is concluded. Assuming that a developing country wants to ensure that an effective intervention will be made available to its population at that time, a prior agreement can assist in this effort through the development of a plan for implementation.

*E. Prior Agreements Would Create a Double Standard with Regard to Clinical Research Conducted in the U.S. and Other Industrialized Countries*

A fifth criticism of using prior agreements for research conducted in developing countries is that such a requirement creates a double standard.<sup>70</sup> However, the fact that use of prior agreements is not the current ethical standard for industrialized countries does not justify a similar practice elsewhere; it simply describes the existing state of affairs in the industrialized world. Moreover, perhaps use of prior agreements in the industrialized world is a goal that we should set to ensure that effective interventions are available to those who need them. Whenever research is conducted in populations with limited access to health care, justice requires pre-trial consideration of post-trial access to effective interventions.

*F. Prior Agreements Can Always Be Breached*

A final criticism is that parties might breach prior agreements.<sup>71</sup> Although breach is always possible, it does not justify rejecting the use of prior agreements. Furthermore, the threat of debarment from future research and ostracism by the international research community would serve, in many cases, as an effective deterrent.<sup>72</sup> Finally, depending on whether there is general compliance with non-binding prior agreements, parties may insist on legally binding documents with enforceable remedies.

### III. PRIOR AGREEMENTS IN USE TODAY IN INTERNATIONAL CLINICAL TRIALS

#### Economic globalization and the Acquired Immunodeficiency

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<sup>70</sup> NUFFIELD COUNCIL ON BIOETHICS, *supra* note 1, at 180.

<sup>71</sup> Glantz et al., *supra* note 9, at 41.

<sup>72</sup> *Id.*

Syndrome (AIDS) epidemic have made the industrialized world more acutely aware of the magnitude of health problems in developing countries and the imbalance in the global burden of disease. These factors have impressed upon us the need for moral progress and for reform of the existing system that keeps the developing world in poor health and poverty and impedes every aspect of its advancement. Increasingly, pre-trial measures are being undertaken to make effective interventions and other research benefits widely available in developing countries where research is conducted. Different types of prior agreements employed by WHO, the International AIDS Vaccine Initiative (IAVI), and VaxGen are discussed below. WHO has successfully used prior agreements to make effective interventions available in developing countries; the other two initiatives, although promising, are newly developed and untested. These examples were chosen because of the availability of a sufficient, although somewhat limited, amount of information concerning the agreements themselves and the context in which they're negotiated.

#### *A. The World Health Organization (WHO)*

WHO, the world's leading international health organization, is an inter-governmental unit of the United Nations system. In conjunction with its role "of harnessing support from among a variety of players to meet its health development agenda,"<sup>73</sup> WHO collaborates with industry to promote research and development of new health-related products and technologies for prevention, diagnosis, control, and treatment of diseases that are of priority to WHO. An essential element of these collaborations is the negotiation of prior agreements to ensure that final products will be made widely available to developing countries at low cost. WHO's partners include pharmaceutical and biotech companies as well as manufacturers of health-related instruments and equipment. In 2000, it was estimated that WHO has employed well over a dozen prior agreements.<sup>74</sup>

Generally, WHO cooperates with industry in two ways. First, it may design, conduct, or fund studies, trials, and other development work on proprietary industry products in which WHO expresses an interest and / or is invited to collaborate. Second, it may license certain intellectual property that it owns to industry for further development into a final product, with or without technical or financial support. WHO usually

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<sup>73</sup> WORLD HEALTH ORG., WHO GUIDELINES ON INTERACTION WITH COMMERCIAL ENTERPRISES 2 (preliminary version July 1999) [hereinafter WHO COMMERCIAL GUIDELINES].

<sup>74</sup> E-mail from P.D. Griffin, Scientist, World Health Organization, to Alice Page, Senior Policy Analyst, National Bioethics Advisory Commission (July 18, 2000) [hereinafter Griffin July Email] (on file with author).

acquires intellectual property through research performed by institutions that it funds. However, such property is of little direct benefit to WHO because it lacks the facilities, resources, and “know-how” to further utilize it.

Prior agreements between WHO and its industrial partners are mindful of WHO’s interest in ensuring that successful products are made available to the public health sector (in particular, to the public health sector of developing countries on preferential terms) as well as industry’s interest in obtaining a reasonable return on its investment.<sup>75</sup> The agreements follow standard principles set forth in WHO’s *Policy on Patents*<sup>76</sup> and its *Guidelines on Interaction with Commercial Enterprises*<sup>77</sup> and are negotiated on a case-by-case basis. As a result, their final terms and conditions may differ depending on a variety of factors, such as ownership of the intellectual property rights in question, the stage of a product’s development at the time of negotiations, and past and expected future contributions to the collaboration by parties. The negotiations are then memorialized in a legally binding document called a Memorandum of Understanding (MOU).<sup>78</sup>

In all its collaborations, WHO requires that products and technologies developed with WHO support will be made generally available to both the public and to public sector agencies. The MOU defines “public sector agency” as “a government, or a department or agency thereof, or a recognized non-profit organization or entity, including the WHO and any other organization within the United Nations system.”<sup>79</sup> Agreements usually provide that a product will be made available to the public either by the industry partner or through a license to WHO if the industry partner decides to abandon the project. The industry partner must further agree to make a product available to public sector agencies of developing countries “in sufficient quantities to meet the needs of such agencies” for distribution in the public sector.<sup>80</sup>

In addition to quantity commitments, pricing commitments are also sought. Pricing commitments obtained from industry partners may differ depending on whether a product will be distributed through the private sector. If distribution will occur through both the private and public

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<sup>75</sup> WORLD HEALTH ORG., POLICY ON PATENTS: INFORMATION PAPER ON WHO PATENTS POLICY § 2.3 (1985).

<sup>76</sup> *Id.*

<sup>77</sup> WHO COMMERCIAL GUIDELINES, *supra* note 73.

<sup>78</sup> WORLD HEALTH ORG., DRAFT MEMORANDUM OF UNDERSTANDING (1999) [hereinafter WHO DRAFT MOU].

<sup>79</sup> *Id.* § 15(a), at 6.

<sup>80</sup> *Id.* § 6, at 3.

sectors, the price for public sector agencies “shall be (i) preferential compared to the Private Sector price, and (ii) set at the lowest possible level permitting a commercially reasonable return on combined worldwide sales of the Compound for Distribution in both Public and Private Sectors.”<sup>81</sup> A product can be sold in the private sector at whatever price the industry partner chooses. Pricing commitments from industry partners can also take the form of “cost, plus a modest mark-up” or a maximum price, depending on the circumstances.<sup>82</sup> “Cost, plus a modest mark-up” can be used at any stage of collaboration, provided terms can be defined and agreed upon. In contrast, a maximum-price commitment can only be used if product development is at such a point that parties can determine what it will cost to make a product.<sup>83</sup> If a product will not be distributed through the private sector, availability to public sector agencies shall be “at the lowest possible, commercially reasonable price.”<sup>84</sup> The same applies for bulk purchases. To a much lesser degree, WHO may receive royalties that are then invested in the public interest either to offset the cost of products or to fund further research to meet the needs of developing countries.<sup>85</sup>

A final item that is negotiated in each case is the period of years for which product availability is assured. Although there is no fixed time, “at the end of the agreed period of time the company concerned must agree to provide technology transfer to enable the country or countries concerned to continue either to manufacture the product themselves or through a sublicensing agreement to have somebody else manufacture it for them....”<sup>86</sup>

### B. *The International AIDS Vaccine Initiative (IAVI)*

IAVI is an international scientific, non-profit organization founded in 1996 with the single aim of accelerating the development of safe, effective, and accessible HIV vaccines for global use. IAVI’s research focus is on vaccines for developing countries. Through the investment of what it calls “social venture capital,” IAVI’s goal is to develop vaccines that “would be

<sup>81</sup> *Id.* § 6(b), at 3.

<sup>82</sup> E-mail from P.D. Griffin, Scientist, World Health Organization, to Alice Page, Senior Policy Analyst, National Bioethics Advisory Commission (Feb. 11, 2000) (on file with author).

<sup>83</sup> Griffin July Email, *supra* note 74.

<sup>84</sup> WHO DRAFT MOU, *supra* note 78, § 6, at 3.

<sup>85</sup> P.D. Griffin, Testimony Before the National Bioethics Advisory Commission 111, 115 (Jan. 13, 2000), *available at*

<http://www.georgetown.edu/research/nrcbl/nbac/transcripts/index.html#jan00>.

<sup>86</sup> *Id.* at 144.

inexpensive to manufacture, easy to transport and administer, stable under field conditions, and require few inoculations.”<sup>87</sup> IAVI is driven by the belief that a vaccine represents the world’s best hope to end the AIDS epidemic.

In 1998, IAVI issued a *Scientific Blueprint for AIDS Vaccine Development*<sup>88</sup> that links promising vaccine approaches with countries in which to test them. IAVI seeks to accelerate product development and clinical trials through public-private partnerships between vaccine developers, manufacturers, and those who will test the vaccines. Because the epidemic is most severe and the need for a vaccine is greatest in developing countries, most of IAVI’s efforts are focused there. These collaborations seek to ensure that people in developing countries for whom particular vaccines are designed benefit from those vaccines once they are developed.

To date, IAVI has invested \$20 million to create six vaccine development partnerships (VDPs) with individuals and entities from both industrialized and developing countries.<sup>89</sup> It also contributes expertise “as

<sup>87</sup> Victor Zonana, *Commonwealth Leaders Urge Greater Support for AIDS Vaccines*, IAVI REP. (International AIDS Vaccine Initiative, New York, N.Y.), Nov.-Dec. 1999, at 5, available at <http://www.iavi.org/reports/63/nov-dec-1999-4.html>.

<sup>88</sup> INT’L AIDS VACCINE INITIATIVE, 1998 SCIENTIFIC BLUEPRINT FOR AIDS VACCINE DEVELOPMENT, available at <http://www.iavi.org/about/98sblblueprint.htm>.

<sup>89</sup> The first VDP, the Oxford / Kenya Partnership, is an academic partnership created in 1998 with the University of Oxford and the University of Nairobi to develop for East Africa two separate vaccine constructs to be used in combination. Phase I clinical trials began in Oxford in 2000 (now in Phase II) and in Nairobi in early 2001. IAVI’s goal is to begin a Phase III trial in East Africa by 2004-2005, assuming the vaccine continues to perform well. INT’L AIDS VACCINE INITIATIVE, IAVI-SPONSORED AIDS VACCINE APPROACHES IN DEVELOPMENT AND TESTING, at <http://www.iavi.org/vaccinedev/pipeline.htm> (last visited Sept. 12, 2002) [hereinafter IAVI VACCINE APPROACHES]; INT’L AIDS VACCINE INITIATIVE, VIRTUAL COMPANY MODEL: VACCINE DEVELOPMENT PARTNERSHIPS, at <http://www.iavi.org/vaccinedev/vdp.htm> (last visited Sept. 12, 2002) [hereinafter IAVI VDP]; 1 NBAC, *supra* note 1, at 105.

The other VDPs encompass a “second generation” of vaccines designed to address “critical outstanding technical challenges.” IAVI VACCINE APPROACHES, *supra*. The second VDP, the Targeted Genetics / Children’s Research Institute / South Africa Partnership, formed in 2000, is with Targeted Genetics Corporation (TGC) of Seattle, Washington, and the Children’s Research Institute (CRI) in Columbus, Ohio. Its purpose is to develop a vaccine for southern and eastern Africa. A vector technology developed by TGC will be utilized to deliver HIV genes as a form of genetic immunization. TGC’s manufacturing process is based on a cell line originally developed by a researcher at CRI, which holds the patent to the technology. The vaccine is designed to give longstanding protection from a single dose and, therefore, may be particularly appropriate for areas where vaccine delivery is difficult. *Id.*; IAVI VDP, *supra*; 1 NBAC, *supra* note 1, at 105.

The third VDP, the Institute for Human Virology / Uganda Partnership, also formed in 2000, is with the Institute of Human Virology at the University of Maryland and the Ugandan Ministry of Health. The vaccine under development uses genetically modified *Salmonella* bacteria as an oral delivery system for DNA. The ease of delivery and extremely

needed, in areas ranging from project management to regulatory affairs and infrastructure for clinical trials.”<sup>90</sup> IAVI’s focus on industrial participation in vaccine development is based on the belief that private sector involvement and ingenuity are crucial.<sup>91</sup> IAVI has been instrumental in structuring prior agreements with industry partners that give developing countries access to IAVI-supported vaccines at reasonable prices and in sufficient quantities. According to IAVI President Seth Berkley, “[d]ealing with the access issue at the start of the process represents a wholly new approach to vaccine development that will ultimately benefit both industrialized and developing countries.”<sup>92</sup> IAVI’s prior agreements with its industrial partners call for reasonable pricing policies for the public sector in developing countries. The public sector includes government health agencies and not-for-profit organizations serving developing countries.<sup>93</sup> In return for financing the early stages of vaccine development, companies agree to make a vaccine available to the public sector in developing countries in quantities reasonable to demand and at manufacturing cost plus a reasonable profit, which is defined. If companies do not comply, IAVI retains the right to transfer the intellectual property and background technology to another manufacturer. If manufacturing costs seem unreasonable, IAVI can obtain alternative bids for production. If a third

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low cost make this a very promising vaccine for large-scale field use. It is hoped that clinical trials can begin in 2003 in Uganda and the United States. IAVI VACCINE APPROACHES, *supra*; IAVI VDP, *supra*; 1 NBAC, *supra* note 1, at 105. The fourth VDP is with Therion Biologics Corporation, the Indian Council of Medical Research, and the Indian Ministry of Health and Family Welfare. The partnership is designed to develop vaccines for India as well as a program for community participation and capacity building to conduct clinical trials in that country. Therion will manufacture vaccine doses for early trials, then transfer the technology to an Indian company for manufacture. IAVI VACCINE APPROACHES, *supra*; IAVI VDP, *supra*.

The other VDPs are with (1) Aaron Diamond AIDS Research Center and (2) Bioption AB. IAVI VACCINE APPROACHES, *supra*.

<sup>90</sup> IAVI VDP, *supra* note 89.

<sup>91</sup> A successful AIDS vaccine will necessarily rely on technologies covered by new and existing patents. Realistically, however, development of an AIDS vaccine by pharmaceutical and biotechnology industries alone is unlikely for four reasons. First, the development costs of a vaccine are high. Second, a very large percentage of the potential vaccine market probably will be in developing countries without resources to buy a vaccine. Third, because of variation in the predominant viral strains in industrialized and developing countries, vaccines may have to be country-specific. Fourth, the highly charged political issue of HIV / AIDS presents a disincentive for vaccine development. Thomas C. Nchinda, *Initiatives in Health Research*, in THE 10/90 REPORT ON HEALTH RESEARCH 121, 122 (Sheila Davey ed., 1999).

<sup>92</sup> Zonana, *supra* note 87.

<sup>93</sup> INT’L AIDS VACCINE INITIATIVE, DRAFT INDUSTRIAL COLLABORATIVE AGREEMENT para. 1(b), at 1 (1999).

party can produce the vaccine at lower cost, the signatory company must match that price or contract the third party for manufacturing. A vaccine can be sold at market price in the industrialized world and in private markets in the developing world. If an industry partner cannot meet its overall obligations, IAVI retains the right to choose from several options to ensure global accessibility.<sup>94</sup>

Investment in industry is not the only component of IAVI's strategy. IAVI is also working with the World Bank on the creation of vaccine purchase funds to provide additional financial incentives for industry to engage in vaccine development. According to Berkley, vaccine purchase funds are "mechanisms that can create a market in the developing world to purchase these vaccines and to distribute them. The idea would be that we—before the vaccine is ever made—would have a mechanism in place to have the vaccines purchased."<sup>95</sup> The creation of purchase funds is based on the notion that although companies should not lose money on the vaccines they produce, the financial return that companies can expect (and must be willing to accept) will differ according to the market in question. The profit margin in the developing world would be next to nothing; however, companies that are willing to deal in those markets receive other important benefits, such as economies of scale and entrée into those markets.<sup>96</sup>

When asked if the types of agreements IAVI has forged will work in other contexts, Berkley explained that he sees IAVI's quest for an AIDS vaccine "as a chance to begin to develop the mechanisms that make sense, that can be used across the whole range of different products. When we sit down and compare the issues on malaria to HIV, they are not that different."<sup>97</sup>

In addition to updating its 1998 *Blueprint* with *Scientific Blueprint 2000: Accelerating Global Efforts in AIDS Vaccine Development*,<sup>98</sup> IAVI created another blueprint, *AIDS Vaccines for the World: Preparing Now To Assure Access*.<sup>99</sup> The latter document "presents a strategy for addressing the many economic, political, and logistical obstacles to immediate and widescale (sic) access in

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<sup>94</sup> *Id.* para. 9, at 5-7; INT'L AIDS VACCINE INITIATIVE, IAVI BACKGROUNDER 2 (1999).

<sup>95</sup> Seth Berkley, Testimony Before the National Bioethics Advisory Commission 271, 302-03 (Jan. 13, 2000), available at <http://www.georgetown.edu/research/nrcbl/nbac/transcripts/index.html#jan00>.

<sup>96</sup> *Id.*

<sup>97</sup> *Id.* at 308.

<sup>98</sup> INT'L AIDS VACCINE INITIATIVE, SCIENTIFIC BLUEPRINT 2000: ACCELERATING GLOBAL EFFORTS IN AIDS VACCINE DEVELOPMENT (2000).

<sup>99</sup> INT'L AIDS VACCINE INITIATIVE, AIDS VACCINES FOR THE WORLD: PREPARING NOW TO ASSURE ACCESS (2000).

the developing world” and seeks to avoid “the typical [ten- to twenty-year] delay in introducing new vaccines to poor countries....”<sup>100</sup> Most recently, IAVI updated its research and development agenda for 2002 to 2004<sup>101</sup> and, to achieve that agenda, created a “virtual vaccine company model” consisting of VDPs, centralized laboratories and reagent production, large-scale development and manufacturing partnerships, partnerships for Phase III clinical trials in developing countries, and “core regulatory dossier design.”<sup>102</sup>

### C. VaxGen

VaxGen, a California-based biotechnology company, developed an AIDS vaccine known as “AIDSVAX.”<sup>103</sup> AIDSVAX is the first AIDS vaccine candidate in the world to enter Phase III efficacy studies. VaxGen raised money to finance its own trials in an effort to get the vaccine tested as quickly as possible.<sup>104</sup> Two trials are underway. The first is taking place in the United States, Puerto Rico, and the Netherlands. Between June 1998 and October 1999, more than 5,400 participants were recruited, mostly men who have sex with men. Bangkok, Thailand is the site of the second trial. Recruitment of 2,500 participants, all intravenous drug users at high risk of HIV infection, began in March 1999 and concluded in August 2000. Primary results from the Thai study are expected later this year.<sup>105</sup>

Thailand was chosen as a study site for several reasons. One is the strong professional relationship that has developed between key

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<sup>100</sup> IAVI Releases Blueprints for Speeding Vaccine Development and Ensuring Access, IAVI REP. (International AIDS Vaccine Initiative, New York, N.Y.), Sept.-Nov. 2000, at 9, available at [http://www.iavi.org/reports/103/IAVI\\_Blueprints3.htm](http://www.iavi.org/reports/103/IAVI_Blueprints3.htm). The Blueprint calls for the following five steps: (1) “[d]evelopment of effective pricing and global financing mechanisms”; (2) “[d]evelopment of mechanisms to reliably estimate demand for specific vaccines and to ensure sufficient production capacity to meet initial demand for an effective vaccine”; (3) “[d]evelopment of appropriate delivery systems, policies, and procedures for the most at-risk populations, especially adolescents and sexually active adults”; (4) “[h]armonization of national regulations and international guidelines governing vaccine approval and use”; and (5) “[e]stablishment of a mass vaccination program in developing countries for at least one under-used pediatric vaccine.” *Id.* at 9.

<sup>101</sup> INT’L AIDS VACCINE INITIATIVE, THE IAVI RESEARCH AND DEVELOPMENT AGENDA 2002-2004, <http://www.iavi.org/pdf/rd-agenda.pdf> (July 2002).

<sup>102</sup> IAVI VDP, *supra* note 89.

<sup>103</sup> Bill Snow, *VaxGen: Pushing the Envelope*, in HIV VACCINE HANDBOOK: COMMUNITY PERSPECTIVES ON PARTICIPATING IN RESEARCH, ADVOCACY, AND PROGRESS 195, 197 (Bill Snow ed., 1999).

<sup>104</sup> *Id.* at 199.

<sup>105</sup> VAXGEN, OUR VACCINE CANDIDATES: VAXGEN CLINICAL TRIALS, at <http://www.vaxgen.com/vaccine/trials.html> (last visited Nov. 14, 2002).

individuals at VaxGen and Thai researchers.<sup>106</sup> Another reason is that the HIV virus strains present in Thailand are homogeneous, making it easier to test AIDSVAX.<sup>107</sup> Finally, WHO and UNAIDS supported the building of infrastructure to conduct vaccine trials, and UNAIDS and the United States Centers for Disease Control and Prevention (CDC) have supported cohort development over a number of years. A cohort of intravenous drug users from methadone clinics run by the Bangkok Metropolitan Association was first compiled, from which research participants were subsequently recruited for the vaccine trial.<sup>108</sup>

The Thai government, the Bangkok municipal government, and Mahidol University have been very proactive in working with VaxGen. Despite the implementation of other interventions, Thailand has one of the fastest growing rates of HIV infection in the world, and the government has made the development of an AIDS vaccine a health priority.<sup>109</sup> As a condition to hosting the study, the Thai government required, first, that any vaccine tested in Thailand have a reasonable likelihood of preventing infection by the particular strains of HIV most prevalent in the country. VaxGen specifically developed AIDSVAX B/E to prevent further infections by the two viral subtypes, B and E, that are prominent in those infected through sexual exposure and intravenous drug use.<sup>110</sup> The Thai government also required that the country receive research benefits in two forms: the product itself and capacity building.<sup>111</sup>

In its discussions with the Thai Ministry of Public Health, VaxGen informally agreed that, should there be a licensed product, the country would receive special treatment from the company in making the product available in Thailand.<sup>112</sup> Specifically, VaxGen agreed to make a concerted effort to decrease the cost of the vaccine for Thailand. If feasible, because Thailand has a strong local pharmaceutical industry, arrangements could be made for bulk shipment of the vaccine with filling and finishing in Thailand.<sup>113</sup> One Thai AIDS researcher described this arrangement as a

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<sup>106</sup> E-mail from Marlene Chernow, Vice President of Product Development and Regulatory Affairs, VaxGen, to Alice Page, Senior Policy Analyst, National Bioethics Advisory Commission (May 1, 2000) [hereinafter Chernow E-mail] (on file with author).

<sup>107</sup> Esparza, *supra* note 12, at 10; Chernow E-mail, *supra* note 106.

<sup>108</sup> Esparza, *supra* note 12, at 9; Chernow E-mail, *supra* note 106.

<sup>109</sup> Esparza, *supra* note 12, at 2, 6, 10; Chernow E-mail, *supra* note 106.

<sup>110</sup> Esparza, *supra* note 12, at 9; Chernow E-mail, *supra* note 106.

<sup>111</sup> Chernow E-mail, *supra* note 106.

<sup>112</sup> E-mail from Donald Francis, President, VaxGen, to Alice Page, Senior Policy Analyst, National Bioethics Advisory Commission (Nov. 17, 1999) (on file with author).

<sup>113</sup> *Id.*

“letter of intent” and the first of its kind for any vaccine trial in the world.<sup>114</sup> Discussions on how to make the vaccine available after study completion are ongoing. Although there is a formal agreement governing the Phase III study itself, the Thai government has requested nothing beyond the “letter of intent” for making the product available.

Many of the benefits that will accrue to Thailand take the form of capacity building. Thai researchers highly value the transfer of such knowledge and technology, which is occurring in three ways as the result of a verbal commitment between VaxGen and Thailand, not as part of the “letter of intent.”<sup>115</sup> First, VaxGen is transferring its data management capabilities to Thailand. A complete data center has been established so that Thai researchers have state-of-the-art hardware and software. VaxGen is also teaching the Thai data management unit how to collect, monitor, and validate data to comply with international clinical research guidelines. Second, the company has developed a repository of laboratory specimens. Thai researchers are learning how to store, track, locate, and connect data to specimens. Third, VaxGen is training Thai researchers in clinical research and good clinical practices for conducting Phase III trials. Thailand’s previous experience has been limited to Phase I and II trials.<sup>116</sup> Overall, the goal is to enable Thailand to function independently and conduct Phase III trials on its own.

In 2000, several allegations were published in the *Washington Post* concerning post-trial benefits sought by Thailand for either research participants or the country itself that VaxGen would not agree to provide.<sup>117</sup> First, VaxGen allegedly refused to pledge care for research participants who become HIV-positive during the trial. Thai health authorities finally agreed to provide the best local therapy, which is far less effective than what subjects would receive if the trial were carried out in the United States. Second, VaxGen allegedly refused to guarantee that its vaccine, if proven effective, would be sold to Thailand at a reduced price: “A ‘gentlemen’s agreement’ the company wrote in 1998 to Thai health officials suggested that if the Thais helped with packaging the vaccine, VaxGen might be able to reduce the country’s costs for the vaccine.”<sup>118</sup> However, according to VaxGen’s President, the company “can’t give (the)

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<sup>114</sup> *Thailand: From “Guinea Pig” Fears to Phase III Trial: An Interview with Natth Bhamarapavati*, IAVI REP. (International AIDS Vaccine Initiative, New York, N.Y.), Sept.-Oct. 1999, at 6-7, available at <http://www.iavi.org/reports/75/sep-oct-1999-6.html>.

<sup>115</sup> Chernow E-mail, *supra* note 106.

<sup>116</sup> Esparza, *supra* note 12, at 4; Chernow E-mail, *supra* note 106.

<sup>117</sup> Mary Pat Flaherty & Doug Struck, *Life by Luck of the Draw*, WASH. POST, Dec. 22, 2000, at A1.

<sup>118</sup> *Id.*

vaccine away and bankrupt the company.”<sup>119</sup> Finally, VaxGen purportedly rejected Thailand’s requests for profit sharing or for a manufacturing plant to be located in the country. One Thai representative who reviewed the study and is now a member of the Thai Senate said, “[W]e were making test subjects available and we were agreeable to that. But on the other hand, we did not have that much bargaining power. Our situation was desperate.”<sup>120</sup> VaxGen has invested almost \$600,000 in equipment and facilities that will remain in Bangkok when the study is over.<sup>121</sup>

### CONCLUSION

Many opportunities and challenges remain for the use of prior agreements in international clinical trials. Some agreements, such as those employed by WHO, have proven successful. Agreements forged by other entities such as IAVI and VaxGen await the judgment of time. What conclusions about prior agreements can be drawn from these examples? Because they are limited in number, and specific factual information about them and the contexts in which they were negotiated is scarce, it is difficult to extract general principles concerning the use of prior agreements in international clinical trials. However, several observations are in order.

It may be important to distinguish, at least in some cases, between situations where a developing country is a party to a prior agreement and those where a developing country, although not a party to an agreement, is its ultimate intended beneficiary. Out of necessity, industry is very likely to play a prominent role in most, if not all, of these arrangements. However, the presence of a third party acting on behalf of, or in conjunction with, a developing country may be critical to the successful negotiation of benefits.

WHO and IAVI have been able to secure fair pricing agreements from industry for the sale of study interventions to developing countries. To what can their success be attributed? Perhaps most importantly, these organizations have strong ties to the industrialized world and have entered into research collaborations on behalf of developing countries. WHO is a powerful, well-established international health organization headquartered in Europe, while IAVI, although a relatively new company based in the United States, is becoming increasingly well-funded by major donors such as the Bill & Melinda Gates Foundation, the Rockefeller Foundation, the World Bank, and the governments of industrialized countries.<sup>122</sup>

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<sup>119</sup> *Id.*

<sup>120</sup> *Id.*

<sup>121</sup> *Id.*

<sup>122</sup> IAVI VACCINE APPROACHES, *supra* note 89.

Furthermore, WHO and IAVI have more experience than many developing countries in negotiating agreements to develop and distribute health care goods and services collaboratively. In addition to economic resources, they possess (or can purchase) the scientific, medical, technological, business, and legal know-how that developing countries may lack. These organizations utilize legally enforceable contracts in their collaborative partnerships.

In contrast, some developing countries are simply unaware of the possibility of obtaining post-trial benefits through prior agreements. Those that negotiate prior agreements may find themselves severely disadvantaged by inequities in bargaining power. These inequities may become especially problematic when a developing country negotiates directly with industry without the assistance of a third party. Because help from the industrialized world is needed to combat AIDS, tuberculosis, malaria, and other diseases that are ravaging their populations, developing countries might accept arrangements that are far less than what distributive justice<sup>123</sup> requires. In VaxGen's case, such a small company may not be financially positioned to subsidize all the benefits Thailand requested.<sup>124</sup> Yet, larger and wealthier sponsors still may not have agreed to Thailand's demands.

Two further observations, also drawn from the VaxGen example, relate to the capacity-building benefits provided to the Thai government. First, the importance of securing such benefits should not be underestimated. Although the provision of successful interventions may help developing countries address particular health problems in the short term, building research capacity better situates developing countries to solve their own health problems in the long run. Second, capacity building in the VaxGen case is proceeding solely on the basis of a verbal commitment. This attests to the importance of the strength of the relationship between collaborative partners and their mutual commitment to the goal of the collaboration.

Finally, while the use of prior agreements in international research is in its infancy and, with a few exceptions, remains largely idealistic, prior agreements show great promise as a way to prevent exploitation of developing countries and of the individuals who serve as research subjects. The endorsement of such agreements in international and national ethical guidelines is a step forward. However, even if the problems inherent in

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<sup>123</sup> See *supra* note 2.

<sup>124</sup> That VaxGen was unwilling to provide state-of-the-art treatment for research participants who became HIV-infected during the trial is not surprising. The high cost of such treatment in AIDS vaccine trials makes this issue one of the most contentious in international research ethics today.

their interpretation and enforcement can be overcome, their widespread use in international collaborative research should be anticipated with cautious optimism. Many human rights treaties, for example, have been in existence for decades and yet, acceptance of, or adherence to, those treaties is far from universal. Only ongoing discourse and debate can persuade individuals and organizations that prior agreements should be used in international research.<sup>125</sup> By no means do prior agreements provide a perfect solution, but, as is always the case, solutions to difficult and complex problems must begin somewhere.

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<sup>125</sup> CIOMS' recent draft revision of its research guidelines directly endorsed prior agreements and defined the term. COUNCIL FOR INT'L ORGS. OF MED. SCIS., DRAFT REVISION OF THE CIOMS INTERNATIONAL ETHICAL GUIDELINES FOR BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS Guideline 6 (2001). This was the first time the term "prior agreement" appeared in international research ethics guidelines. However, in the final version, that provision was eliminated after what must have been a lively and controversial discussion that is likely to be repeated again and again.