



# **Safer, Faster, Cheaper** Improving Clinical Trials and Regulatory Pathways to Fight Neglected Diseases

**Report of the Center for Global Development's Working  
Group on Clinical Trials and Regulatory Pathways**

**Chair**  
Thomas Bollyky



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## Working Group chair

**Thomas Bollyky**, Center for Global Development

## Working Group members

**Vincent Ahonkhai**, Bill & Melinda Gates Foundation

**Ernst Berndt**, MIT Sloan School of Management

**Fred Binka**, INDEPTH Malaria Clinical Trials Alliance

**Michael Brennan**, AERAS Global TB Vaccine Foundation

**Richard Chin**, Institute for OneWorld Health

**Liliana Chocarro**, LC Plus Consulting

**Ralf Clemens**, Novartis

**Iain Cockburn**, Boston University School of Management

**David Dilts**, Knight Cancer Institute and Oregon Health and Science University

**Paul Huckle**, GlaxoSmithKline

**John Hurvitz**, Covington & Burling LLP

**Yuppadee Javroongrit**, Food and Drug Administration, Ministry of Public Health, Thailand\*

**Richard Kingham**, Covington & Burling LLP

**Judith Kramer**, Clinical Trials Transformation Initiative & Duke University School of Medicine

**Marc LaForce**, PATH

**Orin Levine**, Johns Hopkins Bloomberg School of Public Health

**Melinda Moree**, BIO Ventures for Global Health

**Margareth Ndomondo-Sigondo**, New Partnership for Africa's Development\*

**John Purves**, Consultant

**David Shoultz**, Bill & Melinda Gates Foundation

**Wendy Taylor**, U.S. Agency for International Development\*

## Lead author

**Thomas Bollyky**, Center for Global Development

## Staff

**Edward Collins**, Center for Global Development

**Cindy Prieto**, Center for Global Development

**Steve Rosenzweig**, Center for Global Development

\* Participated as an observer and does not endorse or reject any of the analysis or recommendations in this report.

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# Preface

Public and private donors have spent hundreds of millions of dollars to support development of new medicines and technologies to deal with neglected diseases, but they have focused little on the regulatory infrastructure and clinical trial practices necessary to ensure that these new therapies actually reach the low-income countries where they are most needed. How can low-income countries—where few, if any, clinical trials have occurred—be best prepared for the influx of large, pivotal trials needed to support the licensure of novel drugs or vaccines? How can the safety of clinical trials be best safeguarded? How might the huge costs and unnecessary delays of these trials be reduced? This report provides practical answers to these challenges and recommends specific steps that donors, drug and vaccine developers, and regulatory authorities in the developing world should take to get the job done.

Why does this report matter? An estimated one billion people, including 400 million children, suffer from one or more neglected diseases. Malaria, tuberculosis, dengue fever, leishmaniasis, and other neglected diseases kill, disable, and deform millions of people each year. Children, pregnant women, the poor, and politically marginalized suffer the most. Most of these diseases have no effective treatments.

There is hope, however. A confluence of private philanthropy, government intervention, and investment in product development partnerships has yielded a large pipeline of health technologies to treat, prevent, or diagnose neglected diseases—with nearly 240 neglected-disease drug and vaccine candidates now in development.

But before these potentially lifesaving drugs and vaccines can reach patients, their safety and effectiveness must be demonstrated in clinical trials. Two challenges arise. First, these trials must be conducted with highly vulnerable patients in countries where the disease burden exists. Limited regulatory capacity and unclear approval processes in many of those countries, particularly in Africa, delay clinical trials, deter investment, and can place subjects at risk. Compounding these challenges is the need to conduct these clinical trials in multiple infrastructure-poor

countries, each with its own regulatory requirements, interpretations, and lengthy review timelines. Second, under typical current costs per trial, there is not enough funding to support trials for more than a fraction of the candidate drugs and vaccines in the neglected-disease pipeline. Clinical trials are expensive, representing as much as 70 percent of the cost and most of the time required to develop a drug or vaccine. A single late-stage trial requires years to complete and can cost tens or even hundreds of millions of dollars.

Increased funding for late-stage clinical trials and regulatory capacity building in low-income countries is needed, but will not be sufficient. Part of the solution must include reducing the unnecessary costs of these clinical trials and assuring a more streamlined, sustainable approach to regulatory oversight and patient safety in very poor settings.

Under the leadership of Tom Bollyky, the Center for Global Development launched a Working Group on Clinical Trials and Regulatory Pathways in October 2010. Its participants and observers included representatives from donors, regulators, sponsors, and investigators that fund, oversee, and conduct clinical trials in low-income countries as well as legal, regulatory, and global health experts. The Working Group conducted extensive outreach and a detailed assessment of the challenges and opportunities that arise as candidate neglected-disease drugs and vaccines move to late-stage development. Based on analysis of approaches that have succeeded elsewhere, the Working Group proposed a two-fold strategy for improving these clinical trials and the way they are regulated, with the aim of reducing costs, delays, and risks to subjects.

First, the Working Group recommended a more streamlined, better resourced regional approach to clinical trial regulation. A single procedure by which multiple countries can work together to approve and oversee clinical trials would allow participating countries to pool scarce regulatory resources, create an efficient platform for capacity building, reduce inconsistencies across national

requirements, and speed product development and delivery to patients.

Second, the Working Group recommended systematic attention to such practices as simpler trials for licensure, increased and more efficient clinical trial monitoring, and greater emphasis on reporting on and adjusting to problems early in trial design. These and other evidence-based approaches would help focus trials on their key objectives and build quality and cost-efficiency into their design and implementation.

These two recommendations involve strategies that are practical, scalable, and mutually reinforcing. Pooling regulatory and ethics review capacity regionally improves the capabilities of regulators to work with donors and trial sponsors to ensure that trials are efficient, well adapted to the local circumstances, and protective of local subjects. The possibility of better, faster, and cheaper clinical trials, in turn, encourages more clinical research generally in that region, which generates the fees and experience needed to improve local capabilities.

As the Center's 15th report on global health policy issues, this Working Group's excellent contribution continues a proud tradition

of fostering public policies that support market mechanisms—as a way to encourage private, public, and philanthropic investments that work for the world's poor.

Of course, a report is only a first step. Now it is up to the regulatory authorities in low-income countries, the product development partnerships and private firms developing new products, and the regional and global institutions to take up the fight. One step we hope to see: the African Union working with the World Health Organization and the World Bank to put in place an effective regional regulatory institution to approve and oversee clinical trials as well as the speedy registration of new products.

Nancy Birdsall  
President

Amanda Glassman  
Director for Global Health

Center for Global Development

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Many individuals contributed information, ideas, and inspiration for this report. We thank, first, members of the Clinical Trials and Regulatory Pathways Working Group, who devoted their valuable time to thinking through the challenges in clinical trials and regulatory pathways for products for neglected diseases and potential strategies for reducing their costs, delays, and risks to subjects. Throughout, all members excelled in balancing the interests they were closest to—industry, donors, public-private partnerships, academia, or technical and funding agencies—in order to identify solutions that work for all. Working Group members are profiled in appendix A.

We particularly thank the individuals who generously provided the data, analysis, and insights that are the foundation of this report. Iain Cockburn at Boston University generated the data from [ClinicalTrials.gov](http://ClinicalTrials.gov), an international clinical trials registry, that led to many of our insights into the sponsors, product types, locations, and subjects currently involved in neglected-disease clinical trials. John Hurvitz and Dick Kingham, partners at Covington & Burling LLP, together with their colleague Susan Lee, provided institutional and legal analysis that helped translate our ideas on regional approaches to clinical trial oversight into workable proposals. Mike Soenen and Mindy Davis at ClearTrial granted us pro bono access to their web-based clinical trial budgeting and forecasting software, which advanced our understanding of the drivers of unnecessary clinical trial costs and delays. Elizabeth Ponder from BIO Ventures for Global Health shared data from their Global Health Primer on the current state of the neglected-disease product pipeline. Nathalie Strub-Wourgaft at the Drugs for Neglected Disease Initiative, Majda Benhayoun at Global Alliance for TB Drug Development, Joan Herbert at the Medicines for Malaria Venture, and John Boslego, Catherine Hennings, and Marc LaForce at PATH provided generous information and insights into their completed and ongoing neglected-disease clinical trials.

Private interviews and individual correspondence also informed this report. Over the last two years, dozens of people offered their advice and expertise on clinical trials and their regulatory and

ethics oversight. We are indebted to each and every of them. A partial list of these individuals is in appendix B. We regret any omissions.

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# Abbreviations

**AMRH**—African Medicines Regulatory Harmonization Initiative  
**ASEAN**—Association of Southeast Asian Nations  
**AVAREF**—African Vaccine Regulatory Forum  
**CGD**—Center for Global Development  
**CRF**—case report form  
**CRO**—contract research organization  
**CTTI**—Duke University & U.S. FDA’s Clinical Trials Transformation Initiative  
**DNDi**—Drugs for Neglected Diseases Initiative  
**EC**—ethics committee  
**EDC**—electronic data capture  
**EMA**—European Medicines Agency  
**FDA**—U.S. Food and Drug Administration  
**GAVI**—Global Alliance for Vaccines and Immunisation  
**GCP**—good clinical practice  
**GLP**—good laboratory practice  
**HMA**—Heads of Medicines Agencies  
**ICH**—International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use  
**IND**—Investigative New Drug Application  
**IRAS**—Integrated Research Application System  
**IRB**—Institutional Review Board  
**NIH**—U.S. National Institutes of Health  
**NRA**—national regulatory authority  
**PDP**—product development partnership  
**R&D**—research and development  
**SAGE**—WHO Strategic Advisory Group of Experts  
**TB**—tuberculosis  
**UNICEF**—United Nations Children’s Fund  
**VHP**—voluntary harmonization procedure  
**WHO**—World Health Organization



# Executive summary

There has been tremendous progress over the last decade in developing health products for neglected diseases. These include drugs, vaccines, and diagnostics for malaria and tuberculosis, which kill millions of people annually, and for other diseases like Chagas and dengue fever, which may be less familiar, but nonetheless exact a large and often lethal toll in the world's poorest communities. Led by product development partnerships (PDPs) and fueled by the support of the Bill & Melinda Gates Foundation, the U.S. National Institutes of Health (NIH), the Wellcome Trust, and other donors, there are now dozens of candidate products in the pipeline. These drug and vaccine candidates could be, for many neglected diseases, the first new therapies and prevention tools in a generation and, for others, simply the first.

## Clinical development and the challenges ahead

Clinical trials play a central role in successfully moving candidate drugs and vaccines from discovery and into the hands of the populations who need them. They provide the evidentiary basis for the diagnosis, treatment, and prevention of disease. Clinical trials are also the basis for the regulatory approval required before these products may be manufactured and distributed to patients.

An increasing number of candidate drugs and vaccines for neglected diseases are moving to late-stage clinical development. Two substantial bottlenecks threaten our capacity to bring these products to those in need. First, there is not enough clinical research and regulatory capacity in many neglected disease–endemic settings to support the clinical trials that need to occur there in order to complete the development of these products. This lack of regulatory and ethics capacity can undermine the safety of subjects and the validity of clinical data. Second, even with expected attrition in the pipeline, current levels of financing are insufficient to support the clinical development of these products under current cost assumptions. Addressing these related challenges will require not only identifying new sources of funding for large-scale clinical trials

and capacity building—but also devoting more attention to how these trials and their regulatory pathways can be improved to reduce unnecessary costs, delays, and risks to trial subjects.

This Working Group recommends a two-pronged strategy to bring the costs, risks, and finances for clinical trials for neglected-disease products into a better, more sustainable balance.

## Regional regulatory pathways

The Working Group recommends establishing regional pathways for the regulation and ethical review of clinical trials in neglected disease–endemic settings. Moving to a single integrated process by which clinical trials occurring in multiple countries and sites are approved and overseen would improve the coordination and pool the capacity of ethics committees and national regulatory authorities (NRAs) involved, reduce regulatory inconsistencies and overlap, and provide a more attractive platform for external assistance and donor support. In doing so, regional cooperation would offer the opportunity to improve regulatory capacity and reduce clinical trials costs at fairly low expense to donors and local governments.

Based on its review of the precedents for regulatory cooperation and extensive stakeholder consultation, the Working Group recommends a centralized procedure/joint review model in which both NRAs and ethics committees participate. The particular design and adoption of that approach are questions that participating governments and their underlying institutions must decide. The Working Group recommends incorporating the following objectives and parameters:

- *Sovereignty and local accountability.* Regional approaches to clinical trial regulation and ethical review should respect national sovereignty and the goals of local accountability, while striving to achieve the benefits of greater regional cooperation.
- *Capacity through cooperation.* Cooperation on clinical trial regulation should promote regulatory capacity and integration in the context of joint reviews of actual clinical trial applications

rather than pursue the harmonization of laws and regulations in the abstract.

- *Voluntary and, at least initially, non-binding participation.* Governments should have the opportunity to participate and gain confidence in regional clinical trial regulation before being bound by its results. Voluntary participation for NRAs and trial sponsors would be sufficient provided there are incentives for that participation.
- *Broad in function, limited eligibility, and scalable.* To be most effective, regional cooperation should encompass the full range of clinical trial oversight including applications, amendments, inspections, and monitoring. Initially, the pathway should be limited to priority countries and technologies, but expanded as resources, trust, and competence build.
- *Less duplication, more coordination.* Participating NRAs and ethics committees should work in close cooperation, with open communication and a clear division of labor. Ethics and regulatory reviews should be performed simultaneously rather than sequentially.
- *Common documentation, standards, and timelines.* Regulatory cooperation requires common documentation and standards for authorization to be effective and sustainable.
- *Increasing the availability of outside assistance.* Regional cooperation on clinical trial regulation of neglected-disease technologies should include a formal process for requesting outside assistance from the World Health Organization (WHO) and qualified NRAs.
- *Donor funding in the near term, self-supporting over the long term.* A regional regulatory pathway will require seed funding from donors, but should seek to be self-supporting over the long term. A streamlined regional regulatory pathway with more certain regulatory timelines could hold material value for clinical trial sponsors and justify additional application fees.
- *Links to existing structures and initiatives.* The regional regulatory pathway should be designed to evolve from existing regional regulatory networks or economic institutions that offer a political or legal framework for sustainable cooperation.
- *Monitoring and evaluation.* Design of the regional mechanism for clinical trial oversight should include metrics for monitoring and evaluating performance and decision-making.

Based on these principles, the Working Group has identified the minimum requirements for this regional regulatory mechanism

and proposed options in some detail for addressing them. Chapter 4 includes a flowchart that depicts how a mechanism for regional clinical trial review could operate.

## Better, faster, cheaper trials

Numerous PDPs and their industry partners have conducted successful late-stage clinical trials of candidate technologies in low-income settings at relatively modest cost. Budgets for global health, however, are tightening. New donor funding for product development is increasingly scarce. Streamlined regulatory pathways alone will not achieve the cost and time savings required to sustain clinical development of the lifesaving neglected-disease therapies in the pipeline. Better, faster, and cheaper clinical trials are needed. Achieving that objective will require a focus on the key parameters and objectives of the trial, evidence-driven approaches, and early engagement among trial sponsors, investigators, and NRAs. The Working Group recommends the following strategies.

- *Simpler trials for licensure, more support for policy research in phase IV studies.* Embedding neglected-disease epidemiological and policy research into pivotal studies of the safety and efficacy of a candidate product is an expensive way to obtain that research. Pivotal studies must be conducted according to the most stringent international standards and at the limited number of sites capable of supporting such trials. Focusing pivotal trials on the research necessary to support licensure would reduce costs, expedite product registration, and lower site and investigator demands. For this approach to succeed, however, donors must increase funding for the phase IV policy and epidemiological studies necessary to support WHO recommendations on the use of the product and neglected-disease research.
- *Early investigator input and independent advisory committees.* Local investigator and independent stakeholder input should be solicited early in study and protocol design to help spot potential problems and help keep studies simple, feasible, and focused.
- *Pressure-testing protocols.* It is common practice for many multinational pharmaceutical companies to “pressure test” protocols and screening criteria by performing them with dummy subjects and study products prior to enrollment. This approach improves the efficiency of trial design and reduces the number of subsequent protocol amendments. A similar approach should be adopted in neglected-disease product development.



- *Electronic data capture (EDC) and centralized monitoring.* Clinical trial monitoring costs can often account for as much as one-third to two-thirds of the costs of a clinical trial. EDC and centralized statistical sampling are cost-effective and can be adapted for low-resource and rural settings. Donor bulk purchases of equipment, infrastructure, and training would make adopting EDC and centralized monitoring even more economical.

## Toward implementation

Vision, strategic investments, and hard work built the current pipeline of products for neglected diseases. Realizing the promise of that pipeline and ensuring its future vitality will require improved clinical trial practices and an analogous commitment to building regulatory pathways more favorable to trial subjects and current and future innovation.

Opportunities for partnerships exist. Academic centers and public-private partnerships are exploring ways to improve the efficiency of clinical trials without sacrificing scientific rigor or the protection of subjects. Neglected-disease product development is motivating new donor resources and technical assistance for regulatory capacity building in developing countries. Substantial and increasing private industry investment is devoted to conducting biopharmaceutical clinical trials in developing countries. Developed country support for international regulatory cooperation and clinical trial oversight are now matters of enlightened self-interest. Investments in clinical research and efficient, effective regulatory oversight in developing countries are no longer just matters of public health, but legitimate tools for economic development and job creation.

The early priorities for implementation are clear. Regional cooperation could help ensure adequate and more efficient clinical trial oversight in many low- and middle-income settings, but would be particularly beneficial for vaccine trials and Africa. The majority of the products in development for neglected diseases are vaccines. PDPs report longer delays in regulatory and ethics approvals of trials for vaccines than for drug products in neglected disease–endemic countries. Africa is the region with the most limited regulatory and ethics review capacity. Our analysis of data on Clinicaltrials.gov, an international registry of clinical trials, reveals that Africa is also where a disproportionate number of neglected-disease trials are occurring and that there is a strong regional orientation to

the multi-country trials for neglected diseases. Most NRAs and ethics committees in Africa have not yet become entrenched in particular regulatory approaches, making cooperation easier. A WHO-led initiative, the African Vaccine Regulatory Forum, has already conducted three successful, multi-country joint reviews of clinical trial applications. Numerous regional economic communities in Africa are pursuing harmonization of drug registration as part of the African Medicines Regulatory Harmonization (AMRH) initiative. The World Bank has created a trust fund, with \$12.5 million in seed funding from the Bill & Melinda Gates Foundation, to support this effort.

The recommendations in this Working Group report offer practical and scalable ways to address the urgent challenges and opportunities presented by the neglected-disease product pipeline. Moving forward will require collaboration and investment from all key stakeholders.

## Developing country NRAs, ethics committees, and their governments

There is precedent for centralized procedure/joint regulatory review models moving from conception to implementation relatively quickly and yielding fairly immediate benefits. Achieving a similar outcome in this context will require from participating NRAs, ethics commitments, and their governments: political commitment to engage in regulatory cooperation including, where possible, a contribution of funding and dedicated personnel; a memorandum of understanding that defines the scope of cooperation, the identity, responsibilities, and rights of states parties, product and applicant eligibility, and the oversight procedures, standards, and requirements involved; some administrative structure to coordinate cooperation; and enough regulatory and ethics review capacity to participate, or at least a willingness to defer to others until that capacity can be built.

## Clinical trial sponsors

Clinical trial sponsors must demonstrate their support for more streamlined, effective regulation and ethical review of their clinical research by using the regional regulatory pathway, agreeing to allow participating NRAs to share confidential data, and demonstrating a willingness to pay additional fees. Investing upfront resources to build quality and efficiency into clinical trial planning and design can also lower trial-sponsor costs, expedite treatment

access, and preserve scarce resources for other neglected-disease product development.

### Donors and funding agencies

Philanthropic, intergovernmental, and bilateral donors must recognize clinical research and its efficient and adequate oversight in developing countries as priorities for global health and economic development. Donors should provide seed funding to support regional approaches to regulatory and ethics oversight of clinical trials at regional economic communities and the WHO, using multilateral funding platforms like the new World Bank trust fund. Funders of neglected-disease product development should encourage their grantees to use the regional pathways once established. Donors should invest in independent clinical trial planning advisory boards and clinical research and monitoring infrastructure, which can improve the quality and efficiency of neglected-disease clinical research across technologies and product development sponsors.

### Developed country NRAs, academic institutions, and international technical agencies

WHO must continue to provide the technical support, credibility, and convening power, which have been critical to the success

of the Developing Country Vaccine Regulatory Network and the other existing regional approaches to clinical trial regulation. The U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), Health Canada, and other developed country NRAs must increase their existing technical assistance and diplomatic support for regional regulatory and ethics oversight in low- and middle-income countries. Academic centers and intergovernmental institutions working on improving clinical trial practices must extend their research to neglected diseases and the challenges of resource-poor settings.

### Looking ahead

The regional regulatory platforms and cooperation strategies recommended in this report could be expanded over time to support other critical regulatory functions in low- and middle-income countries. Regional cooperation that achieves more certain review times and reduces regulatory inconsistencies in clinical trial oversight could achieve similar objectives for product registration. A regional approach that pools scarce country regulatory resources and provides a sustainable platform for clinical trial oversight capacity building could do the same for post-market drug and vaccine surveillance. These compound benefits of regional platforms for regulatory cooperation provide further compelling justification for stakeholder investment.

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## Chapter 1

# New treatments for neglected diseases

Advances in science and technology have helped solve some of the world's most significant and persistent health problems. Low-cost, simple-to-use technologies have controlled or eradicated infectious diseases like smallpox and polio, reduced disability and infant mortality, and saved countless lives and billions of dollars in low- and high-income countries alike. Over the last decade, the potential promise of such technological solutions to address neglected diseases, which afflict the world's poorest and most politically marginalized people, has captured the attention of philanthropists, policymakers, and private sector leaders.

### The importance of new treatments for neglected diseases

Neglected diseases are a heterogeneous collection of predominantly infectious conditions for which few, if any, effective therapies exist. These diseases include malaria, tuberculosis (TB), and a dozen other parasitic, soil transmitted, bacterial, and tropical infections (box 1.1).<sup>1</sup>

Neglected diseases disproportionately affect the world's poorest and most politically marginalized.<sup>2</sup> They are endemic, for the most part, to Africa, Asia, tropical regions of Latin America, and parts of the Middle East.<sup>3</sup> More than one billion people, including 400 million children, suffer from one or more neglected diseases (table 1.1).<sup>4</sup>

Neglected diseases have a staggering impact on afflicted people and communities. Malaria and TB alone kill an estimated 2.1 million people annually, almost exclusively in low- and middle-income countries.<sup>5</sup> Human African trypanosomiasis, Chagas disease, leishmaniasis, dengue fever and leprosy may be less known to the general public, but are responsible for more than 500,000 deaths annually in poor countries.<sup>6</sup> Other neglected diseases are less deadly, but disable, deform, and increase their sufferers' vulnerability to other infectious diseases like HIV/AIDS. Children and pregnant women suffer disproportionately. In 2008 an estimated 8.8 million children worldwide under the age of five died from largely preventable causes, many of which are related to neglected diseases.<sup>7</sup> Approximately

89 percent of all malaria deaths occur in Africa, primarily in children under five.<sup>8</sup> Neglected diseases adversely affect pregnancies and child development, undermine worker productivity, and perpetuate the cycle of poverty, insecurity, and infirmity in the communities in which they are endemic.<sup>9</sup>

Given that about one in six people worldwide suffers from one or more neglected diseases, it may seem surprising that there are few, if any, effective therapies for them. Historically, there has been little investment in developing new treatments for neglected diseases because most people who suffer from them are desperately poor. Diarrheal diseases, malaria, and other childhood diseases also appear on the developing world's top-10 causes of death, but are nowhere

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### Box 1.1 What is a neglected disease?

Definitions of neglected diseases vary. For the purposes of this report, we have defined neglected diseases as:

1. Chronic parasitic and infectious conditions.
2. That are endemic in low- and middle-income countries, with little or no presence in high-income countries.
3. That disproportionately affect the poor and politically marginalized, particularly children.
4. The interventions for which must be low-cost and suitable for use under difficult and health infrastructure-poor circumstances.

Accordingly, this report defines neglected diseases broadly to include tuberculosis, which has only a relatively modest presence in high-income countries, but not HIV/AIDS, which imposes on a terrible burden on the world's poor, but is endemic in both high- and low-income countries alike.

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**Table 1.1**  
**Global prevalence of selected neglected diseases by WHO region**

Disease	Estimated number of infections (millions)					
	Total	African	Americas	Eastern Mediterranean	South-East Asia	Western Pacific
Chagas disease	8.3	N	8.300	N	0.004	0.002
Cholera	4.0	1.3	N	N	2.5	N
Dengue fever	50.0	—	0.9	N	0.2	0.2
Hookworm	740.0	198.0	50.0	10.0	130.0	352
Human African trypanosomiasis	0.06	0.06	N	N	N	N
Leishmaniasis	1.6	0.27	0.05	0.19	1.1	0.02
Malaria	247.0	—	0.53	5.7	2.4	0.25
Onchocerciasis	37.0	36.63	N	N	N	N
Schistosomiasis	207.0	186.0	C	C	C	C
Tuberculosis	14.0	3.9	0.35	1.0	4.9	2.9
Typhoid fever	22.0	0.4	0.4	—	4.6	—

Notes: N = negligible; C = cases found in some countries; — = data unavailable.

Source: Anis Rassi Jr, et al., "Chagas Disease," *Lancet* 375[2010]: 1388–402; WHO, "Cholera," Fact Sheet No. 107, updated June 2010, <http://www.who.int/mediacentre/factsheets/fs107/en/index.html>; D Sacks, "Global Cholera Estimates," Department of International Health, Johns Hopkins University (2011); WHO, "Dengue and Dengue Haemorrhagic Fever," Fact Sheet No. 117, updated March 2009, <http://www.who.int/mediacentre/factsheets/fs117/en/>; WHO, *Working to Overcome the Global Impact of Neglected Tropical Diseases*, First WHO Report on Neglected Tropical Diseases (Geneva: WHO, 2010); WHO, "Human African Trypanosomiasis (Sleeping Sickness): Epidemiological Update," *Weekly Epidemiological Record* 81[8]: 71–80; WHO, "Malaria," Fact Sheet No. 94, updated April 2010, <http://www.who.int/mediacentre/factsheets/fs094/en/>; WHO, *World Malaria Report: 2010* (Geneva: WHO, 2010); RG Feachem, et al., *Disease and Mortality in Sub-Saharan Africa*, 2nd edition (Washington, DC: World Bank, 2006); WHO, *Global Tuberculosis Control 2010* (Geneva: WHO, 2010); WHO, "Diarrhoeal Disease," Initiative for Vaccine Research website, updated February 2009, [http://www.who.int/vaccine\\_research/diseases/diarrhoeal/en/index5.html](http://www.who.int/vaccine_research/diseases/diarrhoeal/en/index5.html).

on the equivalent list for rich countries. Infectious and parasitic diseases account for one-third of the disease burden in low-income countries and nearly half the disease burden in Africa, but less than 3 percent in high-income countries.<sup>10</sup>

Since drug development for neglected diseases may often be just as expensive and uncertain as it is for diseases that afflict the affluent, the interest of pharmaceutical firms in investing in neglected diseases has been understandably small. Fewer than 40 of the nearly 1,400 new chemical entities approved between 1975 and 1999 were for neglected diseases.<sup>11</sup>

Many neglected diseases have no effective treatments.<sup>12</sup> Many of the drugs and vaccines for neglected diseases date back to the colonial era.<sup>13</sup> Others are new uses of existing drugs and veterinary

products, or were developed for use by developed country militaries serving in disease-endemic areas.<sup>14</sup> Many of these treatments are prohibitively expensive, toxic, and otherwise ill-suited for use by target populations that include pregnant women and children and in impoverished settings with few trained healthcare personnel, limited refrigeration, and sparse healthcare infrastructure.<sup>15</sup> Historical disparities in the availability and application of technological innovation for health have exacerbated the inequities between rich and poor countries.<sup>16</sup>

Effective, safe, affordable, and simple-to-use treatment, prevention, and diagnostic tools for neglected diseases are urgently needed. Vaccines are among the most cost-effective health interventions, preventing diseases that would otherwise require expensive

treatment, and particularly well suited to the needs of resource and infrastructure-poor countries, requiring no costly screening, diagnosis, or follow-up.<sup>17</sup> Improved diagnostics would help ensure that patients get the appropriate treatment, curbing overuse of inappropriate drugs and the rise of drug resistance.<sup>18</sup> Drug resistance, already a serious threat to the efficacy of treatments for malaria and TB, will likely emerge as a problem for other neglected diseases as well.<sup>19</sup> New and better drugs are important, particularly in light of increased drug resistance. Effective drugs, vaccines, and diagnostics suitable for the developing world would reduce the burden of disease and have substantial positive impact on economic growth and poverty reduction.<sup>20</sup>

## A renewed pipeline

Over the last decade, there has been a substantial increase in the attention on global health, including developing new treatments and improving existing ones for neglected diseases. Most of this increased attention has taken two forms.

First, funding for neglected-disease research and development (R&D) has increased dramatically over the last decade, with annual funding reaching \$2 billion in 2009.<sup>21</sup> Half that funding (just more than \$1 billion) comes from two sources: the Bill & Melinda Gates Foundation and NIH.<sup>22</sup> The biopharmaceutical industry has contributed an increasing amount (\$376 million, or 18 percent), mostly in the form of in-kind transfers of technology, expertise, and training.<sup>23</sup> The majority of that R&D funding for neglected diseases (almost \$1.2 billion) goes to two diseases: malaria and TB.<sup>24</sup> Research funding for cholera, dengue, and Chagas has increased in recent years, but diseases like leprosy, Buruli ulcer, and trachoma continue to receive little support.<sup>25</sup>

Second, new partnerships have formed among private, philanthropic, and government actors seeking to meet the health needs of the world's poor. PDPs are structured collaborations between commercial and public sector partners that combine drug and biotech company expertise with public sector funding and understanding of the developing country health needs and regulatory requirements.<sup>26</sup> Collaboration between the biopharmaceutical industry and public sector entities has existed for some time, but the current generation of PDPs represents a more systematic attempt to develop and adapt a portfolio of health technologies for neglected diseases.<sup>27</sup> PDPs receive most of the funding for neglected-disease product development.<sup>28</sup> Some PDPs are disease-, technology-, and

even product-specific; others have broader mandates and manage a sizable portfolio of drug, vaccine, and diagnostic candidates.<sup>29</sup> Most PDPs are based in developed countries, but several partner with research institutions and manufacturers in Brazil, China, India, and other middle-income countries.<sup>30</sup>

As a result of the hard work of the PDPs and the support of the Bill & Melinda Gates Foundation, NIH, the Wellcome Trust, the pharmaceutical industry, and others, dozens of new candidate technologies for neglected diseases are now in the pipeline.<sup>31</sup>

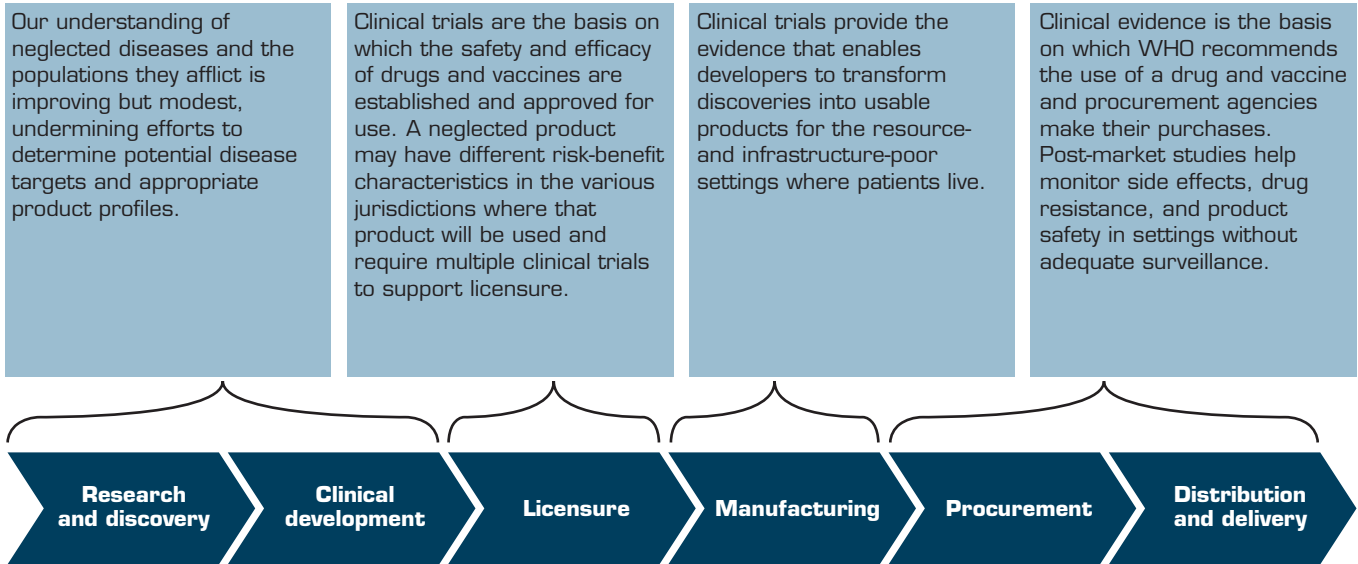
This array of new candidate products offers many potential benefits for health. There is, for example, a malaria vaccine candidate in late-stage clinical testing, which, if approved, will be the first vaccine against malaria (a disease that kills 900,000 annually) and the first vaccine against a parasite approved for use in humans. There are nine new TB vaccine candidates in clinical trials worldwide, including the first late-stage infant study of a TB vaccine in more than 80 years. These therapies could help reduce the 8 million new TB infections and 1.7 million TB-related deaths each year.<sup>32</sup> Several promising vaccine candidates are in late-stage clinical development for dengue fever, which results in substantial morbidity and productivity losses in millions of people worldwide.<sup>33</sup> These drug and vaccine candidates could be, for many neglected diseases, the first new therapies and prevention tools in a generation—and, for others, simply the first.

## Clinical development and the challenges ahead

The emergence of so many promising neglected-disease drug and vaccine candidates is good news, but substantial bottlenecks threaten our capacity to bring these products to those in need.

Drug and vaccine development is an inherently uncertain endeavor generally, with few candidate therapies ever reaching market.<sup>34</sup> Innovative drug and vaccine development for many neglected diseases and their affected populations is unprecedented. The challenges are many. Our understanding of these diseases and patients' needs is limited. The systems to support drug and vaccine registration, delivery, and post-market surveillance are absent or rudimentary in many low-income countries. Government budgets for global health are tightening, and new donor funding for product development and delivery is increasingly scarce. Clinical trials will play an important part in addressing each of these bottlenecks as candidate drugs and vaccines advance from basic

**Figure 1.1**  
**The role of clinical trials in the neglected disease product pipeline**



research to licensure, production, and supply (figure 1.1). The reasons are threefold.

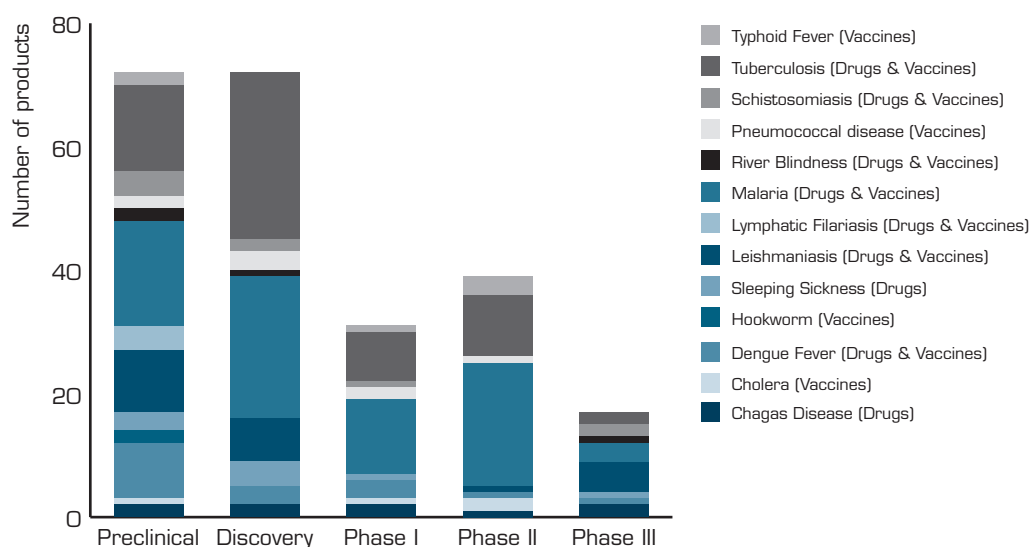
First, clinical trials are foundational to public health and medical innovation. They provide the evidentiary basis for the diagnosis, treatment, and prevention of disease. This role is particularly important for neglected diseases. Much remains unknown about the biology of many of these diseases. The genetic characteristics of the populations and socioeconomic settings in which these diseases are endemic can differ in substantial ways from those in the developed world. Clinical trials will be the means by which these innovative interventions are appropriately designed for their target populations and the basis for the regulatory approval required before these products can be licensed, manufactured, and distributed to

patients. After delivery, post-market drug and vaccine studies will be important to monitor effectiveness, adverse events, emerging drug resistance, and product safety in low-income countries with limited public health surveillance.

Second, clinical testing represents the bulk of the time and cost involved in vaccine and drug R&D. Drug and vaccine clinical trial costs have become a subject of debate in recent years, but there is no question that they are substantial and increasing. As much as 70 percent of drug and vaccine R&D costs are incurred in clinical development.<sup>35</sup> The process typically lasts 8–15 years. An often cited (but controversial) study estimated that \$400 million in clinical trial costs is spent on average to develop a new chemical entity.<sup>36</sup> A 2007 study reported actual clinical trial costs for neglected-disease



**Figure 1.2**  
Neglected disease product pipeline



drugs and vaccines, which ranged from a few million dollars for early stage trials to \$100 million or more for each late-stage clinical trial.<sup>37</sup> The Medicines for Malaria Venture estimates that its clinical development costs for a new malaria combination drug would be \$180–200 million.<sup>38</sup> The later stage clinical development costs for the most advanced and promising malaria vaccine candidate are \$300 million and potentially increasing.<sup>39</sup> Given the expense and time involved, even modest improvements in the efficiency of clinical trials for neglected-disease products could free substantial resources and improve the commercial viability of these drugs and vaccines.

Third, clinical development is the stage at which many of the drugs and vaccines in the pipeline for neglected diseases are now or will soon be (figure 1.2). According to a recent analysis by

BioVentures for Global Health, there are currently 87 candidate drugs and vaccines in the neglected-disease pipeline—70 of which have yet to move to late-stage clinical development.<sup>40</sup> These clinical trials will present challenges for product developers, donors, and regulators alike. Definitive studies of the safety and efficacy of these drug and vaccine candidates must be conducted in patient populations and settings in which that product will ultimately be used. For neglected diseases, these are countries in which few, if any, clinical trials have been conducted, let alone an influx of large, pivotal trials to support licensure of novel drugs or vaccines. The lack of clinical research and regulatory capacity in many of these countries threatens the safety of clinical trial subjects and the validity of clinical trial data, deterring investment in these technologies.



## Chapter 2

# Gaps and obstacles in clinical development

Many factors significantly increase the risk, delays, and cost of clinical trials for the candidate drugs and vaccines in the neglected-disease pipeline. Some are problematic for clinical trials generally. Others are particular to late-stage clinical trials for these candidate drugs and vaccines.

### Challenges with clinical trials generally

Figure 2.1 represents a simplified version of the clinical trial process for an innovative drug candidate in the United States.<sup>41</sup>

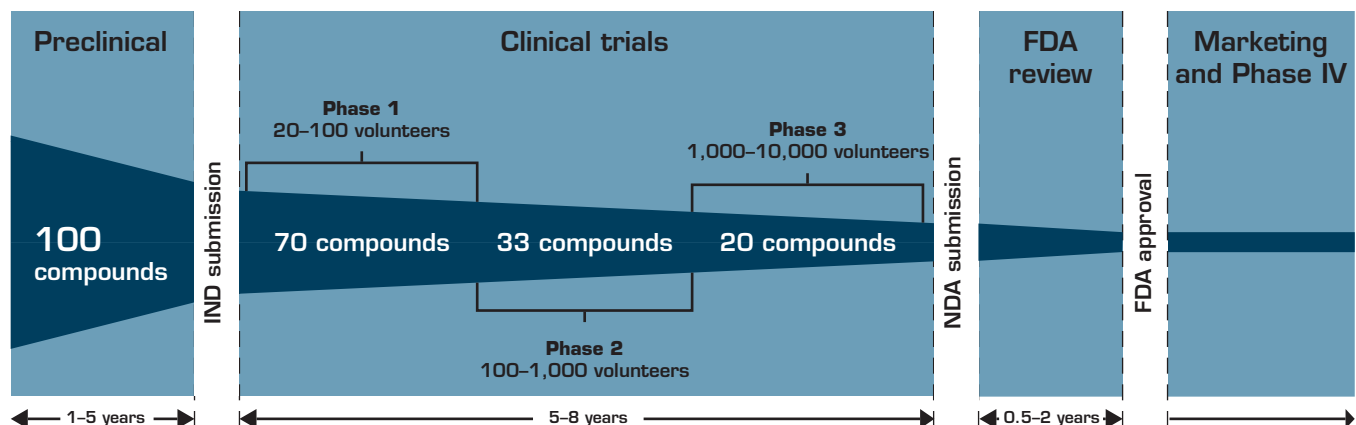
A prospective clinical trial sponsor must complete extensive safety/toxicity studies in animal models to establish that the investigational new drug will not expose human subjects to unreasonable risks when used in limited, early-stage clinical studies. These studies can take one to five years. Once completed, a sponsor organization may file an Investigational New Drug (IND) application with the FDA. An IND may be filed for an unapproved product or for a new indication or patient population for an approved product. It must

contain detailed information concerning the animal pharmacological and toxicology studies, the manufacturing of the product, the investigator, and the protocols for the proposed clinical trials. The IND must also include commitments from the sponsor to obtain informed consent from research subjects and a review of the study by an institutional review board, and to adhere to other U.S. regulations. Once the IND is submitted, the sponsor must wait 30 days before initiating any clinical trials. During this time, the FDA has an opportunity to review and place a clinical hold on the IND. If no hold is placed, clinical testing may begin.<sup>42</sup>

Clinical trials are broadly categorized into four phases.<sup>43</sup>

- Phase I trials determine a dose with an acceptable level of safety and examine the biological and pharmacological effects of the product. These trials can last up to a year and usually involve a hundred or fewer subjects.
- Phase II trials generate a preliminary estimate of a drug or vaccine's efficacy/immunogenicity, safety, dose tolerability, and

**Figure 2.1**  
Clinical trial process for a candidate drug



potential adverse events. These trials typically involve several hundred to a few thousand subjects and last six months to two years. These trials are often run concurrently at multiple clinical trial sites in one or more countries.

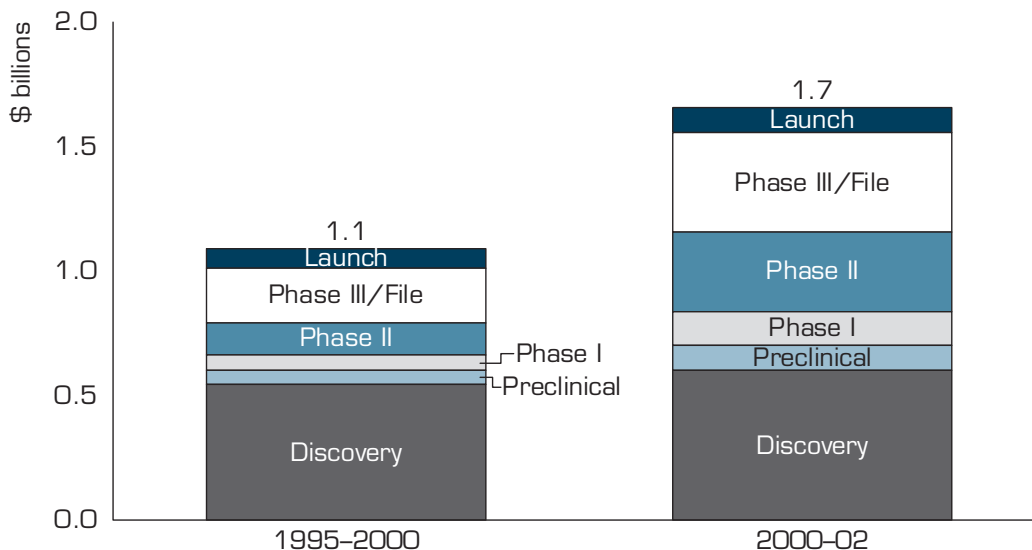
- Phase III trials are large-scale trials intended to provide a more definitive answer on the safety and efficacy of the intervention. Subjects are usually randomly allocated (randomized) to intervention groups, and the study drug or vaccine is assessed in comparison with a control (a known comparator product, often a placebo). These trials can involve hundreds or, more and more frequently, thousands of subjects and require three to five years to complete. It is often necessary to conduct more than one trial to test the product under varied conditions and different disease patterns, patient populations, or indications. If the phase III results demonstrate safety and sufficient efficacy to outweigh the risks of the product in the population and conditions in which it will be used, the manufacturer of the drug or vaccine can submit an application to the NRA to license and market that product.<sup>44</sup>
- Phase IV trials are post-marketing surveillance studies. These trials are used to monitor the safety and effectiveness of the

product and its duration of benefit, and to identify rare serious adverse events that may not become evident until the drug or vaccine is used by many patients. These trials involve thousands of subjects in the general target population, rather than a selected group of subjects who agree to participate in the trial. These trials can last four to six years.

Clinical trials, particularly for drugs and vaccines, have become increasingly expensive. Per subject costs can be as high as \$30,000. Figure 2.2 illustrates an estimate of the growth in total investment required to launch a successful drug over two time periods. Most of the increased cost of the “critical path” period depicts results from clinical development costs.

While costs have increased, the productivity of product development clinical trials has steadily eroded.<sup>45</sup> Between 1991 and 2003, the costs of clinical development increased 7 percent a year after adjusting for inflation, while there was a 34-percent reduction in the number of new drugs approved in same period.<sup>46</sup> Most biopharmaceutical R&D projects fail, with the candidate medicine never making it to market. For every 100 drugs for which an IND application is submitted to the FDA, 70 will successfully complete

**Figure 2.2**  
Investment escalation per successful compound



Source: Bain drug economics model, 2003. Adapted from Jim Gilbert, Preston Henske, and Ashish Singh, “Rebuilding Big Pharma’s Business Model,” *IN VIVO: The Business and Medicine Report* 21(10) [November, 2003].

Phase I clinical testing, 33 will successfully complete phase II clinical testing and proceed to phase III, and, of those, only 20 will be approved for marketing.<sup>47</sup>

The reasons for the increased cost and decreased productivity of clinical development are at least fourfold.

First, clinical trials have become more complicated and costly, in part because the products and outcomes they are designed to evaluate are more complex. Many investigational treatments now target biologically complex chronic illnesses that require longer periods to effectively measure end points.<sup>48</sup> Further, protocols for new biologics have more stringent eligibility requirements and necessitate more elaborate monitoring methods, such as diagnostic assessment of biomarkers, to evaluate safety and efficacy. It is often necessary to conduct more than one phase III trial.

Second, changes in clinical trial regulation have contributed to the growth of clinical trial durations and costs.<sup>49</sup> Regulation of clinical trials is essential for ensuring the safety, well-being, and rights of clinical trial subjects and the validity of clinical data. However, since 1962, when the FDA and other national regulators began regulating the clinical development process, those regulations have tended to accrue, with new regulations adopted in response to specific scandals.<sup>50</sup> Over time, these regulations have accumulated, layering on top of one another, with relatively little subsequent streamlining to address scientific and methodological advances.<sup>51</sup>

An example of this dynamic is clinical trial monitoring and record keeping. These tools are important for protecting the rights and well-being of subjects and preventing clinical trial fraud. However, national and international requirements for clinical trial monitoring and record keeping have increased in complexity in response to episodes of clinical trial data fraud.<sup>52</sup> These requirements now frequently comprise one-third to two-thirds of total clinical trial cost.<sup>53</sup>

Another example is the institutional review board (IRB) system. IRBs, which are usually referred to as ethics committees (ECs) outside the United States, are an important safeguard that helps protect subjects and ensure adherence with national and international standards for biomedical ethics.<sup>54</sup> Over the years, however, the role of IRB/ECs has substantially expanded. IRB/ECs once simply reviewed whether clinical testing met ethical standards; today, they examine trial protocols to ensure that written consent forms are sufficiently simple and clear, monitor the progress of testing, and maintain substantial records of activities. IRB/ECs must

meet in person and devote substantial time to their responsibilities. Many of them lack accountability for the timeliness and quality of their review.

While national and international laws do not generally require each research institution involved in a multi-site study to conduct its own ethical review, most do.<sup>55</sup> Institutions use IRB/ECs for their own institutional risk management beyond what is required for human subject research.<sup>56</sup> Inconsistencies in IRB/EC standards and determinations delay the conduct of a clinical trial and inhibit the ability of investigators to implement the same trial protocol across all studies sites—critical for developing valid trial results.<sup>57</sup> Regional and national review IRB/EC processes are typically additional, rather than substitutes for local institutional review.<sup>58</sup> With trials now often involving multiple, sometimes dozens and hundreds of sites, the costs and time imposed by the IRB/EC system can be substantial.

Third, clinical studies are increasingly conducted on a multi-country and multi-regional basis. This is done to support regulatory approval decisions in target markets and to tap larger pools of treatment naïve potential subjects. Regulatory barriers make conducting those global studies with a single clinical trial protocol difficult.<sup>59</sup> The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) developed good clinical practice guidelines (ICH-GCP) for the design, conduct, recording, and reporting of trials. These guidelines are now the global standard of how trials are run and a legal requirement in many countries.<sup>60</sup> ICH-GCP, however, leaves significant space for interpretation. Accordingly, many countries' regulations are based on ICH-GCP but retain significant differences in their requirements.

Fourth, commercial practices, adopted to improve the speed and regulatory compliance of new product development trials, have transformed clinical trial practices generally, increasing their cost and complexity. A successful trial completed rapidly for patients with a common condition can lead to revenues of tens or hundreds of millions of dollars a year for a pharmaceutical company. Shorter clinical development preserves more of a marketed product's patent life. There are significant competitive advantages to being the earliest product entrant in a therapeutic class. Under this commercial model, speed and reductions in the risk of regulatory non-compliance are a greater priority than cost. Put another way, the commercial aversion to the risks of avoidable clinical trial delays

and regulatory non-compliance is significant given the potential financial rewards that may be lost.

To ensure regulatory compliance, clinical trial protocol designs have become more ambitious and demanding. Consequently, clinical trials have more subjects and more sites per trial than previously. Between 1999 and 2005 the mean number of procedures performed on each study volunteer has increased almost 9 percent annually across all phases and therapeutic areas.<sup>61</sup> The standard operating procedure for many commercial trials involves detailed data collection, extensive auditing of all data points (key or otherwise), and close scrutiny to ensure that the proffered evidence is confirmed, without necessarily achieving a corresponding improvement in patient safety or results.<sup>62</sup> Many argue that commercial trials often “over-interpret” regulatory guidance and requirements, doing more than required and focusing on regulatory compliance instead of the scientific demands of the trial.<sup>63</sup> The cost implications of such practices are significant.

Over the last 20 years these commercial and regulatory pressures have led to a clinical trial support industry and a proliferation of new business models. Clinical trials are often intermediated by commercial contract research organizations (CROs) that recruit clinicians and patients and manage the day-to-day operations of clinical trials.<sup>64</sup> CROs specialize in navigating the maze of clinical trial regulatory requirements and structures and producing trials that meet the needs of NRAs. Site management organizations coordinate with CROs to ensure rapid IRB/EC approval and faster site initiation and patient recruitment. Data management organizations collect, monitor, and maintain clinical trial data and study records. These companies are increasingly part of the standard overhead for conducting clinical trials; it has become difficult to run global trials without their assistance.

These developments affect developed and developing countries alike. Developed country regulatory models and commercial clinical practices are often imported into developing countries and adopted for clinical trials for drugs and vaccines for neglected diseases.<sup>65</sup> Developing country governments adopt the regulations and guidance of the FDA and EMA because they are publicly available and familiar to the commercial clinical trial sponsors that developing country governments hope to attract. Likewise, the same commercial clinical trial practices are employed broadly, including highly cost-sensitive clinical trials in neglected disease–endemic countries, because they are familiar and accepted.<sup>66</sup>

## Challenges with clinical trials for neglected diseases specifically

There are many advantages to clinical research in global health technologies and neglected disease–endemic settings—committed trial sponsors and investigators, low labor costs, significant numbers of willing and treatment-naïve participants, and countries anxious to host innovative medical research to address local health needs. There are also four challenges that compound the difficulties of clinical development generally.

- Complex development pathways and limited clinical trial sites.
- The limited regulatory and ethical review capacity in many neglected disease–endemic settings.
- The particularly difficult regulatory and ethical challenges posed by neglected-disease product development trials.
- The frequent need to conduct these trials in multiple countries.

### Complex development pathways and limited clinical trial sites

Several factors increase the complexity and cost of clinical development of neglected-disease products.

First, the majority of the candidate technologies for neglected diseases are vaccines.<sup>67</sup> The clinical development process for these candidate vaccines is expensive and time-consuming. It is difficult to determine the likely efficacy and immune response of vaccines for many neglected diseases in animal and in vitro models. Accordingly, vaccine developers must test their candidates multiple times in expensive human subject trials to identify the desired formulation before advancing to later stage development. Developers often need to test their candidate vaccine in a series of trials for adult populations in high-income settings, adults in low-income settings, and children in low-income settings before testing the product in their target population—infants in resource-poor settings. Vaccines often require infrastructure such as refrigeration and logistical support for their storage and administration. Finally, longer and larger trials (15,000–70,000 subjects) may be needed before sponsors and regulators can observe the desired immune response and determine the safety of the candidate vaccine.<sup>68</sup>

Second, many neglected diseases must be treated with fixed dose combinations of drugs to avoid the development of drug resistance. Historically, the safety and efficacy of each of the drugs in the combination have needed to be determined independently before clinical trials of the combination drug may occur.<sup>69</sup> This requirement

increases the numbers of clinical trials that sponsors must conduct and lengthens the time required for clinical development of these products.

Third, clinical trials for neglected-disease products must often include research objectives beyond that required to support regulatory approval in order to generate evidence to support a positive recommendation from the WHO on the use of that drug or vaccine. The WHO has strategic advisory committees that provide periodic review of new drugs and vaccines and issue recommendations on their use. The WHO Strategic Advisory Group of Experts (SAGE), for example, issues policy recommendations on strategic and scientific matters related to vaccine use to member state government agencies responsible for the implementation of immunization programs, surveillance of vaccine-preventable diseases, and vaccine safety licensing.<sup>70</sup> These recommendations are enormously influential. Many NRAs will not license a product before the WHO issues a positive recommendation on its use.<sup>71</sup> Bilateral and multi-lateral donor agencies and international organizations such as UNICEF and the Global Alliance for Vaccines and Immunisation (the GAVI Alliance) rely on SAGE recommendations to guide vaccine procurement.<sup>72</sup>

While WHO policy recommendations are an important step in the regulatory and decision-making pathway for global health technologies, the process for generating those recommendations is complex and can be time-consuming. The WHO did not issue positive recommendations on the use of the PCV and Hib vaccines until 7 and 15 years, respectively, after their first licensure.<sup>73</sup> Neglected-disease product sponsors increasingly attempt to expedite the WHO policy process by adding secondary objectives to their phase III interventional trials to generate the evidence that WHO may require on the impact of the candidate product on the disease burden, existing interventions, and in all target populations and settings. Such secondary trial objectives lengthen case report forms, slow trials, raise costs, and increase the likelihood of protocol amendments. Substantial protocol amendments can, in turn, require revising site contracts and budgets, additional investigator training and monitoring, and repeating regulatory approval, ethical review, and the informed consent processes.

Fourth, too few research sites in neglected disease–endemic settings can conduct the trials that must occur to complete clinical development of the candidate products in the neglected-disease pipeline.<sup>74</sup> Clinical trials must be conducted according to international

GCP and good laboratory practice (GLP) standards to satisfy the requirements for product registration in most jurisdictions. Meeting this standard requires adequately trained personnel and sufficient laboratory and IT infrastructure. Capable sites must exist in areas reflecting the target socioeconomic and epidemiological conditions and be able to efficiently enroll sufficient patients.

Through donor support and the tremendous efforts of the WHO and other international organizations, clinical research capacity is improving for some neglected diseases like malaria and in some neglected disease–endemic settings.<sup>75</sup> More remains to be done. Capable clinical trial sites are lacking in rural settings and in regions such as West and Central Africa.<sup>76</sup> Not surprisingly, given the strong correlation between neglected diseases and poverty, these are the same settings where the most neglected diseases are endemic (figure 2.3).

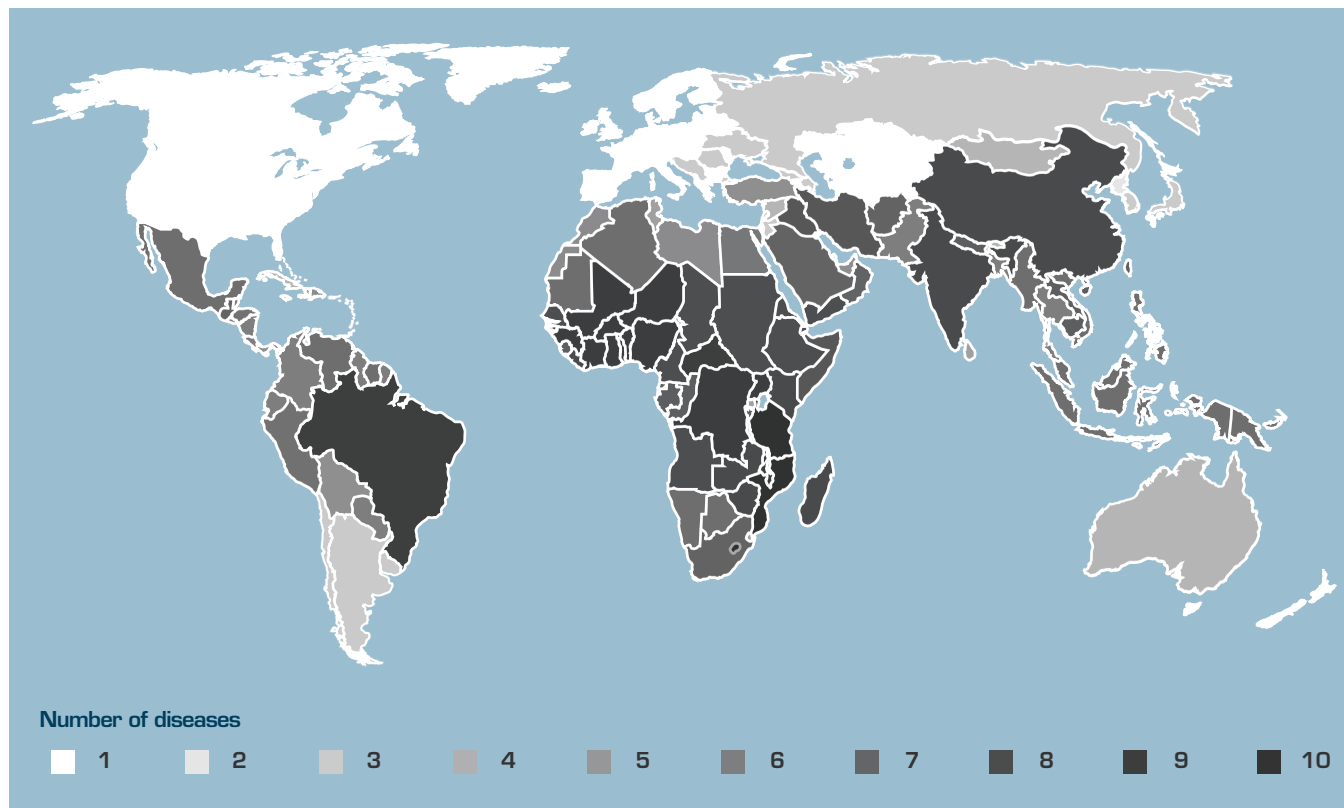
Competition for capable sites and investigators increases costs and adds delays. Where adequate sites do not exist, product sponsors must build them or improve the infrastructure and quality assurance systems of existing ones.<sup>77</sup> Maintaining capable clinical trial sites requires sustained donor support and an adequate and diversified flow of research projects.

### Lack of regulatory capacity hinders trials and could place subjects at risk

Clinical trials must be conducted where the burden of the relevant disease exists. Neglected diseases are endemic primarily in Africa, Asia, and tropical regions of the Americas, with a lower prevalence in the Middle East.<sup>78</sup> Accordingly, approximately two-thirds of the clinical trials for neglected diseases that initiated subject recruitment between 2003 and 2009 were in disease-endemic regions, with nearly a third in Africa (figure 2.4).<sup>79</sup>

The regions with the highest neglected-disease burden are also those with the most poorly resourced and inexperienced regulators and ethics committees. Many neglected disease–endemic countries, particularly in Africa, have weak or no NRAs and little ethical review capacity.<sup>80</sup> Where NRAs do exist, they often lack sufficient legal authority to approve clinical trial protocols, authorize importation of study products, inspect sites, or terminate trials. A 2009 WHO report assessing 22 developing country NRAs in Africa, Asia, and Latin America concluded that two-thirds of these countries had weak or no mechanisms for regulating clinical trials or exerting proper oversight on clinical investigation.<sup>81</sup> Even

**Figure 2.3**  
Geographic distribution of neglected diseases



where the legal framework for clinical trial regulation exists, limited resources and training undermines the effectiveness of NRAs and ethics committees.<sup>82</sup> Regulators and ethics committees often lack sufficient personnel to review clinical trial protocols and inspect sites according to accepted international standards and in a timely fashion. A 2010 WHO study of regulatory systems in Sub-Saharan Africa concluded that GLP and GCP were not a requirement in 22 of the 26 countries surveyed and only 4 of those countries reported conducting inspections of clinical trials.<sup>83</sup>

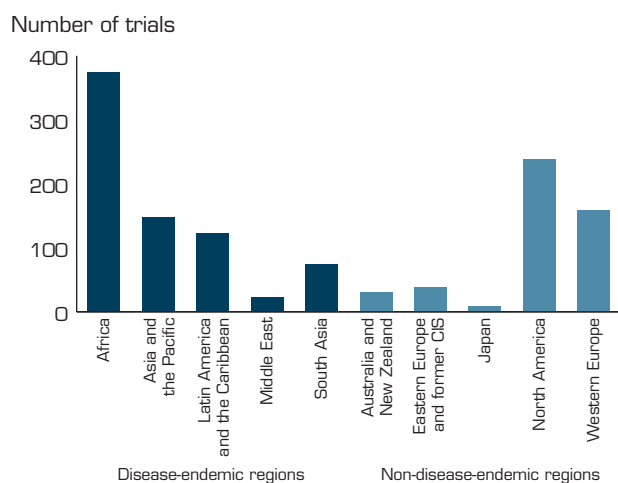
Regulatory pathways and procedures in disease-endemic countries are frequently unclear and may change in unpredictable ways. NRAs and ethics committees have little interaction and duplicate each other's efforts; it may be difficult to determine their respective roles and responsibilities.<sup>84</sup> Regulatory and ethics committees

have highly variable practices, particularly for trial monitoring.<sup>85</sup> Ethics requirements are opaque and overlapping. Information on clinical trial regulatory requirements is not easily accessible to the public. Regulators' guidance may be unavailable or, when given, a moving target.

It can be difficult to conduct ethical, sufficiently regulated trials in such environments. The lack of regulatory and ethics capacity could undermine the safety of subjects and the validity and integrity of clinical data.<sup>86</sup> The inability to understand local laws hinders trial planning, delays trial initiation and patient recruitment, and may lead to regulatory non-compliance. This situation presents challenges for sponsors committed to conducting ethical and sufficiently regulated clinical trials for neglected diseases.<sup>87</sup> The risk of regulatory non-compliance and harm to subjects exposes trial



**Figure 2.4**  
Regional distribution of registered neglected disease trials, 2003–09

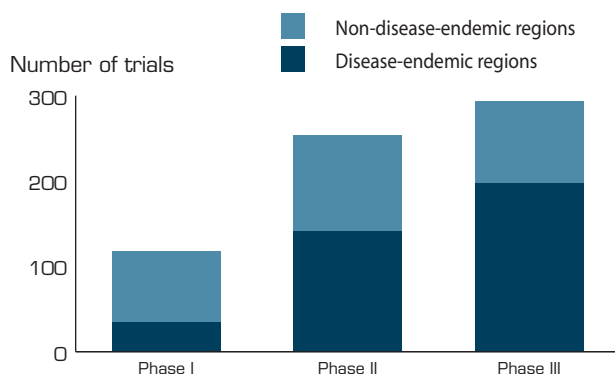


sponsors and investigators to legal liability and reputational risk, deterring private investment.

The proportion of neglected-disease trials in disease-endemic countries, nonetheless, increases for larger, late-stage clinical trials (figure 2.5). This reflects the reality that the definitive studies of the safety and efficacy of therapeutics must generally be conducted in the populations and environments for which they are intended. Late-stage trials tend to involve a greater number of subjects and, often, more complex trial design and procedures. Accordingly, these trials place greater demands on local research and regulatory capacity.

To minimize regulatory risk and uncertainty, many trial sponsors report seeking parallel trial registration with either the EMA or FDA, and conducting the trial in a more developed neglected disease–endemic country such as India or South Africa. These high disease-burden countries have the expertise and legal frameworks to conduct a more competent regulatory and ethics review, but because of resource constraints, that review can take a disproportionately long time. Regulatory approval for trials in the United States and European Union can generally be obtained within 30–60 days. In many neglected disease–endemic countries, approval can take as long as 6–24 months.<sup>88</sup> For products that require multiple trials to

**Figure 2.5**  
Regional distribution of registered neglected disease trials, by phase 2003–09



establish the safety and efficacy of the product in different subject populations, subsequent clinical trial application approvals may take as long as or longer than the original review.<sup>89</sup> Trial protocol amendment approvals that require a few weeks in developed countries can require as long as four months in these settings.<sup>90</sup> In many cases, steps in the regulatory and ethical approval process need to be done in sequence, rather than simultaneously and in parallel, so that more than a year can pass between finalizing a trial protocol and completing all governmental and institutional regulatory and ethics processes.<sup>91</sup> Those delays not only prolong clinical trial initiation and patient recruitment, but also extend the time before new effective products may be registered.

### Neglected-disease trials pose particularly difficult regulatory and ethical challenges

Clinical trials for health products for neglected diseases impose particularly difficult regulatory and ethical challenges that compound the problem of inexperienced and under-resourced NRAs and IRB/ECs. Those challenges are at least threefold.

First, the science is often difficult, imposing additional challenges for the inexperienced regulators and IRB/ECs that must assess the scientific validity and the risk-benefit ratio of the proposed trials.<sup>92</sup> Much remains unknown about many neglected diseases. For many

of these diseases, there may be no validated surrogate marker or immunological correlate of protection.<sup>93</sup> Trials may require clinical endpoints that require significant time to develop or severe disease outcomes or mortality. The most likely scenario for many neglected-disease trials is a partial success at best.

Some neglected diseases require multidrug regimens to address bacterial subpopulations and prevent the development of resistance.<sup>94</sup> Testing drug candidates individually can add years to the development of effective combinations,<sup>95</sup> while testing novel drugs together can make it difficult to assign side effects to a particular candidate drug or interaction between drugs. The U.S. FDA only recently proposed draft regulatory guidelines for clinical trials of novel combination drug regimens, which are limited to treatments for serious and life-threatening diseases for which there are no satisfactory alternatives.<sup>96</sup> The conduct and regulation of novel-combination product trials in the neglected disease–endemic environments will be a significant challenge.

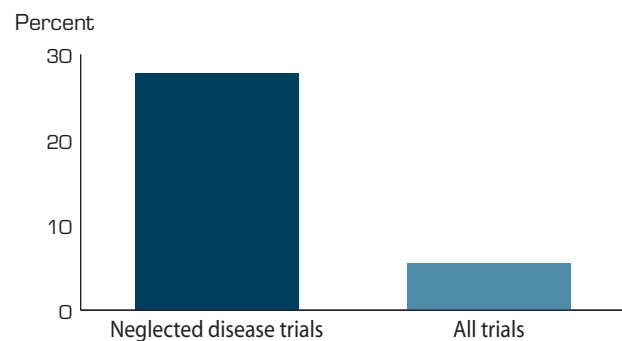
Second, neglected-disease trials present extreme versions of the already difficult ethical challenges of conducting clinical research in developing countries.<sup>97</sup> Clinical trials often must be conducted with highly vulnerable clinical trial subjects in devastatingly poor settings in disease-endemic countries with little healthcare infrastructure. Wide disparities in the education, language, economic, and social standing of investigators and subjects and the poor quality of local healthcare systems may jeopardize the rights of research participants. Subjects may not always understand the investigational nature of therapeutic products and the use of a placebo.<sup>98</sup> Determining the appropriate standard of care to be provided to subjects can be controversial.<sup>99</sup> If an existing drug or vaccine for the disease is available, as is the case with tuberculosis, the ethics and science of the trial design are greatly complicated.<sup>100</sup> The question of what qualifies as fully informed consent is not always simple.<sup>101</sup>

The burden of neglected diseases falls disproportionately on infants and children; the subjects for clinical trials for neglected diseases are frequently pediatric (figure 2.6).

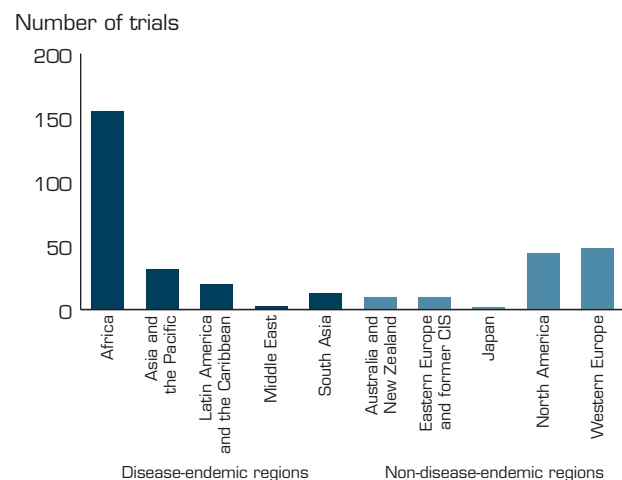
Pediatric trial subjects are particularly vulnerable and, thus, pose difficult ethical and operational challenges. Again, most of these difficult pediatric neglected-disease clinical trials are in Africa—the region with the least regulatory capacity and expertise to oversee them (figure 2.7).<sup>102</sup>

Third, as was indicated previously, most of the candidate products in clinical development to treat neglected diseases are vaccines.

**Figure 2.6**  
Proportion of registered clinical trials involving pediatric subjects, 2003–09



**Figure 2.7**  
Regional distribution of registered pediatric trials, 2003–09



PDPs report much longer delays in regulatory and ethics approvals of trials for vaccines than drug products in disease-endemic countries. These trials must usually be conducted with healthy people, often children. To demonstrate safety and a sufficient immune response, the trials must frequently be large—involving tens of thousands of

clinical trial subjects. The personal benefit to the clinical trial subjects may be limited and provisional, with the greater benefit of the product accruing to the community than to the individual patient.

### Multi-center and often multi-country trials

The challenges of clinical development of neglected-disease products in disease-endemic countries are compounded by the frequent need to conduct these trials at multiple sites in multiple countries. Close to half of the biopharmaceutical and vaccine trials for neglected diseases registered between 2003 and 2009 involved two or more trial sites and nearly a third had sites in multiple countries.<sup>103</sup> The majority of multi-country product development trials for neglected diseases, however, had all their sites within a single geographic region.<sup>104</sup>

These findings about clinical trials for neglected diseases differ from the general trend in two respects. First, a much smaller proportion of clinical trials overall had sites in more than one country (14 percent). This result suggests that clinical trial sponsors avoid conducting clinical trials in multiple countries, perhaps due to the need to navigate multiple oversight processes and NRAs. By contrast, the greater use of sites in more than one country in neglected-disease trials most likely reflects either the limited site capacity in disease-endemic countries (requiring sites in other countries) or the need to test the candidate product in settings with different epidemiological, service delivery, and socioeconomic conditions or with different strains of the disease.

Second, the overwhelming majority (73 percent) of multi-country clinical trials involved sites in multiple geographic regions.<sup>105</sup> This suggests that, as a general matter, once a sponsor decides to run a trial with sites in more than one country, that sponsor chooses sites in countries with the most research capacity, favorable regulatory system, and patient recruitment potential. By contrast, the regional concentration of the sites in multi-country product development neglected-disease clinical trials suggests that the choice of those sites is driven by the presence of the disease burden rather than the regulatory or research qualities of the host country.

Whatever the motivation, the need to navigate regulatory and ethics requirements in multiple jurisdictions adds delays, costs, and uncertainties to the already time-consuming, costly, and risky clinical development process.<sup>106</sup> Multiple regulators and IRB/ECs reviewing the same protocols and consent forms waste scarce in-country regulatory capacity and resources.<sup>107</sup> Regulatory authorities and IRB/ECs in different disease-endemic countries often impose different or inconsistent requirements or review timelines.<sup>108</sup> Those inconsistent requirements necessitate multiple trial protocol submissions, resulting in divergent regulatory decisions and requests, which delay trial initiation.<sup>109</sup> These regulatory differences frequently extend to adverse event reporting and other compliance requirements, increasing trial costs. The resulting regulatory cacophony in most cases affords no obvious benefit to scientific rigor, quality, or protection of trial subjects.



## Chapter 3

# The need for a more sustainable strategy

As a result of the foregoing challenges, two substantial bottlenecks loom as more of the candidate drugs and vaccines in the neglected-disease product pipeline move to late-stage clinical development.

First, the clinical research and regulatory capacity in many neglected disease–endemic settings is not adequate to support the clinical trials that need to occur there in order to complete the development of these products. The scarcity of GCP/GLP-capable clinical research sites in neglected disease–endemic settings delays patients’ access to potential lifesaving interventions, increases costs of existing sites, and compels sponsors to invest in and maintain new sites. The lack of regulatory and ethics capacity could undermine the safety of subjects, the foremost goal of all clinical research, and the validity of clinical data.<sup>110</sup> The risk of regulatory non-compliance and harm to subjects exposes trial sponsors and investigators to legal liability and reputational risk, deterring private investment. Finally, regulatory bottlenecks extend the duration of clinical development, estimated to represent as much as half the cost of conducting clinical research.<sup>111</sup>

Second, even with expected rates of attrition, there is insufficient financing available to support the clinical development of the candidate products in the neglected-disease pipeline as it stands now under current cost assumptions.<sup>112</sup> Clinical development costs for neglected-disease therapies remain high, even with the commitment, expertise, and efficiencies that PDPs have brought to the process.<sup>113</sup> A 2008 report by the Dalberg Advisors, for example, estimates that while \$500 million had been spent building the current pipeline of candidate drugs for neglected diseases, an estimated \$6–10 billion would be needed to complete their clinical development.<sup>114</sup> The Dalberg estimate did not include vaccines, which tend to be more expensive and represent most of the products in the pipeline for neglected diseases.<sup>115</sup> Other projections of clinical development costs for the neglected-disease product pipeline are similarly daunting.<sup>116</sup>

Part of the answer to these twin challenges must include more funding for late-stage clinical trials and the training programs, infrastructure, and sites in neglected disease–endemic settings needed

to run them pursuant to good clinical and laboratory practice standards. Global health donors and product developers are making progress on building clinical research capacity in many low- and middle-income countries.<sup>117</sup> Investment in regulatory and ethical review capacity, however, is still lacking.<sup>118</sup> Regulatory and ethical review capacity is seen as the obligation of government and public health institutions, not trial sponsors and philanthropic donors. Poor-country governments with competing demands on their scarce resources have been slow to invest in regulatory and ethics review capacity. WHO technical assistance programs—such as the Special Program on Tropical Disease Research, European and Developing Countries Clinical Trials Partnership, the Malaria Clinical Trials Alliance, the Strategic Initiative for Developing Country Capacity in Ethical Review, and other donor initiatives—have made commendable efforts on clinical research and regulatory capacity building and deserve further support.

It must be acknowledged, however, that substantial increases in the funding for global health technology development may well not be forthcoming in the current economic environment. While neglected-disease R&D costs are rising, government budgets for global health are tightening, and new donor funding for product development is increasingly scarce. The 2010 G-Finder report indicated that funding for PDPs and product development has begun to decline in the last two years, with a shift in funding toward basic research and self-funded government initiatives.<sup>119</sup> Donor and sponsor insistence on approximating rich-country clinical development models under difficult poor-country conditions will only lead to a further escalation of delays, complications, and costs. A country-by-country approach to research and regulatory capacity building is not feasible. Greater attention to cost-containment is needed.

Developing more efficient clinical trial practices and a rigorous regulatory environment more friendly to the conduct of clinical trials in neglected disease–endemic settings would result in multiple winners: trial subjects and patients, global health interests, the

multinational pharmaceutical industry, developing country governments, and developed country regulators. More efficient clinical trial practices and better defined and streamlined regulatory pathways would improve the commercial viability of neglected-disease product development and encourage private investment in clinical research capacity in disease-endemic countries. Improvements in the certainty, sufficiency, and efficiency of regulatory oversight would benefit clinical trial subjects, sponsors, and foreign and host governments alike. And, attracting more clinical trial activity to neglected

disease-endemic settings would increase the sustainability of their clinical trial sites.

The following chapters describe two complementary approaches—regional pathways for clinical trial regulation and ethical review and simpler, more efficient clinical trials—put forward by this Working Group to help achieve these objectives. Together, these approaches form a single strategy to help bring the costs, risks, and financing for neglected-disease clinical trials into a more sustainable balance.

## Chapter 4

# Regulatory pathways

While donors have increasingly seen the value in devising products for neglected diseases, a coherent plan for building the requisite regulatory infrastructure to develop and deliver these therapies to patients is lacking. New strategies are needed to leverage existing resources and opportunities for networking in order to establish clear and accelerated regulatory pathways for this neglected-disease clinical research and to improve the quality of its regulatory review and ethical oversight.<sup>120</sup>

### A regional pathway for clinical trial regulatory and ethical review

This Working Group recommends building a regional pathway for the regulation and ethical review of clinical trials for neglected-disease technologies. This would entail a centralized procedure/joint review model in which both NRAs and ethics committees participate. Such an approach would promote cooperation between ethics committees and NRAs, avoid unnecessary duplication and multiplication of efforts, and provide a platform for external assistance and donor support.

A single regional pathway with integrated regulatory and ethics reviews for clinical trials would have four advantages.

First, it would improve the quality of clinical trial regulation and the protection of the clinical trial subjects in participating disease-endemic countries by pooling scarce regulatory resources. A regional platform would also magnify the impact of dollars spent to support clinical trial regulatory capacity building in disease-endemic regions and developing countries.

Second, a regional integrated pathway for regulation of clinical trials would help reduce regional inconsistencies in regulatory and ethics requirements and their interpretation. It would also limit the number of regulatory and ethics reviews and compliance obligations required for multi-country clinical trials. In doing so, such a pathway would expedite trial initiation and reduce the cost and uncertainty of conducting clinical trials in participating neglected disease–endemic countries.

Third, it would reduce the unnecessary costs, delays, and uncertainties of conducting clinical trials in disease-endemic countries, reducing barriers to new private sector investment and expediting patients' access to potential treatments.<sup>121</sup> Given the scale of funding required for clinical development, modest improvements in efficiency would yield substantial savings that could be used to develop other products for neglected diseases.

Fourth, a more cost- and time-efficient regional regulatory approach with more certain review timelines and procedures would help attract private clinical trial activity to neglected disease–endemic regions and investment in local and regional research capacity.<sup>122</sup>

Regional regulatory cooperation, however, is not without its challenges. Governments value their sovereignty in regulatory affairs and are understandably protective of the independence and local accountability of their regulatory authorities and ethics committees. Plurilateral cooperation requires a supporting infrastructure and administration. Regional regulatory cooperation will require sustained investments of political will and staff-level commitment.

There are good reasons to believe that regional regulatory cooperation can succeed in this context. The relevant regulatory authorities, ethics committees, and legal frameworks for neglected diseases are still evolving and have not yet become entrenched in individual or idiosyncratic approaches to clinical trial oversight. This is particularly true in Africa. Cooperation is far easier in sectors not yet regulated or where the regulation is developing or rapidly changing.<sup>123</sup> Further, the governments in these countries have economic incentives to build clinical trial capacity, including income from the trials, benefits to public health, and economic development. More so than most international harmonization initiatives, cooperation on the regulatory and ethical review of clinical trials would appeal to the range of policymakers, regulators, and health officials necessary to bring such initiatives forward. Finally, the importance of this initiative for global health and the neglected-disease product pipeline will inspire outside technical

assistance and resources in the manner that other regulatory cooperation efforts may not.

## Precedents

The Working Group reviewed a variety of precedents and potential models for regional regulatory pathways involving both developed and developing countries. The following potential precedents are listed in order of increasing formality.

### AVAREF

The African Vaccine Regulatory Forum (AVAREF) is a network of 19 African countries that the WHO identified as likely settings for clinical trials of priority vaccines. The purposes of the AVAREF initiative are to address the lack of technical expertise and capacity in its participating countries and to improve interaction among participating NRAs and IRB/ECs. AVAREF conducts an ad hoc joint regulatory and ethics review process for vaccine clinical trials in Africa.<sup>124</sup> It also works with the WHO Pan-African Clinical Trial Alliance project, which is intended to establish a standing, functional collaborative network of NRAs and IRB/ECs for approval, oversight, and registration of medicines/vaccines interventional clinical trials. The WHO coordinates, organizes, and funds AVAREF activities.

Working with trial sponsors, the WHO facilitated joint reviews by African NRAs and ethics committees of trial protocols in conjugate meningitis A and malaria vaccine clinical trials and joint inspections of the sites involved. These reviews were predicated on common dossiers and criteria for approval, developed by the WHO. Use of common documentation and criteria did not require changes in national laws because both were designed to encompass the participating countries' clinical trial requirements. Participating regulatory authorities entered into confidentiality agreements with sponsors to facilitate the sharing of information. Product sponsors provided their applications and supporting documentation in both English and French. The AVAREF joint review processes permitted the involvement of outside experts from developed country regulatory authorities.

The joint review process in AVAREF did not culminate in a joint opinion or approval recommendation. Its results are not binding and do not replace national reviews. Ethics committees participated only after making independent determinations to approve the trial. The process did not include a provision for joint review of study protocol amendments after initial approval of the trials. Even so,

the process has been widely viewed as successful, improving the capacity and coordination of participating NRAs and ethics committees and encouraging the use of defined review timelines and common documentation.<sup>125</sup>

### HMA Voluntary Harmonization Procedure

In 2009 the Heads of Medicines Agencies (HMA), a network of the Heads of the NRAs in the European Economic Area, introduced a voluntary harmonization procedure (VHP) for interventional clinical trials with sites in multiple EU member states. Currently, it is necessary to submit an application to each EU member state in which a clinical trial will be conducted. To constrain the duplication of ethics review efforts for international multisite studies, the European Union restricted each participating country to a "single opinion" representing the ethics review for that country, "notwithstanding the number of Ethics Committees" involved.<sup>126</sup> Despite that requirement and the common documentation, standards, and procedures that the EU Clinical Trials Directive mandates, significant differences have persisted in member states' interpretation of these requirements and regulatory and ethical review times.<sup>127</sup> The HMA VHP is meant to reduce these differences by providing a common application, a single application point, and a coordinated initial assessment of applications.

EU NRAs decide to participate in the VHP on a case-by-case basis upon filing a clinical trial application with the VHP but are required to make that decision within five days of its submission. Participating regulatory authorities jointly review the clinical trial application and issue an opinion of its acceptability within 60 days. A VHP coordinator administers the procedure and communication with the applicant and participating NRAs. For each review, one of the participating NRA is charged with developing consensus on the list of questions for applicants and the joint opinion. If the application is acceptable, the VHP coordinator notifies the applicant and formally submits the application with each participating NRA pursuant to the EU Clinical Trials Directive.

If the decision is not unanimous, the opinion identifies the dissenting NRA(s) and their questions about the application. Applicants may resolve those questions with the dissenting NRA(s) or decide to skip filing their clinical trial application with that country. Participating NRAs are not legally bound by their decisions in the VHP but are expected to comply and agree, by virtue of their participation in the process, to decide upon the clinical trial applications from the



VHP within 10 days. Substantial amendments for VHP-approved clinical trial applications may also be submitted to the VHP. The VHP amendment assessment and approval procedures are essentially the same as for the initial application, but the review timelines are shorter. It should be noted, however, that although the VHP procedure is voluntary, it operates within the framework of the EC.

The VHP is relatively new, but the early results have been favorable.<sup>128</sup> Participation is high. The VHP process received more than 100 applications since 2009, with many more expected in 2011. Seven NRAs participate in VHP reviews on average, but one review involved 18 NRAs. Review and decision timelines are, on average, shorter than the ones prescribed under VHP procedures and are getting even shorter. VHP meetings have been used as platforms for clinical trial assessor training. Participating in joint reviews improves the clinical trial oversight capacity of smaller EU member countries that do not otherwise receive a high volume of clinical trial applications. The HMA plans to extend the VHP process to IRB/ECs in the coming years.

### The EMA centralized procedure

The EMA centralized procedure provides a single application, single evaluation, and a single review process allowing direct access to all national markets of the European Union.<sup>129</sup> It is an intriguing model for several reasons.

First, the principle motivation for establishing the centralized procedure was not regulatory harmonization, but rather the pooling of regional regulatory expertise on a difficult regulatory problem. European Community NRAs lacked expertise in the novel techniques needed to assess biotechnology products.<sup>130</sup> The centralized procedure enabled regulators to work together on biotechnology product registration applications with the intention of achieving a common decision.<sup>131</sup> These circumstances are similar to the situation in many neglected disease–endemic countries for difficult neglected-disease product development trials.

Second, the centralized procedure did not require the harmonization or dissolution of participating NRAs, often a sensitive issue of national sovereignty and employment.<sup>132</sup> Member states agreed, however, to use common product information documents, which later became obligatory.

Third, the centralized procedure evolved fairly quickly. International and regional regulatory harmonization efforts are notoriously complex, expensive, and arduous.<sup>133</sup> The European Commission had

been working on pharmaceutical registration harmonization since 1975, but its efforts were focused on its slow developing mutual recognition process.<sup>134</sup> The European Commission created the forerunner to the centralized procedure to address the biotechnology problem in 1987 and formalized it six years later. It was the first EU-wide drug regulatory procedure in which at least one member state had not issued a prior approval of a product before the procedure started.<sup>135</sup>

Fourth, the centralized procedure has been scalable. It was initially mandatory for a small, defined list of biotechnology and high-technology products and optional for all non-biotechnological drugs considered potentially innovative. Over the years this mandatory list has expanded to include medicines for HIV/AIDS, cancer, diabetes, neurodegenerative diseases, all designated orphan medicines, and all veterinary medicines intended for use as performance enhancers.

Fifth, the centralized procedure has been enormously successful. Within its first year of formal operation, two-thirds of the centralized applications that industry filed were done so voluntarily.<sup>136</sup> The procedure effectively integrated the drug approval process for newer therapies that might have otherwise proved controversial across EU markets.<sup>137</sup> The U.S. Government Accountability Office estimates that the centralized procedure saved an estimated 40 percent of the cost and, more important, greatly reduced approval times over obtaining separate marketing authorizations in, at that time, 15 EU member states.<sup>138</sup>

### The Integrated Research Application System in the United Kingdom

The Integrated Research Application System (IRAS), launched in 2008 in the United Kingdom, is another promising model of a centralized, integrated clinical trial regulatory and ethics review pathway. IRAS provides a single integrated application point for regulatory and ethics review of multi-site and single-site clinical trials in the United Kingdom; only issues of local ethical concern are assessed by local IRB/ECs. The system reduces bureaucratic burden, particularly for multi-site studies. It helps eliminate duplication; studywide checks are performed only once. IRAS also improves national ethics review consistency and creates a single secure online database and document repository.

\* \* \*

Drawing from these precedents, the Working Group recommends adopting a centralized procedure/joint review model in which

participating NRAs and IRB/ECs jointly review clinical trial applications for candidate neglected-disease technologies and perform inspections of trial sites. Such an approach would promote cooperation between ethics committees and regulatory authorities, avoid unnecessary duplication and multiplication of efforts, and provide a platform for potential external assistance and support.

### Goals of major constituents

A regional approach to clinical trial and ethical review will succeed only if it satisfies the interests of its major constituents: participating governments, trial sponsors, and the donors that must provide seed funding and technical assistance to launch and sustain the regional pathway.

- *Country interests.* The Working Group identified the following potential interests for NRAs, ethics committees, and their governments to participate in regional cooperation on clinical trial regulation: pooling NRA and ethics committee capacity and improving the quality of clinical trial reviews; attracting outside technical assistance and clinical trial activity to participating countries; and expediting the development of locally relevant products.
- *Sponsor interests.* The Working Group identified the following potential interests of clinical trial sponsors in participating in a regional pathway for clinical trial regulation and ethical review: adopting more cost- and time-efficient regulatory and ethical review processes; improving the quality of the regulatory and ethical review of trials conducted in support of product registration; gaining access to populations in countries that otherwise would not have adequate regulatory capacity to support those trials; and the long-term development of clinical regulatory and research capacity in countries that could host future trials.
- *Donor interests.* Potential donors fall into two categories—those sponsoring neglected-disease product development, and those supporting global health and international economic development generally. The interests of the first category are effectively the same as trial sponsors. The second category of donors has interests in global health technology development, but also in supporting regulatory capacity as a means of attracting clinical trial activity and foreign investment and improving the research capabilities of these countries.

Many of the goals of these potential constituents are immediate in this context. Dozens of new candidate technologies for neglected

diseases are now in the pipeline and potentially moving to late-stage clinical development in the next 5–10 years. A regional pathway for these multinational trials could do much to help address looming challenges around funding and clinical research and regulatory capacity, but the time to pursue such an effort is now, before the influx of these trials.

Under these circumstances, the standard approach to international regulatory cooperation and harmonization may not suffice. Participating governments do not have the time or resources to develop their own regulatory capacity, review each other's laws and make amendments to ensure their consistency, engage in information sharing and joint inspections to build trust and identify future needs, and eventually move to regulatory cooperation and harmonization.

The alternative is that relevant regulators and ethics committees agree to cooperate on addressing a small set of priority products or challenges. The cooperation is substantive, though not necessarily immediately binding, and initially narrow, restricted to a product class or specific regulatory activity. As trust builds among the participants, the cooperation deepens and may become binding and the scope of cooperation can expand to include other products and regulators. The advantages of this second approach are that the capacity of regulators is built by working together on addressing a specific regulatory challenge, rather than in the abstract; regulatory cooperation harmonizes interpretation and application as well as the underlying regulation; and the process can be fast—the EMA centralized procedure required just six years to move from concept to implementation. Since the regulatory cooperation involved is substantive and begins from the outset, however, the disadvantages of this approach are that it requires an administrative structure to coordinate that cooperation; some political commitment by the participants to engage in that cooperation; and the capacity to participate or at least a willingness to defer to others until that capacity can be built.

### Principles for effective regional cooperation on clinical trial oversight

In pursuing potential regional approaches to clinical trial regulation and ethical review, the Working Group recommends that government and donors incorporate the following design objectives:

1. *Respect sovereignty and local accountability.* Regional approaches to clinical trial regulation and ethical review should respect national sovereignty and the goals of local accountability, while

striving to achieve the benefits of greater regional cooperation. They should seek to regionalize and streamline as many aspects of clinical trial review as possible, but recognize that certain aspects (such as ethical norms and specific elements of informed consent) will remain inherently national and even local. Regional approaches should avoid, to the extent possible, the need to harmonize national laws or regulatory requirements. The legitimacy of the effort will depend on the ability of national governments and ethics committees to exercise their legal authorities to oversee clinical research as part of a regional process.

2. *Voluntary and, at least initially, non-binding.* Governments should have the opportunity to participate and gain confidence in regional clinical trial regulation before being bound by its results. Voluntary participation for regulatory authorities and trial sponsors is sufficient provided there are incentives for that participation. These incentives could include the improved functioning of the regulatory pathway, fee sharing arrangements, donor support and technical expertise, and links to other clinical research networks or initiatives.
3. *Broad in function, limited in scope, and scalable.* To facilitate clinical research and the capacity of its participants, regional cooperation must include ethical and regulatory reviews and the full range of relevant regulatory functions—reviews of clinical trial applications, protocols, and amendments; inspections and monitoring of clinical trial sites; and severe adverse event reporting. The scope of that participation should be narrow, however. Regional approaches to clinical trial oversight should begin with regions and types of products for which coordination is most urgently required to promote public health. Like the EMA centralized procedure, this regulatory pathway could be expanded over time to include other products and additional parties over time as confidence in the pathway is built.
4. *Capacity through cooperation.* Cooperation on clinical trial regulation should promote capacity, a sense of ownership, and increased integration among participating regulatory authorities and ethics committees. These goals are best accomplished in the context of reviews of actual clinical trial applications rather than in harmonization efforts done in the abstract.
5. *Reduce duplication and promote coordination in regulatory and ethical reviews.* Participating regulatory authorities and ethics committees should work in close cooperation, with open communication, and a clear division of labor. Ethics and regulatory reviews should be simultaneous rather than sequential.
6. *Common documentation, standards, and timelines.* Agreement among participating regulatory authorities on common documentation for clinical trial applications and on international standards for authorization is necessary for meaningful regulatory cooperation and to improve the predictability and efficiency for sponsors. The pooling of regional regulatory and ethical review resources should allow the setting of more ambitious timeframes than would be possible on a national basis. Recent experiences suggest regional regulatory cooperation functions better in one language. The need to accommodate multiple languages has added costs, delays, and operational challenges to other regional regulatory initiatives, such as AVAREF.
7. *Outside assistance.* Regional cooperation on clinical trial regulation of neglected-disease technologies should include a formal process for outside assistance, when requested by its constituents, from the FDA, EMA, or other qualified regulatory authorities.<sup>139</sup> WHO's technical support and convening power will also be critical in launching regional approaches to clinical trial regulation in low- and middle-income countries.
8. *Self-supporting.* A regional regulatory pathway will require seed funding from donors, but should seek to be self-supporting over the long term. Most neglected disease–endemic countries now charge clinical trial application fees. A streamlined regional regulatory pathway with more certain regulatory timelines would hold material value for clinical trial sponsors and may justify additional fees.<sup>140</sup> Fees and increased commercial clinical trial activity could help induce countries to participate and invest resources in the pathway. A long-term goal should be to increase the resources at the disposal of participating national authorities, rather than diverting them from other regulatory priorities.
9. *Link to existing structures and initiatives.* The regional regulatory pathway should be designed to evolve from existing regional regulatory networks or regional economic institutions that offer an existing political or legal framework for cooperation.<sup>141</sup> Creating a new freestanding institution to manage this regional regulatory pathway should not be necessary.
10. *Monitoring and evaluation.* The design of the regional mechanism for clinical trial review should identify metrics for monitoring and evaluating its performance and the quality of its

decision-making. Such monitoring and evaluation are needed to improve the outcomes of the regional mechanism, to increase the capabilities of its constituent regulatory authorities and ethics committees, and to sustain donor and sponsor participation.

## Requirements and options for a regional clinical trial review mechanism

The baseline requirements of any successful regulatory cooperation are sufficient political will and bureaucratic buy-in on the legitimacy of the exercise. Particularly given that participation in this particular review mechanism would likely be voluntary, there must also be willingness of private actors—donors and potential applicants—to participate and support the regional pathway.

Beyond these baseline requirements, the Working Group identified several other minimum requirements for a successful regional review mechanism:

- A designated and responsible point of contact at each of the participating NRAs.
- A secretariat, even if modest and rudimentary, to ensure predictable and consistent functioning of any cooperative regulatory effort.
- A framework agreement that outlines the basic procedures, requirements, product eligibility, and scope of cooperation.
- Common requirements for dossiers and submissions.
- Agreed-upon standards for approving a clinical trial.
- Defined roles for participating ethics committees and regulatory authorities.
- A regional entity to host and help coordinate the initiative.
- Seed funding from donors.

## Designated point of contact

The need for a designated and responsible point of contact at each participating regulatory authority for successful functioning of a regional mechanism is self-evident. The availability of such personnel is another matter. Many potentially participating national regulatory authorities have limited personnel or expertise to devote to a regional regulatory process. Clinical trial regulation is just one of many responsibilities for staff. Some NRAs largely outsource this process to outside committees of experts. Given these circumstances, seed donor funding may be required to fund the personnel necessary to participate in the regional mechanism until it can generate sufficient fees to become more self-supporting.

## Secretariat

The secretariat, even if modest and rudimentary, is necessary to ensure predictable and consistent functioning of any cooperative regulatory effort. It could operate as part of a host organization or under its own legal personality, allowing it to receive and hold funds, hire staff and enter into contractual arrangements. The secretariat could include an oversight board, including representatives from each participating country government, community representatives, and donors. It could also include regional committees comprised of representatives of participating regulatory authorities and national ethics committees. Finally, the secretariat should include a director and small handful of staff hired and overseen by the oversight board.

## Framework agreement

Bilateral and plurilateral regulatory cooperation agreements are not a new idea or untested proposition.<sup>142</sup> The approach of an international agreement on deep substantive engagement on a few matters, which can then be expanded and increasingly legalized over time, has precedents in regional economic cooperation, regional trade agreements, and plurilateral approaches to agricultural and environmental standard setting.<sup>143</sup> The basic framework agreement should include the objectives, definitions, and scope of cooperation; the identity, responsibilities, and rights of states parties; product and applicant eligibility; a process for adopting of common standards and documentation; protection of confidential data; the creation of any intermediary advisory or management structure; funding; and provisions for entry into force, withdrawal, termination, amendment, and dispute resolution. The agreement need not be a formal treaty; it can be a memorandum of understanding between participating states, NRAs, and ethics committees with attachments describing the parameters and details of its terms.<sup>144</sup>

The framework agreement should provide a mechanism for the secretariat and committees to develop guidance, template laws, and standards in other relevant areas (such as good manufacturing practices for investigation products, clinical trial registration, and access to post-treatment benefits) as experience, capabilities, and trust among participating countries increases. The procedure could provide for board endorsement of these procedures before forwarding to the participating countries and ethics committee for a decision on their adoption.

## Basic procedures

There are many options here. A sponsor of a proposed multinational trial of an eligible vaccine could, at its option, file a clinical trial application with the secretariat (as in the EMA VHP) or directly to participating agencies (as in AVAREF). The regional committees of NRAs and ethics committee representatives would conduct the review. The full committees could participate in their respective reviews and joint inspections (as in AVAREF), or regulators with weaker capacities could be paired with regulators with stronger expertise and resources to act as rapporteurs for the committees (as in the EMA centralized procedure). Given the capacity building objectives in this context, it may be advisable to begin with full committee reviews. The framework agreement can provide for the development of alternative review procedures in the future. The secretariat, on its own or at the request of the committees, could seek assistance from the list of external regulatory experts that the WHO maintains for use by its developing country members.

The committees (or rapporteurs) can prepare an assessment report and joint recommendation, upon which the participating NRAs and ethics committees may act. In the case of a recommendation for regulatory approval, participating NRAs could be required or asked to decide within a defined period whether to adopt that recommendation (as in the EU VHP). NRAs that depart from the recommendation could be required or asked to provide a written opinion on the reasons for the departure, as in the EU VHP, to provide transparency and a basis on which to evaluate decision-making in the pathway. For the ethics review, the regional committee of national ethics committee representatives could review the master protocol and forward the application to local ethics committees to assess potential local concerns. Figure 4.1 depicts how a mechanism for regional clinical trial review could operate.

Similar procedures could be adopted for the review of substantial protocol amendments. The framework agreement could create a mechanism for compiling safety reports from sponsors on ongoing trials so that safety information is available to the committees as they monitor the progress of studies and evaluate protocol amendments.

## Product eligibility

Our analysis of clinical trials registered on Clinicaltrials.gov suggests there is a strong regional orientation to those multi-country trials for neglected-disease products. The majority of the products in development for neglected diseases are vaccines. Vaccines for

neglected diseases present particularly difficult regulatory and ethics challenges to national regulatory authorities and ethics committees, which would benefit from the pooled regulatory resources of this regional pathway. The framework agreement should provide a procedure for the parties to expand the scope of eligible products, should they agree to do so.

## Scope

The framework agreement could be designed in a number of ways to achieve its aims. The agreement could, from the outset, provide that participants will cooperate on ethical review and clinical research and the full range of relevant regulatory functions—joint reviews of clinical trial applications, protocols, and amendments; joint inspections and monitoring of clinical trial sites; and a joint non-binding opinion on approval of multi-country trials. Alternatively, the framework agreement could begin with cooperation on a subset of activities such as joint reviews of applications and amendments and include a provision for cooperation on the remaining functions upon the achievement of defined milestones (duration of cooperation or number of reviews).

## Common dossiers

Dossiers for regulatory review could build on the application template that the WHO developed for AVAREF. Requirements for submissions for review by ethics committees could incorporate elements from ICH-GCP guidance on informed consent and ethics review.

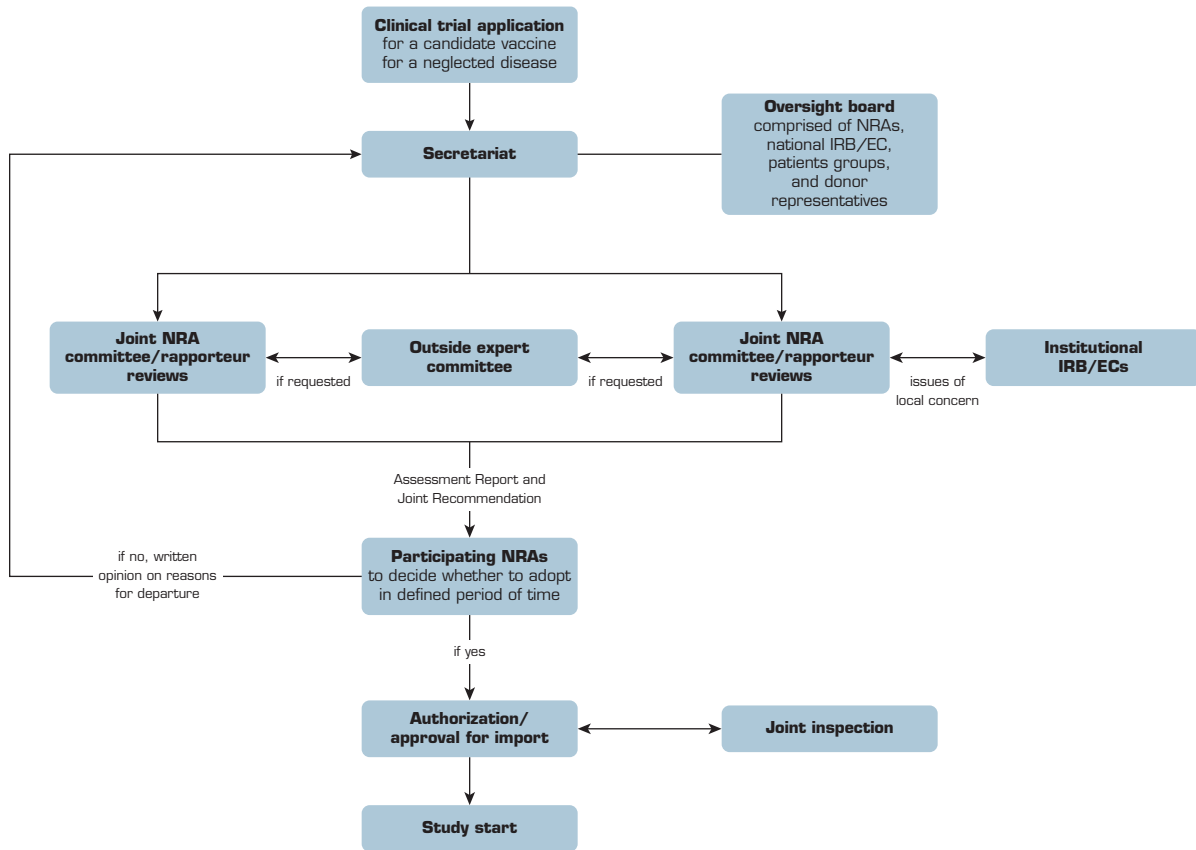
## Common standards for regulatory and ethical approvals

Standards for regulatory approval of clinical trials should ensure that trials do not present an unreasonable risk to study subjects and that the anticipated therapeutic or public health benefits of proposed trials justify any risks, while standards for ethics review should protect the rights of subjects and ensure that informed voluntary consent is obtained. These standards must be compatible with the applicable international standards.

## Distinct roles for NRAs and ethics committees

The roles for regulators and ethics committees in clinical trial authorization are distinct—the former focus on preclinical and clinical safety, protocol design, investigator and site capabilities, and drug

**Figure 4.1**  
**Potential pathway for regional, integrated regulatory and ethics oversight of clinical trials**



quality; and the latter on informed consent, risk-benefit assessment, and protection of the rights of human subjects in accord with local and international standards. Regional clinical trial oversight may achieve those objectives by defining the roles of participating regulatory authorities and ethics committees and promoting their coordination by including members of the ethics committees in joint site inspections and as observers in joint regulatory reviews.

### Potential parties

There is a strong case that African regulators and ethics committees would benefit the most from a regional mechanism for regulatory and ethical review for neglected-disease interventional trials. Our

analysis of clinical trials registered on Clinicaltrials.gov reveals that a disproportionate number of neglected-disease trials are in Africa. Similarly, Africa is the region with most limited clinical research and regulatory capacity.

### Host

The creation of a new freestanding institution to host the regional regulatory pathway should not be necessary. Factors in choosing a host institution should include its credibility with participating NRAs, IRB/ECs, and clinical trial sponsors; its accountability to participating governments and clinical trial subjects; its ability to attract financial support and technical assistance from donors,

developed country NRAs, and intergovernmental institutions; its administrative capacity and experience in coordinating regional regulatory initiatives; and its independence from the clinical trial sponsors and product developers.

The precedents that the Working Group reviewed on regional regulatory cooperation suggest two conclusions. First, the WHO's convening power, technical support, and credibility with low- and middle-income country NRAs and ethics committees have been critical in launching the existing regional approaches to clinical trial regulation. Second, regulatory cooperation is most likely to succeed when it is operates within a political and legal framework, such as a regional economic community.<sup>145</sup> An approach that combines these contributions would be the most promising.

## Funding

Startup funding would be required to finalize the framework agreement, generate a common dossier and standards for approving a

clinical trial, establish a secretariat to coordinate the process, and support participation by NRAs and national IRB/ECs that otherwise lack the resources to do so. The costs need not be extensive.<sup>146</sup> This funding could come from philanthropic sources, development banks, and governments concerned with global health and economic development.

The window of opportunity for donor support is narrow. The attention span of donors is short, and the precedent for aid for regulatory capacity building in developing countries is limited. The prospects for obtaining the necessary support and technical assistance from global health donors will be much enhanced if this funding needed is modest and short in duration and its returns are relatively certain. Accordingly, the framework agreement should provide for a process for generating and sharing clinical trial application fees. It should also provide for modest contributions from the better resourced participating governments to support its function.





## Chapter 5

# Better, faster, cheaper clinical trials

Neglected-disease product developers have conducted successful late-stage clinical trials of candidate technologies in low-income settings at relatively modest cost.<sup>147</sup> It can be done. Budgets for global health are tightening, however. New donor funding for product development is scarce. Streamlined and more efficient regulatory pathways alone will not achieve the cost- and time-savings required to sustain clinical development of the lifesaving neglected-disease therapies. Better, faster, and cheaper clinical trials are needed.

### The obstacles

Three obstacles must be overcome to improve the design and planning of clinical trials for neglected-disease interventions.

First, clinical trial design and practice are, as a general matter, precedent-driven. Sponsors and investigators design studies to look like the studies that regulators and ethics committees have approved before. Regulators and investigators approve studies that resemble the studies that have succeeded in the past. This inflexible, precedent-driven approach to clinical trial practice and regulation contributes to the skyrocketing costs, increasing duration, and growing complexity of clinical trials generally, but presents a particular problem in the neglected-disease context.

There is little useful, relevant precedent on clinical trial practice to draw from in many low-income countries. Few have conducted interventional clinical trials for regulatory approval in these resource- and infrastructure-poor environments. Developed country regulatory models and commercial clinical development practices are often imported into developing countries. While the high costs and inefficiencies of clinical trial data monitoring and record keeping are lamentable in developed countries, there is clinical research and regulatory infrastructure to support it, and consumers have so far been willing and able to absorb the cost. This is not the case in the neglected-disease context. Clinical development of neglected-disease technologies is a highly cost-sensitive endeavor. The clinical research and regulatory capacity in many neglected disease–endemic countries is rudimentary.

Approximating rich-country clinical development models under these conditions is not tenable.

Second, clinical trials of neglected-disease interventions often include secondary outcomes beyond what is needed for product approval. There may be no funding for conducting research on neglected diseases and their patient populations other than interventional clinical trials. Pivotal phase III clinical trials are often used to address the policy interests of donors and the WHO.

Secondary trial outcomes are justified in many cases, but increase the complexity of study protocols and case report forms (CRFs). More complex protocols are more difficult for investigators to understand, which in turn can lead to poor data collection and quality, a particular problem for investigators with limited experience.<sup>148</sup> Trial monitoring costs rise with the length and complexity of the CRFs used to collect patient data.<sup>149</sup> Complex study protocols and CRFs increase the likelihood of protocol amendments. When substantial, protocol amendments require regulatory and ethics committee approval, revised documentation, and investigator training and monitoring. Particularly in settings where local regulatory authorities and ethics committees do not have the capacity to process such amendments in a timely manner, substantial costs and months of delay can be added to an ongoing trial.

Third, the limited expertise and experience of NRAs, ethics committees, and investigators in many neglected disease–endemic countries hinders the adoption of the newest and emerging approaches to reducing clinical trial costs and delays. For example, it will be difficult in these circumstances to implement adaptive clinical trial designs, which can improve the flexibility and efficiency of clinical trials by allowing the modification of their design and statistical procedures while the trial is ongoing, based on the data accrued.<sup>150</sup> Pooling regional ethics and regulatory capacity would help address this issue, but will be insufficient if not paired with the support of more experienced external regulators and increased collaboration among trial sponsors, investigators, and regulators.

## Building quality into trial planning, design, and initiation

Clinical trial design and procedures must reflect the scientific and policy goals of the trial and be tailored to the setting, subjects, and intervention. Quality and cost-efficiency must be built into pre-trial planning and design. Doing so requires a focus on the key parameters and objectives of the trial, evidence-driven approaches, and engagement by trial sponsors, investigators, and regulators.<sup>151</sup> In this manner, the Working Group's first set of recommendations—pairing pooled regional regulatory capacity with more easily accessible external experienced regulator input—establishes the necessary foundation for its second set of recommendations—building quality and cost-efficiency into pre-trial planning and design. In particular, the Working Group recommends the following approaches.

### Simpler trials for licensure, more support for policy research in phase IV studies

Policy and epidemiological research is essential to advance our understanding of neglected diseases and the populations who suffer from them. Such research is also necessary to support the WHO recommendations on a product's use that the GAVI Alliance, UN agencies, and developing countries require before licensing and procuring the product. However, embedding research on policy objectives and neglected-disease epidemiology into pivotal phase III study of the safety and efficacy of a product is an expensive way to obtain this information. Phase III trials must be performed according to strict international standards to support licensure. There are a limited number of sites in neglected disease–endemic environments capable of conducting trials according to those rigorous international standards. Candidates often fail in phase III, rendering such policy research moot.

Focusing pivotal trials on the research necessary to support licensure would reduce costs, expedite product registration, and lower site and investigator demands. To succeed, however, simpler, phase III trials for licensure must be paired with increased donor funding for the phase IV observational studies necessary to support WHO policy recommendations on its use and improve our understanding of neglected diseases and the populations they affect.

### Early investigator input and independent advisory committees

Local investigator and independent stakeholder input should be solicited early in the study design. This can be done by involving

investigators from proposed sites and experts with relevant developing country–trial experience in the review of proposed protocols to spot potential problems upfront and help keep the studies simple, feasible, and focused. Involving local investigators in trial design and operations has the additional benefit of improving the investigator's understanding and investment in the trial, training, and long-term career development.

There are precedents for such an approach. For instance, the Drugs for Neglected Diseases initiative (DNDi), a PDP, employs “platforms for clinical research.”<sup>152</sup> These are networks of investigators and stakeholders with a mixture of expertise around a specific disease that help DNDi determine program needs, target product profiles, and trial designs. DNDi also uses these platforms for investigator training and peer-to-peer communication on best practices.

Many PDPs and donors also employ independent scientific advisory boards to assist in developing target product profiles and clinical trial design. These committees are not typically charged with advising on the efficiency of clinical trial design or staffed with the necessary expertise to do so, but there is no reason this cannot occur in the future. When experienced in resource-poor settings and priced appropriately, CROs and clinical trial budgeting companies can also play a useful role.

### Pressure-testing protocols

Researchers, trial sponsors, and donors spend significant time negotiating the design of the trial and its protocol, and, on reaching agreement, they are understandably anxious to initiate the trial. Too little field-testing occurs to ensure that protocols are efficient and feasible for the setting in which they will be implemented.

It is common practice for many multinational pharmaceutical companies to pressure test protocols by performing them with dummy subjects and study products prior to initiating enrollment. This approach increases upfront expenses, but reduces overall trial costs by improving the efficiency of trial design and helping to avoid protocol amendments. A similar approach should be adopted in neglected-disease product development.

### Early engagement with regulators and ethics committees to streamline trial initiation

Designing and initiating a multi-center phase III study of the safety and efficacy of a drug or vaccine requires the cooperation

and coordination of the many participants responsible for scientific review, data management, safety/ethics review, regulation, contracting and grants, and the performance of the study. Process mapping research in the other contexts has demonstrated that significant time and resources are wasted waiting for the responses from the other participants that could be obtained through direct engagement.<sup>153</sup> The resulting delays in trial initiation can span years and hinder patient enrollment, increase costs, and reduce the likelihood of the trial's success.<sup>154</sup>

Similar process mapping research would be enormously useful in the global health technology context. In the interim, the regional mechanism for regulatory and ethical review should be designed in a manner that permits opportunities for direct engagement with trial sponsors in order to reduce delays in trial initiation. Other methods of reducing the time required for trial initiation, such as standardizing site contracts, are producing results for other clinical trial networks and warrant consideration in neglected-disease product development.<sup>155</sup>

### Clinical trial monitoring

Clinical trial monitoring costs can often account for one-third to two-thirds of the costs of a clinical trial. As part of its efforts, the Working Group performed extensive consultations on the applicability and potential utility in the neglected-disease context of electronic data capture (EDC) and statistical sampling techniques, used increasingly in commercial trials to reduce data monitoring costs. The feedback and evidence are compelling.

Using EDC instead of paper CRFs is often cited as the single most effective step that a sponsor can take to reduce the cost and duration of a clinical trial. EDC allows for real-time access to data, reduces the need for on-site monitoring, and limits data errors,

cleaning time, and processing costs.<sup>156</sup> A recent study of a phase III trials conducted between 2006 and 2008 demonstrated a median reduction of over 300 days in the time required for subject management.<sup>157</sup> Another recent analysis by Duke University and Oxford University, modeling the potential economic savings of various clinical trial practices, found EDC to result in a 10-percent reduction in clinical trial costs.<sup>158</sup> EDC also improves the quality and speed of data collection and monitoring by improving the visibility of safety issues and limiting the acceptable range of data fields, which helps investigators quickly identify data entry errors and reduces the need for subsequent data cleaning.

EDC is already available and increasingly used in neglected disease–endemic settings with good clinical research infrastructure and resources (such as South Africa, Uganda, and parts of India and Latin America). The challenge in the most resource-poor settings is spotty Internet access, unreliable electricity, the cost of EDC equipment, and the variation in EDC programs that commercial sponsors use. Workarounds are possible, however.<sup>159</sup> Some sponsors have successfully implemented satellite-based systems in rural and resource-poor settings in Africa at modest cost. Laptops and wireless modems have succeeded in settings where electrical supply is unreliable. Given the small number of donors in neglected-disease product development, EDC appears to be an obvious candidate for bulk purchasing and infrastructure investment.

The Working Group also found compelling evidence on the benefits of central statistical sampling as a means of reducing the cost and burden of data verification and site monitoring.<sup>160</sup> Commercial pharmaceutical companies apparently already use such practices in developed country settings. Improved collaboration with regulators would help ensure the acceptability of this approach.



## Chapter 6

# Toward implementation

Recommendations in this report can be implemented independently or simultaneously—they are mutually reinforcing. Pooling regulatory and ethics review capacity regionally improves the capabilities of regulators with which neglected-disease product sponsors and investigators must work to ensure trials are efficient, well adapted to the local circumstances, and protective of local subjects. The possibility of conducting better, faster, and cheaper clinical trials in a country or region, in turn, encourages sponsors to conduct more clinical research there, generating the fees and experience necessary to improve the capabilities of local regulators and IRB/ECs.

Realizing these complementary strategies will require collaboration and investment from all key stakeholders. These contributions must include:

- *From host national regulatory authorities, IRB/ECs, and their governments:* a political commitment to engage in regional regulatory cooperation, including, where possible, a contribution of funding and personnel; an agreement to a common application and framework agreement that outlines the regional clinical trial application process, requirements, and assurances of protection for confidential data; a fee-sharing arrangement with other participating NRAs; a willingness to engage external expertise, when needed; and a willingness to work with trial sponsors, as appropriate, to build quality and efficiency into clinical trial planning and design.
- *From trial sponsors:* participation in the regional regulatory and ethics review pathway and full compliance with its terms; an agreement to allow regulators to share confidential data; payment of additional fees to use the regional pathway; and investment of upfront resources to improve the overall efficiency and quality of clinical trials.
- *From donors:* making high-quality regulatory and ethics review of clinical trials in low- and middle-income countries a priority for global health and economic development; requiring product development grantees to use that pathway; seed funding

to launch regional regulatory cooperation and to support the participation of low-income country regulators; and supporting independent clinical trial planning advisory boards, EDC monitoring equipment and platforms, and other infrastructure investments that can improve the quality and efficiency of neglected-disease clinical research across technologies and product development sponsors.

- *From developed country regulators and international technical agencies:* sustained investment in technical assistance and diplomatic support for regional approaches to improve regulatory and ethics oversight in low- and middle-income countries and facilitate neglected-disease product development.

The prospects for generating these contributions from stakeholders are improved by two factors: the globalization of clinical research, and existing regulatory initiatives and funding platforms on which stakeholders may build.

## Globalization of clinical research

The motivations for stakeholders to invest in regional regulatory cooperation and more efficient clinical trial practices extend beyond neglected diseases and global health.

Substantial and increasing private industry investment is devoted to conducting biopharmaceutical clinical trials in developing countries. China, Argentina, Russia, and India are the fastest growing countries in terms of clinical trial activity, but such activity is increasing in other low- and middle-income countries as well.<sup>161</sup> This investment is motivated by the spiraling costs of clinical trials and the difficulty of recruiting large numbers of treatment-naïve people in developed countries as well as firms' strategic interest in establishing "footholds" in emerging markets.<sup>162</sup> Conducting clinical trials in low- and middle-income countries can often reduce trial costs by more than 50 percent and increase the speed of patient enrollment several-fold.<sup>163</sup>

Many developing countries have exhibited corresponding interest in attracting such clinical trial activity. As an important and

growing source of foreign revenue, clinical trial activity represents hundreds of millions of dollars of investment in some low- and middle-income countries.<sup>164</sup> There are potential spillover benefits to clinical research as well: diffusion of medical knowledge and effective medical practice; increased resources and training for hospitals, medical schools, and regional research centers; long-term development of domestic life sciences industries; and greater patient access to high-quality medical care.<sup>165</sup> Accordingly, low- and middle-income country governments view clinical trial activity as not only promoting the development of new medicines to address local needs but also as spurring local job creation and economic development.<sup>166</sup>

As a result, there is a growing trend of low- and middle-income countries investing in clinical trial site capacity, GCP training programs, and streamlining regulatory requirements as a matter of industrial policy. In 2008 the Indian government invested in IRB/EC training and simplified regulatory procedures for the import of study materials as part of a larger effort to attract more clinical trial activity.<sup>167</sup> In 2004 China passed new regulations to streamline regulatory requirements, impose GCP standards, and introduce compulsory GCP training.<sup>168</sup> Argentina and Brazil have likewise invested in clinical trial site capacity and streamlined regulatory requirements to attract more foreign trials. These trends are not only prevalent in the large emerging economies; there are reports of Panama, Peru, and Rwanda building clinical trial sites to host vaccine and drug trials as well.

In this context, investments in improving clinical research and regulatory capacity and efficiency in neglected disease–endemic countries must be seen not just as matters of global health, but as legitimate goals for economic development and increasing indigenous innovative capacity. This is a sea change that presents opportunities for tapping new sources of investment from industry, local governments, and international bilateral and multilateral donors that fund economic development projects.

Like other regulators, however, the FDA and EMA have limited capacity, mandates, and opportunities to monitor the conduct and quality of clinical research and ensure the safety of subjects in foreign jurisdictions. In fiscal year 2008, for example, 80 percent of the applications for drugs and biologics approved by the FDA used data from overseas clinical trials, but the FDA inspected fewer than 1 percent of the foreign sites involved.<sup>169</sup> Without an IND, a sponsor is not required to notify the FDA of an overseas clinical

trial, and FDA may be completely unaware of the existence of that trial until the sponsor applies for licensure. Accordingly, the EMA and FDA have expressed interest in supporting more information sharing, capacity building, and a robust international framework for the oversight of international clinical trials.<sup>170</sup> This interest creates potential opportunities to tap the technical support and resources that these agencies can mobilize to improve the regulatory and ethical review capacity of priority countries for global health technology development.<sup>171</sup>

### Existing initiatives

Regional efforts on clinical trials and medicines regulation in low- and middle-income countries already exist and should be leveraged in support of neglected-disease product development. AVAREF and related WHO efforts in the Developing Country Vaccine Regulatory Network, Association of Southeast Asian Nations, and the Pan-American Health Organization have all launched programs on clinical trial regulation. Numerous regional economic communities in Africa are pursuing the harmonization of drug registration as part of the African Medicines Regulatory Harmonization (AMRH) initiative and have clinical trial regulation on their future agendas.<sup>172</sup> The World Bank has established a trust fund, financed with a start-up investment of \$12.5 million from the Bill & Melinda Gates Foundation, to support these efforts.<sup>173</sup> The analysis and recommendations provided by this Working Group provide practical and scalable ways to adapt and coordinate these WHO and AMRH efforts to address the challenges and opportunities presented by the neglected-disease product pipeline: an influx of large complex trials over the next 5–10 years, and substantial donor interest in the success and adequate oversight of those trials. The World Bank trust fund is a potential platform from which to finance these efforts.

There are also numerous new initiatives researching innovative approaches to improve the efficiency of clinical development without reducing its rigor and protection for subjects. In 2007 the FDA launched a public-private partnership with Duke University as the convener—the Clinical Trials Transformation Initiative (CTTI)—with the goal of identifying clinical trial practices which through broad adoption will increase the quality and efficiency of clinical trials.<sup>174</sup> Clinical research groups from Duke, McMaster, and Oxford Universities have initiated the Sensible Guidelines for the Conduct of Clinical Trials Project to advocate for the simple design

of large-scale trials in order to reduce costs and improve patient participation.<sup>175</sup> The research from these and other initiatives has not yet focused on trials in resource-poor developing country settings, but may have some applicability or be adaptable for these settings. These initiatives are potential partners in improving the efficiency

and quality of neglected-disease clinical trials. The concerns that these clinical research initiatives seek to address—rising costs and decreasing productivity—are most urgent in the neglected-disease context, where there is inadequate funding and infrastructure to support such inefficiency.

# Looking ahead

The regulatory and financing challenges involved with developing and delivering innovative neglected-disease drugs and vaccines to the patients who need them will not end with clinical development. Before a drug or vaccine may be marketed or distributed, the appropriate regulatory authority for that jurisdiction must confirm the safety, quality, and efficacy of that product. Adequate post-market surveillance is required to ensure the safety and effectiveness of the novel drugs and vaccines that millions of children and adults in developing countries may soon receive for malaria, TB, dengue fever, and other neglected diseases.

Many low-income country NRAs have limited experience, resources, and mandates for assessing, approving, and registering innovative products. Few low- and middle-income countries have functional post-market safety systems, and most do not yet report adverse events. The WHO and established NRAs can support but not replace the local regulatory oversight required for products launched simultaneously in developing countries or intended for their exclusive use. Consequences of these regulatory shortcomings for the success of expanded treatment and immunization efforts

can be significant. After a long and costly development process, substantial delays in registration and products reaching market are an obvious deterrent to drug and vaccine development. Without timely and accurate safety information, poor quality products can unnecessarily harm patients. Real or rumored adverse events can undermine public confidence and cause lasting damage to treatment and immunization programs.

The regional regulatory platforms and cooperation strategies recommended in this report could be expanded over time to support and build capacity for other critical regulatory functions in low- and middle-income countries as well. Regional cooperation that achieves more certain review times and reduces regulatory inconsistencies in clinical trial oversight could achieve similar objectives for product registration. A regional approach that pools scarce country regulatory resources and provides a sustainable platform for clinical trial oversight capacity building could do the same for post-market drug and vaccine surveillance. These compound benefits of regional platforms for regulatory cooperation provide further compelling justification for stakeholder investment.



# Appendixes

## Appendix A

# Working Group members

### **Vincent Ahonkhai**, Bill & Melinda Gates Foundation

Vincent Ahonkhai is the Senior Regulatory Officer at the Bill & Melinda Gates Foundation. He recently retired as Vice President of Regulatory Affairs at GlaxoSmithKline, where he specialized in clinical safety, managed the pharmacovigilance department, and gave a physician's perspective for pharmaceutical development. Ahonkhai has also held senior positions at Merck and R.W. Johnson Pharmaceutical Research Institute. His areas of expertise include both U.S. and global drug development, and he has overseen a product development portfolio that includes antibiotics, antivirals, and vaccines. A pediatrician by training, Ahonkhai is a long-standing member and fellow of several professional organizations including the American Medical Association, National Medical Association, American Society for Microbiology, Infectious Diseases Society of America, Pediatric Infectious Diseases Society, and American Academy of Pharmaceutical Physicians. After completing medical school and internships in Nigeria, he obtained additional training in pediatric residency followed by a fellowship in infectious diseases at the State University of New York–Downstate Medical Center.

### **Ernst Berndt**, MIT Sloan School of Management

Ernst Berndt is the Louis E. Seley Professor in Applied Economics at the MIT School of Management. His research examines how medical innovations have affected the cost of disease treatment, factors affecting the globalization of clinical trials, incentives to induce research and development into third world clinical diseases, how industry funding of the U.S. Food and Drug Administration through user fees has affected review times and safety withdrawal rates, and the impact of direct-to-consumer marketing of prescription pharmaceuticals on drug utilization. In addition, Berndt is director of the Biomedical Enterprise Program, a joint program of MIT Sloan and the Harvard-MIT Division of Health Sciences and Technology. He also serves as director of the National Bureau of Economic Research Program on Technological Progress and Productivity Measurement. He is a prolific and highly cited researcher

in the fields of industrial organization, applied microeconomics and health economics, as he was named the “Most Cited Economist under 40” in 1985. Berndt received his Ph.D. from University of Wisconsin-Madison and his B.A. from Valparaiso University, where he is a distinguished alumnus.

### **Fred Binka**, INDEPTH Malaria Clinical Trials Alliance

Fred Binka serves as the Executive Director of the INDEPTH Network, a population and health NGO in Ghana, and is an Associate Professor of Epidemiology for the School of Public Health at the University of Ghana. His research topics include strengthening research capacity in the public health sector, malaria epidemiology, and malaria intervention treatments. He also has worked as a medical officer for the World Health Organization, for the Liberty Medical Centre in Nigeria, and for the Ministry of Health in Ghana. He has served on several committees, such as PATH Canada, the African Medical Research Foundation, the Global Alliance for Vaccines and Immunisation, and the World Health Organization. In 2001 Binka was the first recipient of the Rudolf Geigy Award, recognizing his “outstanding contributions to Malaria control and health development in Africa.” He received his Ph.D. in Epidemiology from the University of Basel in Switzerland, his M.P.H. from the Hebrew University in Jerusalem, and his M.D. from the University of Ghana.

### **Thomas Bollyky**, Center for Global Development (Chair)

Thomas J. Bollyky is a research fellow at the Center for Global Development (CGD), where his research focuses on legal and regulatory issues in global health, technological innovation and delivery, and international trade. He is also an Adjunct Professor of Law at Georgetown University and serves on the Institute of Medicine's committee on strengthening regulatory systems in developing countries. Prior to coming to CGD, Bollyky was Director of Intellectual Property and Pharmaceutical Policy at the Office of the United States Trade Representative, a Fulbright Scholar to

South Africa, where he worked as a staff attorney at the AIDS Law Project, and a senior attorney at Debevoise & Plimpton LLP. He is a former law clerk to Chief Judge Edward R. Korman and an International Affairs Fellow at the Council on Foreign Relations. Bollyky received his B.A. in Biology and History at Columbia University and his J.D. at Stanford Law School, where he was the President of the Stanford Law & Policy Review. He is a member of the New York and U.S. Supreme Court bars and the American Society of International Law.

**Michael Brennan**, AERAS Global TB Vaccine Foundation

Michael Brennan is the Senior Advisor for Global Affairs at the AERAS Foundation. He develops strategies for the timely introduction of new TB vaccines into low-income countries, and he works closely with national regulatory authorities that are responsible for clinical trial approval and new product licensure. Brennan also heads projects on the development of correlates and biomarkers for TB vaccines. Prior to joining AERAS, he spent more than 20 years at the U.S. Food and Drug Administration, where he was an associate director at the Office of Vaccines Research and Review, and was head of the TB vaccine program. In 2001 he worked in Geneva assisting the WHO in its development of a new Tuberculosis Vaccine Initiative. Brennan has published more than 90 scientific articles on vaccines and infectious diseases, and his early research paved the way for widespread whooping cough immunizations. An authority on vaccine development and regulatory review, he sits on several international advisory committees, including the Stop TB Partnership, the WHO, and the U.S. National Institutes of Health. He received a Ph.D. from Albany Medical College.

**Richard Chin**, Institute for OneWorld Health

Richard Chin is the Chief Executive Officer of OneWorld Health and a physician with extensive expertise in drug development, having overseen more than 45 Investigational New Drug (IND) Applications and multiple drug approvals worldwide. He has also authored several textbooks on clinical trial medicine. Previously, he was CEO of OXiGENE and Senior Vice President and Head of Global Development for Elan Corporation. He has also held various clinical and scientific roles for Genentech, including Head of Clinical Research for the Biotherapeutics Unit. Chin was named by *Businessweek* in 2006 as one of the youngest 99 public company CEOs in the United States. He is an Associate Professor

at the UCSF School of Medicine and currently serves on the Boards of Directors at RXi Pharmaceuticals and Genmedica Therapeutics. Chin holds an M.D. from Harvard Medical School and the equivalent of a J.D. from Oxford University, where he studied under a Rhodes scholarship.

**Liliana Chocarro**, LC Plus Consulting

Liliana Chocarro worked for the National Control Laboratory in Argentina for 15 years, where she was the Head of Viral Vaccines from 1982 to 1989. She moved to Canada in 1990 and worked as a consultant to industry, NGOs, and WHO since 1996. Chocarro worked at WHO headquarters in Geneva from 2004 to 2010 where she was responsible for Regulatory Pathways at the Vaccines Department. She has worked to strengthen the regulatory authorities in developing countries, improve the training of health regulators, and increase coordination between bodies relevant to policy decisions regarding vaccines. Among other activities, Chocarro established and was the Secretariat of the Development Country Vaccines Regulators' Network and African Vaccine Regulatory Forum. In October 2010 she returned to Canada and her consulting business—LC Plus Consulting—where she focuses on regulatory pathways for the evaluation of medicinal products from clinical development to post-marketing stage development of training programs, and providing technical support to WHO, Health Canada, and various NGOs. Chocarro received her Ph.D. in Executive Management from Bircham International University and her bachelor's degree in Biochemistry from the University of Buenos Aires.

**Ralf Clemens**, Novartis

Ralf Clemens is the Head of Vaccines Development for Novartis Vaccines and Diagnostics, where he is responsible for clinical research and development, pharmacovigilance, regulatory activities, and program management. Previously, he was Vice President and Director of Pharmaceuticals and Vaccines at GlaxoSmithKline's Latin America and Caribbean offices and Head Vaccines Clinical R&D at GSK Biologicals in Belgium. He is a trained physician, with specialization in the fields of anesthesiology, intensive care medicine and tropical diseases. Since 1995, Clemens has been a visiting professor and advisor in Clinical Tropical Medicine to the Faculty of Tropical Medicine at Mahidol University in Bangkok, Thailand. He also was a member of the Advisory Board of the UN International Vaccine Institute in Seoul, Korea, and he is a member

of various scientific societies. Clemens received his medical and academic degrees from the Johannes-Gutenberg University in Mainz, Germany. He is also a graduate of the Advanced Management Program for Senior Executives at the Wharton Business School.

**Iain M. Cockburn**, Boston University, School of Management

Iain Cockburn is a Professor of Finance and Economics at Boston University's School of Management and a consultant at Analysis Group. An industrial organization economist and econometrician, he specializes in the pharmaceutical, biotechnology, and healthcare industries. His research interests include the economics of innovation, intellectual property, pharmacoeconomics, productivity measurement, competitive strategy, and applied econometrics. Cockburn is a Research Associate at the National Bureau of Economic Research in Cambridge, Massachusetts, a former Associate Editor of *Management Science*, and a Coeditor of the *Journal of Economics and Management Strategy*. His research in economics and management is published widely in leading journals including the *Strategic Management Journal*, *American Economic Review*, *RAND Journal of Economics*, *Health Affairs*, and the *Journal of Industrial Economics*. Cockburn received his Ph.D. in Economics from Harvard University and a B.Sc. from the University of London.

**David Dilts**, Knight Cancer Institute and Oregon Health and Science University

David Dilts is Director of Clinical Research for the Knight Cancer Institute and Professor of Healthcare Management at the Oregon Health and Science University. Formerly, he held the sole joint professorship between the Owen Graduate School of Management and the Vanderbilt University School of Engineering, where he was the founding director of the Engineering Management Program. Dilts was also co-director of the Center for Management Research in Healthcare, which exchanges knowledge between management research and healthcare to dramatically impact practice of medicine and streamline the clinical trials process. His work has been published in more than 160 articles, conference papers, presentations, and books, covering a wide range of topics from complexity in supply chain networks to delays in opening oncology clinical trials. Dilts is a frequent speaker at national and international conferences, most recently at the Institute of Medicine's meeting on the standards for developing surrogate biomarkers.

**Paul Huckle**, GlaxoSmithKline

Paul Huckle is Senior Vice President for Global Regulatory Affairs at GlaxoSmithKline (GSK). He is responsible for worldwide filing of new submissions and support for existing licenses for the GSK pharmaceutical portfolio. Huckle provides regulatory counsel to senior GSK leadership, oversees staff at all GSK development sites, and leads any regulatory action to resolve major project or product challenges and issues pertaining to regulatory compliance. Prior to entering the regulatory field, he worked for 10 years in pharmaceutical development, responsible for leading the development of prescription and OTC products for U.S. and non-U.S. markets. Huckle holds an Honors Degree in Pharmacy and Ph.D. in Pharmaceutics from the University of London, and is a Registered Pharmacist.

**John Hurvitz**, Covington & Burling LLP

John Hurvitz is a partner at Covington & Burling LLP, based in Washington, DC, who represents life sciences clients throughout the United States, Europe, and Asia. He co-chairs Covington's Life Sciences Industry Group and heads the firm's Technology Transactions Group. Previously he worked with the Center for Global Development on developing and implementing an incentive-based market mechanism to stimulate the commercialization of vaccines for unmet health needs such as HIV/AIDS, malaria, and tuberculosis. He represented the Global Alliance for Vaccines and Immunisation (GAVI Alliance) and the World Bank in connection with their development of a pilot program for Advanced Market Commitments. He has also represented international health organizations like the GAVI Alliance, the International AIDS Vaccine Initiative, the Global HIV Vaccine Enterprise, PATH, and the Center for Global Development. He received his J.D. from Yale University and his B.A. from Haverford College.

**Yuppadee Javroongrit**, Food and Drug Administration of Thailand\*

Yuppadee Javroongrit is the Assistant Director and Head of International Affairs of Thai FDA, where she has worked to improve the regulation of clinical trials and to harmonize Thailand's pharmaceutical industry with the Association of Southeast Asian Nations. Prior to her current post, she was a pivotal member of the Inspection Division of Thai FDA, where she combated the use of counterfeit drugs and strengthened Thailand's drug system policies for

the quality assurance of active pharmaceutical ingredients. Since 2000 she has participated in many regional and global forums on pharmaceutical regulation and presented at the National Seminar on Clinical Trials of Thailand. Javroongrit obtained her Ph.D. in Industrial Pharmacy at the Massachusetts College of Pharmacy and Health Sciences.

**Richard Kingham**, Covington & Burling LLP

Richard Kingham is a partner at Covington & Burling LLP, where he concentrates on food and drug law. He has acted for most of the major pharmaceutical manufacturers and biotechnology companies in the United States and Europe, as well as trade associations such as the Pharmaceutical Research and Manufacturers of America, the Consumer Healthcare Products Association, and the National Pharmaceutical Council. He has represented pharmaceutical manufacturers in administrative investigations, criminal prosecutions, and congressional hearings, advised in connection with state and federal enactments relating to liability and compensation for vaccine-related injuries, and represented research-based biotechnology companies on legal and policy issues relating to follow-on biological products. Kingham has served as a member of committees of the Institute of Medicine of the National Academy of Sciences, the National Institutes of Health, and the World Health Organization and has taught food and drug law at the University of Virginia and Georgetown University.

**Judith Kramer**, Clinical Trials Transformation Initiative & Duke University School of Medicine

Judith Kramer is an Associate Professor of Medicine at Duke and the Executive Director of an FDA-initiated public-private partnership, the Clinical Trials Transformation Initiative (CTTI), which seeks to identify practices that through broad adoption will improve the quality and efficiency of clinical trials. CTTI convenes experts in the field, undertakes projects to identify existing issues related to current practice, designs models for improvement, and develops recommendations to inform participants and policymakers involved in the clinical research enterprise. For 10 years she worked at Burroughs Wellcome Co., where she became Vice-President and Director of U.S. Clinical Research, responsible for antiviral, oncology, neurology/psychiatry, cardiovascular and pulmonary clinical research. From 1997 to 2006 Kramer was Chief Medical Officer at Duke Clinical Research Institute (DCRI), and in that role

provided guidance and consultation for the formation of DCRI's regulatory affairs and quality assurance functions. She is trained in clinical pharmacy, is board certified in general internal medicine, and received her M.S. in Pharmacy and M.D. from the University of North Carolina at Chapel Hill.

**Mark LaForce**, PATH

Mark LaForce directs the Meningitis Vaccine Project, a Bill & Melinda Gates Foundation-funded partnership between PATH and the World Health Organization aimed at eliminating the epidemic of meningitis from Sub-Saharan Africa through the development, licensure, and widespread use of conjugate meningococcal vaccines. Before joining PATH, he held academic and administrative positions at the University of Colorado and the University of Rochester schools of medicine. He also served on immunization advisory committees for the U.S. Centers for Disease Control and Prevention and for the American College of Physicians. From 1994 to 2001 LaForce led the Steering Committee on Epidemiology and Field Research for WHO's vaccine cluster. From 1998 to 2001 he was president of the Armed Forces Epidemiological Board. He has published more than 150 papers and book chapters on pulmonary defense mechanisms, clinical infectious diseases, epidemiology, and vaccinology. LaForce received his medical degree from Seton Hall College of Medicine and Dentistry and completed his internal medicine and infectious diseases training on the Harvard Service at Boston City Hospital.

**Orin Levine**, Johns Hopkins Bloomberg School of Public Health

Orin Levine is Executive Director of the International Vaccine Access Center (IVAC) at the Johns Hopkins Bloomberg School of Public Health, leading a team dedicated to accelerating access to lifesaving vaccines through evidence-based policies. He is also an Associate Professor in the Department of International Health at Johns Hopkins and serves as Co-chair of the Sabin Institute's Pneumococcal Awareness Council of Experts, a small group of global experts who advocate for investment in pneumonia prevention. Dr. Levine has frequently served as a consultant to the Global Alliance for Vaccines and Immunisation, to the World Health Organization, and to governments of individual countries on the prevention of pneumonia strains with vaccination. Prior to leading IVAC, he worked at both the Centers for Disease Control and Prevention and at the National Institutes of Health. An expert on pneumonia

and meningitis vaccines, Levine has authored or co-authored more than 75 research papers and book chapters. He earned his Ph.D. in Epidemiology from Johns Hopkins University and his bachelor's degree from Gettysburg College.

**Melinda Moree**, BIO Ventures for Global Health

Melinda Moree is Chief Executive Officer of BIO Ventures for Global Health. Previously, she was the Principal Investigator on the Malaria Policy Project conducted with the Center for Global Development, was a member of the team evaluating the International AIDS Vaccine Initiative, and consulted with the Global Alliance for Vaccines and Immunisation. Until early 2007 she was the Director of the Malaria Vaccine Initiative, a public-private partnership with the mission to accelerate the development and increase the availability of malaria vaccines in developing countries. She was also a manager of advanced research at EKOS Corporation and a researcher at University of Washington School of Medicine. She was awarded a fellowship from the American Association for the Advancement of Science and Diplomacy, which funded her work on public-private partnerships for the development of technologies and diagnostics for the developing world. Moree received her Ph.D. in Medical Microbiology from the University of Maryland at Baltimore.

**Margareth Ndomondo-Sigonda**, New Partnership for Africa's Development\*

Margareth Ndomondo-Sigonda is currently the Pharmaceutical Coordinator for the New Partnership for Africa's Development (NEPAD), where she has worked to enhance the regulatory capacity of the health sectors across Africa and to harmonize African pharmaceutical regulations. Her project, the African Medicines Regulatory Harmonization Initiative, is being implemented in collaboration with the African Union Commission, Pan African Parliament, and regional economic communities—with the partnership of the World Health Organization, the World Bank, and the Bill & Melinda Gates Foundation. Prior to joining NEPAD, she was the Director General of the Food and Drugs Authority for Tanzania, where she effected sizable progress in the initiative to harmonize pharmaceutical regulations and researched the impact of accredited drug dispensing outlet programs aimed at improving patient access to medicines. She has also served as a consultant on regional harmonization of medicines regulation across Africa and

in the Caribbean. She has participated in many prominent conferences and forums, including the Strategies for Enhancing Access to Medicines Conference and the International Conference on Local Pharmaceutical Production in Africa.

**John Purves**, Consultant

John Purves is a life sciences consultant, having recently retired from the European Medicines Agency (EMA), where he worked for 14 years as head of the Quality of Medicines Sector. He has been actively involved in Regulatory Marketing Authorizations for pharmaceutical products that deal with recombinant-DNA, Biosimilars, and Influenza. Prior to joining the EMA, he was manager of the biotechnology and biological unit, for 21 years, at the United Kingdom's Medicines and Healthcare Products Regulatory Agency, where he was involved with the drafting of both legislation and EU guidelines that dealt with the manufacturing and controlling of recombinant-DNA products and products derived from human plasma. He also oversaw efforts to minimize the risk of the transmission of the spongiform encephalopathy to humans. Purves graduated in pharmacy from the Heriot Watt University in Edinburgh in 1968 and received his doctorate in pharmaceutical microbiology from the University of Strathclyde in 1973. Following university, he worked in research and development at Smith and Nephew Limited in the United Kingdom.

**David Shoultz**, Bill & Melinda Gates Foundation

David Shoultz is the Deputy Director in the Global Health Program of the Bill & Melinda Gates Foundation, where he is responsible for strategic planning and management in the Infectious Diseases Division. In addition, he is an affiliate assistant professor at the University of Washington in the departments of Global Health and Epidemiology. Shoultz has more than 15 years of experience serving as a business development executive in product development companies, including Biomedical Systems, PRA International, and PPD Development. He has also served on the Advisory Board for the Biotechnology Laboratory Training program at Bates Technical College, the Board of Directors for Tacoma Goodwill, the Board of the Tacoma Goodwill Heritage Foundation, and the Advisory Board for the University of Washington's Extension Certificate Program in Basic Bioscience. In late 2010 he joined the Board of Directors of the Geneva Foundation and in 2011 he was asked to serve as the inaugural chair of its Scientific Advisory Committee.

Shoultz holds both M.S. and Ph.D. degrees from the University of Washington Department of Epidemiology, and will receive his M.B.A. from the Seattle University Albers School of Business & Economics in 2012.

**Wendy Taylor, U.S. Agency for International Development\***

Wendy Taylor serves as Senior Adviser on Innovative Finance and Public-Private Partnerships at the U.S. Agency for International Development, where she has helped launch the President's \$63 billion Global Health Initiative. Prior to her appointment, she was a Senior Vice President at Malaria No More and founded Bio Ventures for Global Health, a non-profit that has engaged the biopharmaceutical industry to develop medicines for diseases of the

developing world. Taylor served as Director of Regulatory Affairs and Bioethics for the Biotechnology Industry Organization, where she negotiated the third reauthorization of the Prescription Drug User Fee Act on behalf of the biotech industry and developed the organization's first global health program. She also has extensive experience in the executive and legislative branches of the U.S. government, including the Office of Management and Budget. Taylor received her M.P.P. from the Kennedy School of Government at Harvard University and B.A. from Duke University. She serves on the North American Board of Medicines for Malaria Ventures.

*\* Participated in the Working Group as an observer and does not endorse or reject any of the analysis or recommendations in this report.*

## Appendix B

# Individuals consulted

During the course of this project, many individuals offered comments, critiques, and suggestions. These individuals are listed below, but bear no responsibility for the content or recommendations of this report. We apologize for any omissions.

Vivek Ahuja, Baxter India  
 Mark Barnes, Harvard University  
 Chantal Bélorgey, Agence Française de Sécurité Sanitaire des Produits de Santé  
 Joan Blair, U.S. Food and Drug Administration  
 John Boslego, PATH  
 Marie-Charlotte Bouesseau, World Health Organization  
 Robert Califf, Duke Translational Medicine Institute and Duke University Medical Center  
 Kalipso Chalkidou, UK National Institute for Health and Clinical Excellence  
 Keith Chirgwin, Merck  
 Michael Collins, Novartis  
 Rory Collins, Oxford University  
 Nora Dellepiane de Rey Tolve, World Health Organization  
 Ciro de Quadros, Sabin Institute  
 Wouter Deelder, Dalberg Global Development Advisors  
 Jose Di Fabio, Pan American Health Organization  
 Roland Dobbelaer, Consultant  
 Marie-Claude Dubois, GlaxoSmithKline  
 Stephan Duparc, Medicines for Malaria Venture  
 Laura Efros, Merck  
 Eric Eisenstein, Duke University  
 Chris Elias, PATH  
 Pat Fast, International AIDS Vaccine Initiative  
 Adam Fimbo, Tanzania Food & Drug Authority  
 Jorge Flores, PATH  
 Diedre Fruh, United State Senate  
 Jesse Goodman, U.S. Food and Drug Administration  
 Steve Goodman, Johns Hopkins Bloomberg School of Public Health  
 James Greenwood, Biotechnology Industry Association  
 Victoria Hale, Medicines360  
 Blair Hanewell, Bill & Melinda Gates Foundation  
 Alice Hogans, U.S. House of Representatives  
 Hendrik Hogerzeil, World Health Organization  
 Peter Hotez, Sabin Institute  
 Michael Johnson, U.S. National Institutes of Health  
 Anthony Kalpana, PATH  
 Nancy Kass, Johns Hopkins Bloomberg School of Public Health  
 Kim Kertson, PATH  
 Hannah Kettler, Bill & Melinda Gates Foundation  
 Paul Lalvani, RaPID Pharmacovigilance Program  
 Trudy Lang, Oxford University  
 Jonathan Levin, Stanford University  
 Christian Loucq, PATH  
 Precious Matsoso, South African Medicines Control Council  
 Bill McConagha, United States Senate  
 Megan McBride, International AIDS Vaccine Initiative  
 Bob Meyer, Merck  
 Charles Mgone, European Developing Counties Clinical Trials Partnership  
 Jessica Millman, Bill & Melinda Gates Foundation  
 Chris Milne, Tufts Center for the Study of Drug Development  
 Julie Milstien, Consultant  
 Helen Byomire Ndagije, National Drug Authority, Uganda  
 Pieter Neels, European Medicines Agency  
 Robert “Skip” Nelson, U.S. Food and Drug Administration  
 Sergio Andrade Nishioka, World Health Organization  
 Robert Oerlich, World Bank  
 Jayesh Pandit, Department of Pharmacovigilance, Kenya  
 Ok Pannenberg, World Bank  
 Mark Paxton, PhRMA  
 Joan Pettit, Johns Hopkins Bloomberg School of Public Health  
 James Platts, Bill & Melinda Gates Foundation  
 Regina Rabinovich, Bill & Melinda Gates Foundation



Sara Radcliffe, Biotechnology Industry Association  
Lembit Rago, World Health Organization  
Robert Ridley, World Health Organization  
Michael Robertson, Merck  
Alvin Roth, Harvard School of Business  
Leonard Sachs, U.S. Food and Drug Administration  
Jerry Sadoff, formerly AERAS Global TB Vaccine Foundation  
Barbara Savarese, PATH  
Joshua Sharfstein, formerly U.S. Food and Drug Administration  
Rebecca Sheets, U.S. National Institutes of Health  
Walter Straus, Merck  
Nathalie Strub, Drugs for Neglected Diseases Initiative

Jeremy Sugarman, Johns Hopkins Bloomberg School of Public Health  
Ted Tsai, Novartis  
Vivian Tsu, PATH  
Sean Tunis, Center for Medical Technology Policy  
Marie-Chantal Uwamwezi, GlaxoSmithKline  
Saul Walker, U.K. Department for International Development  
Stuart Walker, CMR International Institute for Regulatory Science  
Christine Wasunna, Kenya Medical Research Institute  
Tim Wells, Medicines for Malaria Venture  
Janet Woodcock, U.S. Food and Drug Administration  
Salim Yusuf, McMaster University

# Notes

1. This report uses neglected diseases broadly to refer to malaria, TB, cholera, dengue fever, treponematoses, leptospirosis, strongyloidiasis, foodborne trematodiasis, neurocysticercosis, scabies, typhoid and paratyphoid, 13 parasitic and bacterial infections, 3 soil-transmitted helminth infections (ascariasis, hookworm, and trichuriasis), lymphatic filariasis, onchocerciasis, dracunculiasis, schistosomiasis, Chagas disease, human African trypanosomiasis, leishmaniasis, Buruli ulcer, leprosy, and trachoma.
2. World Health Organization, World Malaria Report 2010 xi, xii, 61 (2010); Philip Musgrove & Peter Hotez, *Turning Neglected Tropical Diseases into Forgotten Maladies*, 28 *Lancet* 1691, 1693 (2009).
3. World Health Organization, Working to overcome the global impact of neglected tropical diseases 3 (2010); Kenneth Gustavesen & Christy Hanson, *Progress in Public-Private Partnerships to Fight Neglected Diseases*, 28 *Health Aff.* 1745 (2009). TB is a worldwide problem, but the vast majority of cases occur in Southeast Asia and the Pacific, Africa, and a handful of countries in the former Soviet Union. World Health Organization, Global Tuberculosis Control 2010, 1 (2010).
4. Global impact of neglected tropical diseases, *supra* note 3, at iii.
5. Global Tuberculosis Control 2010, *supra* note 3, at 1, 5; World Malaria Report 2010, *supra* note 2, at 61.
6. Irene Kuepfer & Christian Burri, *Reflections on clinical research in sub-Saharan Africa*, 39 *International Journal for Parasitology* 947 (2009).
7. UNICEF, Table of Basic Indicators, accessed at [http://www.unicef.org/rightsite/sowc/pdfs/statistics/SOWC\\_Spec\\_Ed\\_CRC\\_TABLE%201.%20BASIC%20INDICATORS\\_EN\\_111309.pdf](http://www.unicef.org/rightsite/sowc/pdfs/statistics/SOWC_Spec_Ed_CRC_TABLE%201.%20BASIC%20INDICATORS_EN_111309.pdf) (last visited June 16, 2010).
8. World Health Organization, World Malaria Report 2009 27 (2009).
9. Peter J. Hotez et al., *The antipoverty vaccines*. 24 *Vaccine* 5787 (2006). See also Global impact of neglected tropical diseases, *supra* note 3, at iv, 3, 15-16, 89 (describing the debilitating health effects and billions of dollars of lost productivity caused by individual neglected diseases).
10. Emmanuel Hassan et al., *Rand Europe, Intellectual Property and Developing Countries* 30 (2010).
11. Tufts Center for the Study of Drug Development, *Drug Approvals for neglected diseases increase along with more R&D Funding*, 11 *Impact Report* (2009).
12. Global impact of neglected tropical diseases, *supra* note 3, at 151 (citing the lack of effective treatments for leishmaniasis, trypanosomiasis, and dengue); Sarah E. Frew et al., *A Business Plan to Help the 'Global South' in its Fight Against Neglected Diseases*, 28 *Health Aff.* 1760, 1761 (2009) (reporting that there are no effective treatments for Buruli ulcer or Chagas disease).
13. Solomon Nwaka et al., *Advancing drug innovation for neglected diseases—criteria for lead progression*, 3 *PLoS Negl Trop Dis.* e440 (2009).
14. See Hassan et al., *supra* note 10, at 30; Patrice Troullier et al., *Drug Development for Neglected Diseases: A Deficient Market and a Public Health Failure*, 359 *Lancet* 2188 (2002).
15. Robert Hecht, Paul Wilson, & Amrita Palriwala, *Innovative Health R&D Financing for Developing Countries: A Menu of Innovative Policy Options*, 28 *Health Aff.* 974 (2009) (reporting that the treatments for TB require six months administration and the treatments for Chagas disease and leishmaniasis are toxic); Monique F. Mrzcek & Elias Mossialos, *Stimulating pharmaceutical research and development for neglected diseases*. 64 *Health Policy* 75, 78 (2003).
16. Christopher J. Elias, *Policies and Practices to Advance Global Health Technologies*, Center for Strategic and International Studies, Global Health Policy Center Report 7 (2009).
17. Institute of Medicine, *The U.S. Commitment to Global Health: Recommendations for the New Administration* 26 (2008). Over a 20-year period, even a partly effective malaria vaccine could

- avert 10,000 deaths and 16,000 severe cases of malaria per million people in malaria-endemic countries. A vaccine to prevent dengue fever would reduce 82 percent of the mortality and morbidity of a mosquito-borne viral disease that causes tens of millions of illnesses and thousands of deaths annually. An improved typhoid vaccine could help reduce the estimated 216,000 deaths that occur annually, mostly in school age children and adults. Hecht, Wilson, & Palriwala, *supra* note 15, at 974-75.
18. BioVentures for Global Health, *The Diagnostics Innovation Map 7* (2010).
  19. Preventative chemotherapy is increasingly being used to prevent the spread of certain neglected diseases. As the use of this treatment expands, drug resistance is likely to become a problem. global impact of neglected tropical diseases, *supra* note 4, at 148. See also Rachel Nugent, Emma Back, & Alexandra Beith, *The Race Against Drug Resistance*, A Report of the Center for Global Development's Drug Resistance Working Group (2010) (describing, in detail, the challenge presented by drug resistance to global health).
  20. Ruth Levine et al., Center for Global Development, *Making markets for vaccines: ideas to action 11* (2005)
  21. These data have been adapted from the 2010 G-Finder Report to exclude HIV/AIDS funding. See Mary Moran et al., *Policy Cures, G-Finder Report: Neglected Disease Research and Development—Is the Global Financial Crisis Changing R&D?* 19-63 (2011).
  22. *Id.* at 78.
  23. Again, this figure excludes industry funding for HIV/AIDS. *Id.* at 74.
  24. *Id.* at 19.
  25. *Id.* at 19, 30-38.
  26. Elias, *supra* note 16, at 6-7.
  27. Levine et al., *supra* note 20, at 19.
  28. See Mary Moran et al., Wellcome Trust, *The New Landscape of Neglected Disease Drug Development*, 8 (2005) (reporting that PDPs manage more than three-quarters of the neglected-disease drug development projects).
  29. Roy Widdus, *Public-private partnerships for health: their main targets, their diversity, and their future directions*, 79 *Bulletin of the World Health Organization* 713 (2001) (reporting the significant variation in the structure of PDPs and their purposes). Examples of PDPs include Aeras Global TB Vaccine Foundation ([www.aeras.org](http://www.aeras.org)), Drugs for Neglected Diseases Initiative (DNDi) ([www.dndi.org](http://www.dndi.org)), Global Alliance for TB Drug Development ([www.tballiance.org](http://www.tballiance.org)), Institute for One World Health ([www.oneworldhealth.org](http://www.oneworldhealth.org)), Malaria Vaccine Initiative ([www.mmv.org](http://www.mmv.org)), the Medicines for Malaria Venture ([www.mmv.org](http://www.mmv.org)), and the Pediatric Dengue Vaccine Initiative ([www.pdvi.org](http://www.pdvi.org)).
  30. Peter J. Hotez, *Neglected Tropical Disease Control in the 'Post-American World,'* 4 *PLoS Negl Trop Dis.* e812 (2010).
  31. According to a recent and thorough analysis by BIO Ventures for Global Health, there are 237 drug and vaccine candidates for neglected diseases in development. This figure does not include diagnostics or products for HIV/AIDS. BIO Ventures for Global Health, *Global Health Primer*, available at [www.bvgh.org/GlobalHealthPrimer.aspx](http://www.bvgh.org/GlobalHealthPrimer.aspx) (last accessed April 22, 2011).
  32. L.F. Barker et al., *New Tuberculosis Vaccines: What is in the Pipeline* in *The Art & Science of Tuberculosis Vaccine Development* (Norazmi, Acosta, & Saramorto eds. 2010).
  33. Bruce Y. Lee et al., *Economic Value of Dengue Vaccine in Thailand*, 84 *Am. J. Trop. Med. Hyg.* 764 (2011).
  34. See, e.g., Levine et al., *supra* note 20, at 18 (reporting that for one drug to be approved by FDA, a firm typically screens 5,000–10,000 compounds. Of these, an average of 250 compounds survive preclinical testing, only 5 are approved for clinical testing, and only 1 succeeds in obtaining FDA approval).
  35. Global Alliance for TB Drug Development, *Economics of TB drug development* (Pekar ed. 2001), available at [http://www.tballiance.org/downloads/publications/TBA\\_Economics\\_Report.pdf](http://www.tballiance.org/downloads/publications/TBA_Economics_Report.pdf) (accessed December 18, 2010).
  36. Joseph A. DiMasi, Ronald W. Hasen, & Henry G. Grabowski, *The Price of Innovation: New Estimates of Drug Development Costs*, 22 *Journal of Health Economics* 151 (2003) (concluding that the average costs of trials is on the order of \$400 million per new chemical entity). But see Donald W. Light, Jon Kim Andrus, & Rebecca N. Warburton, *Estimated research and development costs of rotavirus vaccines*, 27 *Vaccine* 6627 (2009) (estimating actual R&D costs for a rotavirus vaccine could be as low as \$172 million).
  37. Mary Moran et al., Health Policy Division, The George Institute for International Health, *The Malaria Product Pipeline: Planning for the Future* 34 (2007).

38. Medicines for Malaria Venture, *Ensuring Success and Targeting Eradication: MMV Business Plan 2008-2012*, 31 (2008).
39. The Bill & Melinda Gates Foundation has provided approximately \$290 million for clinical development of this product. One of the vaccine developers estimated that as much as \$400 million had been spent on its development, and further clinical trials would yet be needed. Susan Dentzer, *Eliminating Neglected Diseases in Poor Countries: A Conversation with Andrew Witty*, 28 *Health Aff.* w411 (2009).
40. See BVGH Global Health Primer, *supra* note 31. For the purposes of this report, the Working Group has focused on diseases that are almost exclusively endemic in low- and middle-income countries and, thus, excluded some diseases that BVGH has included in its Global Health Primer—HIV, rotavirus, shigellosis, and enterotoxigenic *Escherichia coli*.
41. We focus on clinical development of drugs in the United States only as an example of the clinical trial process. Neglected-disease clinical development may not involve filing an IND in the United States. Other countries use different terminology and regulatory procedures for clinical development. The regulatory pathways for clinical development of vaccines, devices, and diagnostics are also different. For instance, many countries do not require extensive clinical testing of medical devices and diagnostics.
42. An approved IND also allows a clinical trial sponsor to transport the investigational drug across state lines.
43. Over the years, these “phases” have started to break down and overlap. Sometimes, phase I and II trials are combined. Conversely, phase II trials are sometimes divided into Phase IIa, which assesses dosing requirements, and Phase IIb, which studies efficacy.
44. In the United States the application is called a New Drug Application (NDA) for most synthesized molecules and a Biologic License Application for most biologics.
45. See U.S. Government Accountability Office (GAO), *New Drug Development: Science, Business, Regulatory, and Intellectual Property Issues Cited as Hampering Drug Development Efforts*, GAO-07-49 15 (2006) (indicating that the rate of NDAs fell more than 38 percent between 1994 and 2004).
46. Eric Eisenstein et al., *Sensible approaches for reducing clinical trials*, *Clinical Trials* 75, 83 (2008), but see Ernst Berndt et al., *The Impact of Incremental Innovation in Biopharmaceuticals: Drug Utilisation in Original and Supplemental Indications*, 2 *Pharmacoeconomics* 69 (2006) (arguing that increases in approvals of new dosages, formulations, or indications should not be discounted since these incremental innovations may have substantial health benefits).
47. Peter Barton Hutt et al., *Food and Drug Law: Cases and Materials*, 624 (3rd ed. 2007).
48. Kenneth Getz et al., *Assessing the Impact of Protocol Design Changes on Clinical Trial Performance* 15 *American Journal of Therapeutics* 450 (2008).
49. See Leila Duley et al., *Specific Barriers to the Conduct of Randomized Trials*, *Clinical Trials* 40, 44 (2008) (arguing that clinical trial regulations have made even “low cost” trials expensive).
50. See GAO, *supra* note 45, at 31 (citing industry analyst reports and a European Commission study that determined that the U.S. FDA began to demand more complex regulatory requirements in response to a series of high-profile drug withdrawals between 1997 and 2001).
51. See Robert M. Califf, *Clinical Trials Bureaucracy: Unintended Consequences of Well-Intentioned Policy*, 3 *Clinical Trials* 496 (2006); Seth Glickman et al., *Ethical and Scientific Implications of the Globalization of Clinical Research*, 360 *New England Journal of Medicine* 816, 818 (2009).
52. GAO, *supra* note 45. While the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use’s good clinical practice guidelines (ICH-GCP) are virtually silent on randomization, which is foundational to the scientific exercise of clinical trial design, their most extensive prescriptions are on data monitoring. See Guideline E6 of ICH-GCP §§ 4.7, 5.18.
53. Eisenstein et al., *supra* note 46.
54. FDA investigational new drug regulations define institutional review boards as the oversight bodies “designated by an institution to review, approve initiation of and conduct periodic review of biomedical research involving human subjects. [Their] primary purpose is to assure protection of rights and welfare of human subjects.” 21 CFR Part 56 (2010).
55. Jerry Menikoff, *The Paradoxical Problem with Multiple-IRB Review*, 363 *N Engl J Med* 1591, 92 (2010).
56. Institute of Medicine, National Academy of Sciences, *Transforming Clinical Research in the United States: Challenges and Opportunities: Workshop Summary* 31-32 (2010).

57. *Id.* at 32.
58. Duley et al., *supra* note 49, at 44.
59. See Mark Paxton & Jean-Louis Saillot, *Industry Efforts on Simultaneous Global Development*, 43 *Drug Information Journal* 339 (2009).
60. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceutical for Human Use, Guideline for Good Clinical Practice E6 (R1) (June 10, 1996). ICH-GCP is somewhat controversial as some have argued that the guidelines are unscientific and place unnecessary resource pressures on non-commercial trials and developing country national regulatory authorities, which were not involved in developing the guidelines. See Alex D. McMahon et al., *The Unintended Consequences of Clinical Trials Regulations*, 6 *PLoS Medicine* 1 (2009); David A. Grimes, *The Good Clinical Practice guideline: A Bronze Standard for clinical research*, 366 *Lancet* 172 (2005).
61. Getz et al., *supra* note 48.
62. For example, the standard operating procedures for many industry-sponsored trials call for every case report form to be reviewed in person by a monitor who physically visits the enrolling site—a very expensive practice. Califf, *supra* note 51, at 500. See also Salim Yusuf, *Randomized Clinical Trials, Slow Death by a Thousand Unnecessary Policies*, 171 *Canadian Medical Association Journal* 889, 890 (2004).
63. See, e.g., Salim Yusuf et al., *Sensible Guidelines for the conduct of large randomized trials*, 5 *Clinical Trials* 38-39 (2008); Eisenstein et al., *supra* note 46, at 83; Duley et al., *supra* note 49, at 44.
64. Academic health centers share of the clinical trials funding pie dropped from 80 percent in 1991 to 30 percent in 2002; 70 percent of drug companies employed CROs in their projects. CROs now are a multi-billion dollar industry. Christopher-Paul Milne, *Harbingers, or Harvesters of change?* *Outsourcing* 13 (2004).
65. Trudy Lang et al., *Clinical Research: Time for Sensible Guidelines*, *The Lancet Online*, February 21, 2011.
66. See, e.g., Moran et al., *supra* note 28, at 5-26 (noting that, in 2005, one-third of PDPs used CROs to support their R&D process, which generally charged full commercial rates for their services).
67. According to the BVGH Global Health Primer, *supra* note 31, 45 of the 84 candidates in clinical development for neglected diseases are vaccine candidates.
68. Accordingly, the clinical development of vaccines is also more expensive than drugs. For instance, a novel TB drug is estimated to cost \$115–240 million, including the cost of failure, but vaccine development from research and discovery through to product registration is estimated at \$200–500 million, including the cost of failure. See Mary Moran et al., *The George Institute for International Health, G-Finder Report: Neglected Disease Research and Development—How Much are We Really Spending* 45 (2008).
69. These are new efforts afoot to permit clinical trials of novel multidrug regimes. See notes 94-96 *infra* and accompanying text.
70. Phillippe Duclos et al., *Establishing global policy recommendations: The Role of the Strategic Advisory Group of Experts on Immunization* 10 *Expert Rev. Vaccines* 163 (2011).
71. Elias, *supra* note 16, at 8.
72. Duclos et al., *supra* note 70.
73. Julie Milstien et al., *WHO policy development processes for a new vaccine: case study of malaria vaccine*, 9 *Malaria J.* 182 (2010).
74. See, e.g., Christo Van Niekerk & Ann Ginsburg, *Assessment of global capacity to conduct tuberculosis drug development trials: do we have what it takes?*, 13 *Int'l J Tuberc Lung Dis* 13 (2009) (assessing potential clinical trial sites for TB drug development and associated mycobacteriology laboratories in 39 countries and finding that most would require six months to be made ready and that a significant number would require one to two years).
75. Moran et al., *supra* note 37, at 42 (reporting that there would be 23 capable malaria clinical trial sites in Africa by 2008).
76. Kuepfer & Burri, *supra* note 6; Moran et al., *supra* note 37, at 42.
77. Moran et al., *supra* note 37, at 52 (estimating site building in neglected disease—endemic settings can cost as much as \$2–3 million).
78. Musgrove & Hotez, *supra* note 2, at 1693.
79. Using data from Clinicaltrials.gov, we quantified country-specific participation in clinical trials initiating subject recruitment between January 1, 2003, and December 31, 2009, and aggregated them into geographic regions. Bioinformatics and keyword methods were used to classify trials by type of intervention, sponsor, study phase, and therapeutic area.

Information on trial size and number of sites was used to allocate subjects to countries. The proportion of trials of relevant studies not registered on Clinicaltrials.gov is not known but is thought to be smaller post-2005, after the International Committee of Medical Journal Editors initiated a policy requiring investigators to deposit information about trial design into an accepted clinical trials registry before beginning patient enrollment. Multiple international clinical trials registries are in use.

80. Diadié Maïga et al., *Regulatory oversight of clinical trials in Africa: Progress over the past 5 years*, Vaccine (2009) (citing a WHO Regional Office for Africa (WHO/AFRO) study that determined 36 percent of its member states lack IRBs); World Health Organization, Report on Workshop on Regulatory Procedures for Clinical Evaluation of Vaccine, Addis Ababa, September 21–23, 2005 (concluding that only 4 of 13 attending governments had NRAs involved in clinical trials review, authorization of importation of clinical batches, and/or inspection of clinical trial sites); Networking for Ethics on Biomedical Research in Africa, Final Report 94 (2006) (determining that 10 of 15 African countries assessed either lacked legal or regulatory requirements for the ethical conduct of human clinical research or had not implemented the legislation that existed).
81. World Health Organization, Assessment of Medicines Regulatory Systems in 22 WHO Member States: A Summary of Results (2009).
82. Glickman et al., *supra* note 51, at 820 (monitoring guidelines are only effective to the degree to which they are implemented); Kuepfer & Burri, *supra* note 6, at 950 (many ethics committees in Africa lack funding, infrastructure, training, and standard operating procedures); Dalu Zhang et al., *An assessment of the quality of randomised controlled trials conducted in China*, 9 Trials 22 (2008) (finding that fewer than 11 percent of reports of randomized clinical trials conducted in 2004 mentioned ethical approval and only 18 percent adequately discussed informed consent); Samiran Nundy et al., *A new colonialism? Conducting clinical trials in India*, 352 New England Journal of Medicine 1633 (2005) (reporting that fewer than half the large hospitals in India have institutional review boards and most which do lack standard operating procedures and the expertise with which to evaluate protocols).
83. World Health Organization, *Regulatory harmonization: updating medicines regulatory systems in Sub-Saharan African countries*, 24 WHO Drug Info. 6, 18 (2010).
84. Maïga et al., *supra* note 80. In Africa, in particular, research ethics committees often predate the involvement of NRAs in clinical research and have historically filled that regulatory role. Kuepfer & Burri, *supra* note 6, at 950.
85. Networking for Ethics, *supra* note 80, at 94, 95–97.
86. For example, the U.S. FDA will accept data from a foreign clinical study involving a drug or a biological product only if the trial subjects gave their informed consent, an IRB approved and monitored the trial—and internationally recognized GCPs were followed. 21 CFR 312.120 (2009).
87. Helen A. Fletcher et al., *A New Vaccine for Tuberculosis: The Challenges of Development and Deployment*, 6 Bioethical Inquiry 219, 224 (2009).
88. Deborah Cook, *Randomized Trials in Vulnerable Populations*, 5 Clinical Trials 61 (2008) (noting that it took 9–18 months in some developing country trials to obtain import licenses as well as national regulatory approval). See, e.g., Kathryn Senior, *Experts Warn of Regulatory Hurdles Stalling Drug Trials* 8 The Lancet Infection 281 (2008) (reporting that University of London Phase II and Phase III rifamycin trials in South Africa were delayed two years due to regulatory hurdles and that a large-scale Radboud University medical center trial of high-dose rifampicin in Tanzania was delayed for a full year because of complications in the regulatory approval process).
89. One PDP has shared with CGD the regulatory review times for its various vaccine trials in Finland, India, Kenya, South Africa, and Sweden. Original clinical trial application (CTA) review times were 13.7 months in India, 10.2 months in Kenya, and 5.8–7.3 months in South Africa versus 2.9 and 2.8 months in Finland and Sweden, respectively. Approval times in South Africa for additional trials involving a product for which the RSA Medicines Control Council had previously approved a CTA ranged from 5.1 to 9.9 months. See PDP Regulatory Review timetable (on file).
90. See PDP Regulatory Review timetable (on file).
91. Duley et al., *supra* note 49, at 44; see also Networking for Ethics, *supra* note 80, at 97 (outlining the sequential regulatory and ethics review processes, for example, in Nigeria, Tanzania, and Uganda).

92. See Ezekiel Emanuel et al., *What makes clinical research in Developing Countries Ethical?* 189 *Journal of Infectious Disease* 930 (2004); World Medical Association, Declaration of Helsinki, Art 12, 21.
93. See, e.g., Fletcher et al., *supra* note 87, at 221. Immunological correlate of protection is a measurable indication that a subject is immune, in the sense of being protected, against developing the disease at issue.
94. See, e.g., Zhenkun Ma et al., *Global Tuberculosis Drug Development Pipeline: the need and the reality*, *The Lancet Series*, at 5-6, available at <http://www.thelancet.com/series/tuberculosis> (last visited on May 19, 2010).
95. Critical Path to TB Drug Regimens, *Global Partners Join Forces to Speed Development of New TB Combinations*, Press Release (March 18, 2010) (announcing a partnership of the Bill & Melinda Gates Foundation, the Global Alliance for TB Drug Development, the Critical Path Institute, and numerous pharmaceutical companies to pursue clinical development of TB drug candidates in combination, arguing that testing these products individually would add as much as 20 years to development time).
96. Center for Drug Evaluation and Research, U.S. Food and Drug Administration, United States Department of Health and Human Services, Draft Guidance for Industry Codevelopment of Two or More Unmarketed Investigational Drugs for Use in Combination (December 2010). See also Janet Woodcock et al., *Development of Novel Combination Therapies*, 364 *New Eng. J. Med.* 985 (2011).
97. See Glickman et al., *supra* note 51, at 818; Ezekiel Emanuel et al., *What makes clinical research in Developing Countries Ethical?* 189 *Journal of Infectious Disease* 930 (2004).
98. Michael T. Krosin et al., *Problems in comprehension of informed consent in rural and peri-urban Mali, West Africa*, 3 *Clinical Trials* 306 (2006) (reporting that a survey of participants in a malaria vaccine trial in Mali revealed that most did not understand the side effects or that they were enrolled in an investigation).
99. See generally *Ethical Issues in International Biomedical Research: A Casebook 3-5* (Lavery, Grady, Wahl, Emanuel eds. 2007) (describing the controversy over placebo trials in Africa, the Caribbean, and Southeast Asia during the mid-1990s to determine the effectiveness of less complex, lower cost alternative regimens to the proven method of preventing mother-to-child transmission of HIV).
100. For diseases like HIV/AIDS and malaria, where no current vaccine exists, the ethics trial design focuses on appropriate sample size and placebo selection. Fletcher et al., *supra* note 87, at 221. In the case of tuberculosis, the inquiry is more complicated. There is an existing licensed TB vaccine—Bacille Calmette Guèrin (BCG). It is a widely used, live attenuated vaccine, but estimates of its efficacy range from 0–80 percent. Dixie E. Snider Jr., *Ethical Issues in Tuberculosis Vaccine Trials*, 30 *Clinical Infectious Diseases* S271-275 (2000). The vaccine has efficacy against childhood TB, but this decreases over time, and revaccination does not confer protection. A new, more reliably efficacious, and safer vaccine is necessary to control the global spread of tuberculosis. There have been questions whether new TB vaccines can be safely and effectively used in populations already immunized with the BCG vaccine, see Michael J. Brennan, *The Tuberculosis Vaccine Challenge*, 85 *Tuberculosis (Edinb)* 7-12 (2005), and the ethics of trials designed to show the non-inferiority of new vaccines over BCG. Fletcher et al., *supra* note 87, at 222-23.
101. Caroline Kithinji & Nancy E. Kass, *Assessing the Readability of Non-English-Language Consent Forms: The Case of Kiswahili for Research Conducted in Kenya*, IRB: Ethics & Human Research 10 (July-August 2010) (finding that consent forms demonstrated to be readable in English may not be readable when translated into local languages).
102. Of the 233 pediatric clinical trials for neglected diseases in disease-endemic countries registered on Clinicaltrials.gov and initiating recruitment between 2003 and 2009, 155 were in Africa.
103. An analysis of Clinicaltrials.gov data reveals that 272 of the 902 biopharmaceutical and vaccine trials for neglected diseases between 2003 and 2009 were multi-country trials.
104. Our analysis of Clinicaltrials.gov data indicates that 112 neglected-disease trials were multi-region as well as multi-country. We did not break these multi-region trials down by product type, so we can determine only that at least 155 of the 272 of multi-country neglected-disease product development trials occur within a single region. The proportion may be higher.
105. Our analysis of Clinicaltrials.gov data indicates that 8,026 of the universe of 66,169 registered trials initiating subject

recruitment between 2003 and 2009 involved sites in two or more countries. Of these multi-country trials, 5,888 had sites in two or more geographic regions (such as Africa, Asia, and Western Europe.).

106. See Duley et al., *supra* note 49, at 44 (noting that in large trials involving multiple developing countries, the collective process of obtaining regulatory and IRB approvals, importing drugs, and negotiating contracts can add 12–24 months to trials and millions of dollars in expenses).
107. Califf, *supra* note 51.
108. See World Health Organization, TRREE-for Africa and the Institute of Health Law (University of Neuchâtel), *The Ethical and Regulatory Review Mechanisms of Clinical Trials in Africa: Overview of the Situation in the AVAREF Members Countries* (2009) (revealing spectacular variety in the ethical and regulatory review mechanisms in assessed African countries); Pan American Health Organization, *Report on the assessment of the situation of Good Clinical Practices in 12 Latin American countries* (2000) (finding that 10 of 12 Latin American countries with clinical trial regulations had different requirements regarding ethics committees, informed consent, research on vulnerable populations, and certification of researchers and research centers).
109. See Chris Granger, Duke Clinical Research Institute, *Minimizing delays within regulatory agencies*, presentation at Sensible Guidelines Conference (September 5, 2009), available at <http://www.ctsu.ox.ac.uk/projects/sg> (noting regional differences in regulatory delays in five trials with delays ranging from 15 to 90 days in the United States, Japan, United Kingdom, Germany, and France for unapproved drugs as opposed to 39 days to 10 months for India, Argentina, and China).
110. Declaration of Helsinki.
111. Institute of Medicine, *supra* note 56, at 33.
112. Moran et al., *supra* note 37, at 6-7, 34 (estimating that as much as \$639 million would be required to cover the outstanding costs of clinical development and manufacture of new malaria drugs and vaccines in the next five years).
113. The costs of neglected-disease R&D may be lower than other drug development projects due, in part, to the lower costs of capital for philanthropic-funded programs. Mary Moran, *A Breakthrough in R&D for Neglected Diseases: New Ways to Get the Drugs We Need*, 2 PLoS Medicine e302 (2005).
114. See Paul L. Herrling, *Making Drugs Accessible to Poor Populations: A Funding Model*, Global Forum Update on Research for Health 152 (2008) (citing a study, commissioned by International Federation of Pharmaceutical Manufacturers & Associations and Novartis).
115. See BVGH Global Health Primer, *supra* note 31.
116. Hecht, Wilson, & Palriwala, *supra* note 15, at 976 (reporting that only 40 percent of the funding needed to develop safe and effective TB vaccines by 2015 has actually been committed); Moran et al., *supra* note 37, at 6-7 (estimating—based on current portfolios, approaches, and policies—that approximately \$561 million to \$639 million will be needed to cover just the outstanding costs of clinical development and manufacture of new malaria drugs and vaccines in the next five years); Levine et al., *supra* note 20, at 20 (reporting that, even at the lowest estimates, pursuing a single malaria candidate vaccine through the later phases of clinical trials, regulatory approval, and production would exceed the total public and philanthropic funds presently available for the development of malaria vaccines generally).
117. Ramadhani Abdallah Noor, *Health Research in Africa*, 1125 *Acta Tropica* 563, 567 (2009); see, e.g., Center for Vaccine Development (CVD), University of Maryland, CVD Facilities, (describing the Malaria Research Center, laboratory facilities, and fields sites that the CVD, Mali Ministry of Health, and Bill & Melinda Gates Foundation built in Mali), available at [http://medschool.umaryland.edu/CVD/facilities\\_mali.asp](http://medschool.umaryland.edu/CVD/facilities_mali.asp). The challenge for these new sites will be their sustainability if the flow of research projects to these settings does not increase and diversify. See Carel Ijsselmuiden et al., *Evolving Values in ethics and global health research*, 5 *Global Pub. Health* 154, 157-58 (2010).
118. Noor, *supra* note 117, at 564.
119. 2010 G-Finder Report, *supra* note 21, at 10, 81.
120. Noor, *supra* note 117, at 568.
121. See Frew et al., *supra* note 12, at 1763 (noting that many emerging economy companies regard neglected diseases as business opportunities); Moran et al., *supra* note 28, at 65-66 (noting that existing neglected-disease markets—particularly for TB, malaria, and possibly leishmaniasis—offer unexploited opportunities with comparable returns to average orphan markets that attract small firms, but that the barriers of



- conducting large-scale clinical development, *inter alia*, deter such investment).
122. Ernst R. Berndt, *The Globalization of Clinical Trials for New Medicines into Emerging Economies: Where are They Going and Why?* (2007) (manuscript on file with author) (noting that the speed of recruiting patients and completing the trials is widely reported as a critical consideration in choosing a trial site).
  123. OECD Regulatory Policy Conference, Regulatory Policy: Towards a New Agenda: Pathways to the future, 33 (2010).
  124. Maïga et al., *supra* note 80.
  125. See *id.*
  126. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001. *On the approximation of the laws, regulations and administrative provisions of the member states relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.* (<http://www.eortc.be/Services/Doc/clinical-EU-directive-04-April-01.pdf>)
  127. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations, and administrative provisions of the member states relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, OJ L121, 1.5.2001, p.34. MSD response to Assessment of the functioning of the “Clinical Trials Directive” 2001/83/EC – Public consultation paper, Brussels, December 22, 2009. Available at, [http://ec.europa.eu/health/files/clinicaltrials/docs/responses\\_2001-20/merck\\_sharp\\_dome.pdf](http://ec.europa.eu/health/files/clinicaltrials/docs/responses_2001-20/merck_sharp_dome.pdf) (last accessed on April 20, 2011).
  128. Heads of Medicines Agencies, Guidance document for a Voluntary Harmonisation Procedure (VHP) for the assessment of multinational Clinical Trial Applications – Version 2, CTFG//VHP/2010/Rev1 (March 2010), available at [http://www.hma.eu/uploads/media/VHP\\_version\\_2\\_March\\_2010.pdf](http://www.hma.eu/uploads/media/VHP_version_2_March_2010.pdf) (last visited July 27, 2011); Interview with Chantal Belorgey, Co-Chair of HMA Clinical Trial Facilitation Group and Head of the Department of Evaluation of Clinical Trials, Agence Française de Sécurité Sanitaire des Produits de Santé, August 4, 2011.
  129. Council Regulation (EEC) no. 2309/93 22 July 1993.
  130. U.S. Government Accountability Office (GAO), Report to the Chairman, United States Senate Committee on Labor and Human Resources, European Union Drug Approval: Overview of New European Medicines Evaluation Agency and Approval Process 4 (1996).
  131. It was initially known as the “concertation procedure.” EC Directive 87/22 for high-technology or biologically derived products.
  132. Alar Irs et al., *Development of marketing authorization procedures for pharmaceuticals*, in *Evaluating Pharmaceutical for Health Policy and Reimbursement* (ed. Nick Freemantle & Susan Hill, 2004) (noting that initially normal national regulatory reviews occurred after the committee review in the centralized procedure).
  133. Suzanne Hill & Kent Johnson, UK Department for International Development, *Emerging Challenges and Opportunities in Drug Registration and Regulation in Developing Countries* (2004).
  134. The mutual recognition process did not initially require participating states to accept as authoritative the product review conducted by other member state agencies and, consequently, each country continued to perform its own product review before coming to a decision about product approval. This duplication of effort among the different NRAs undermined the success of the process. Elaine M. Healy & Kenneth Kaitin, *The European Agency for the Evaluation of Medicinal Products’ Centralized Procedure for Product Approval: Current Status*, 33 *Drug Information Journal* 969, 970 (1999).
  135. Irs et al., *supra* note 132.
  136. Overview of New European Medicines Evaluation Agency, *supra* note 130, at 12.
  137. *Id.* at 1-4.
  138. *Id.* at 10.
  139. Julie Milstien & Lahouari Belharbi, *Regulatory Pathways for vaccines for developing countries*, 82 *Bulletin of World Health Organization* 128, 132 (2004) (arguing that a collective expert committee approach would expand the ability of NRAs in this region to address the needs of the specific epidemiological situation of these countries). Ideally, the EMA and/or FDA would enter into a memorandum of understanding with the participating governments to provide the necessary technical and/or financial support at expert committee level.
  140. The establishment of review fees, in exchange for more certain review timelines, was used to improve regulatory capacity

in the United States. The Prescription Drug User Fee Act (PDUFA) was enacted in 1992 and renewed in 1997 (PDUFA II), 2002 (PDUFA III), and 2007 (PDUFA IV.) Under sections 735 and 736 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. §§ 379g and 379h), FDA has the authority to assess and collect user fees for certain drug and biologics license applications submitted to the agency for review. FDA sets these fees on a yearly basis.

141. See, e.g., the Southern African Development Community, Pan American Health Organization, and the Association of Southeast Asian Nations.
142. See Keith Maskus & Yin He, “Trans-Atlantic Regulatory Cooperation in Pharmaceuticals: An Intellectual Property and Trade Perspective,” at 19-22 German Marshall Fund Academic Policy Research Conference Paper, May 8–9, 2008, Ford School, University of Michigan (describing the 1997 U.S.-EU Mutual Recognition Agreement on pharmaceutical regulatory cooperation, which included a framework agreement and six sectoral annexes), available at [http://www.fordschool.umich.edu/news/event\\_details/reg\\_coop\\_and\\_comp\\_08/documents/Maskus\\_Paper.pdf](http://www.fordschool.umich.edu/news/event_details/reg_coop_and_comp_08/documents/Maskus_Paper.pdf) (last visited December 20, 2010). Irs et al., *supra* note 132 (arguing that long-term, successful intergovernmental regulatory cooperation requires a binding legal framework).
143. See Kenneth W. Abbott & Duncan Snidal, *Pathways to International Cooperation* in *The Impact of International Law on International Cooperation: Theoretical Perspectives* 57-60 (Benvenisti & Hirsch, eds., 2004) (citing the formation of the European Union, the North American Free Trade Agreement, the Food and Agriculture Organization, and the United Nations Environment Program as examples).
144. See Kenneth W. Abbott, *An International Framework Agreement on Scientific and Technological Innovation and Regulation*, Working Paper 2-3 (2009), available at [http://papers.ssrn.com/sol3/papers.cfm?abstract\\_id=1414430](http://papers.ssrn.com/sol3/papers.cfm?abstract_id=1414430) (arguing that such international framework agreements have been useful in international environmental law because they are flexible, more easily negotiated than formal treaties, and facilitate the cooperation and involvement of three sets of actors: international (participating states), transgovernmental (constituent regulators and agencies of the state’s parties), and transnational (relevant private actors with issues at stake)).
145. Many of the relevant regional economic communities have mandates to engage in regulatory cooperation and harmonization among member states to promote objectives such as trade in goods and services, health, integration, or pharmaceutical development. See, e.g., Treaty for the Establishment of the East African Community (EAC), (As amended on December 14, 2006, and August 20, 2007), Art. 118 (a), (d), (e), (g); Memorandum of Understanding Concerning Cooperation on Standards and Conformance, Association of Southeast Asian Nations, Art. 2; Treaty Establishing a Common Market between the Argentine Republic, the Federal Republic of Brazil, the Republic of Paraguay and the Eastern Republic of Uruguay, 1991, at Article 1.
146. According to WHO and HMA officials, the principal costs of HMA and AVAREF involve the small number of staff serving in their respective secretariats; plenary meetings to conduct training and agree to common documentation and assessment criteria; and smaller satellite activities such as joint reviews. VHP clinical trial applications are filed electronically, the joint assessments are conducted by phone and secure email, and the secretariat staff consists of a single person. According to a WHO official, the costs of operating AVAREF—including support for the participation of the member NRAs, IRB/ECs, and outside experts—are significantly less than \$1 million annually.
147. See, e.g., Samba O. Sow et al., *Immunogenicity and Safety of a Meningococcal A Conjugate Vaccine in Africans*, 364 *New Eng. J. of Med.* 2293 (2011) (describing the successful development by the PATH Meningitis Vaccine Project of the meningitis vaccine).
148. Institute of Medicine, *supra* note 56, at 33.
149. *Ibid.*
150. See Shein-Chung Chow & Mark Chang, *Adaptive design methods in clinical trials – a review*, 3 *Orphanet H. Rare Dis.* 11 (2008) (describing the range of approaches to adaptive trial design and some of their associated regulatory and practical challenges).
151. Institute of Medicine, *supra* note 56, at 90. Developing the tools and methods for building quality into the design and execution of clinical trials is the objective of the Clinical Trials Transformation Initiative, a promising public-private partnership established by initiated by the U.S. FDA and convened by Duke University through a memorandum of understanding between Duke and the FDA. See Clinical

- Trials Transformation Initiative, <https://www.trialstransformation.org/>.
152. <http://www.dndi.org/overview.html>.
  153. See David Dilts, *Phase III Clinical Trial Development: A Process of Chutes and Ladders*, 16 *Clin. Can. Res.* (2010) (reporting that in the examined phase III collaborative cancer trials required 769 steps, 36 approvals, and a median of 2.5 years before study opening).
  154. *Id.*
  155. Institute of Medicine, *supra* note 56, at 90 (reporting that site contracting is often responsible for months of delays to trial initiation).
  156. *Global Clinical Trials: Effective Implementation and Management* 471 (Chin and Bairu eds., 2011).
  157. Thompson Reuters, *Information Technology is Improving Clinical Practice* (2011).
  158. Eisenstein et al., *supra* note 46 (focusing on selective site visits combined with electronic data capture, centralized monitoring, and statistical sampling techniques).
  159. *Global Clinical Trials*, *supra* note 156, at 471.
  160. Eisenstein et al., *supra* note 46.
  161. Fabio A. Thiers et al., *Trends in the Globalization of Clinical Trials*, *Nature Review Drug Discovery* (2007).
  162. See, e.g., Glickman et al., *supra* note 51, at 818 (citing low labor costs for health professionals and investigators in emerging markets as a source of savings); Shonagh McVean, *Foreign Biotech Trials in Asia: Emerging Trends*, *PharmaFocus Asia* (2007) (noting that costs of conducting clinical trials in India averaged \$3,000 per patient as opposed \$30,000 in the United States).
  163. *Global Clinical Trials*, *supra* note 156, at 6.
  164. See, e.g., Indian Ministry of Commerce and Industry, *Report of the Task Force: Strategy for Increasing Exports of Pharmaceutical Products* 69 (2008) (estimating that the clinical trial activity in India would be worth \$300 million in 2010).
  165. Thiers et al., *supra* note 161; Glickman et al., *supra* note 51, at 818.
  166. MRCT Project Report: *Enhancing Respect for Research Participants, Safety, and Fairness in Multi-Regional Clinical Trials* (March 18, 2010).
  167. Indian Ministry of Commerce and Industry, *supra* note 164; Krishan Maggan, *Regulatory Reforms and GCP Trials with New Drugs in India*, *Clinical Trials* 461-67 (2004) (describing 2005 reforms in India to address regulatory streamlining and informed consent adherence).
  168. Hepeng Jia, *China Beckons to Clinical Trial Sponsors*, *Nature Drug Discovery* (2005).
  169. The figures are similar for trials occurring in neglected disease-endemic regions where the FDA inspected only 0.8 percent of trial sites involved in approved U.S. drug or biologic applications in fiscal year 2008. Office of Inspector General, U.S. Department of Health and Human Services, *Challenges to FDA's Ability to Monitor and Inspect Foreign Clinical Trials*, OEI-0-08-00510, 30-33 (2010).
  170. The European Medicines Agency Working Group on Third Country Clinical Trials, European Medicines Agency, *Draft Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted in third countries and submitted in marketing authorisation applications to the EMA*, EMA/712397/2009 (May 26, 2010); Margaret A. Hamburg, M.D., U.S. Commissioner of Food and Drugs, *Food and Drugs: Can Safety Be Ensured in a Time of Increased Globalization?* Remarks at Council on Foreign Relations, January 31, 2011.
  171. Michael Brennan, *The U.S. Food and Drug Administration provides a pathway for licensing vaccines for global diseases*, 6 *PLoS Medicine* e1000095 (2009).
  172. Dr. Ibrahim Assane Mayaki, Chief Executive Officer, NEPAD, *Report on the Programmatic Activities of the Agency for the Period: July to December 2010* 42-46 (2011), at <http://www.nepad.org/system/files/ACTIVITY%20REPORT%20of%20CEO%20for%2041st%20SC%20meeting%20xxx%20-%20Dec%202010.pdf> (last visited on June 29, 2011).
  173. East African Community, 38 *Update Issue* 7 (2011).
  174. More than 60 organizations make up CTTI, including U.S. government and international agencies, industry representatives (pharmaceutical, biotech, device, and clinical research organizations), patient and consumer representatives, professional societies, investigator groups, academic institutions, and other interested parties. See *Clinical Trials Transformation Initiative*, <https://www.trialstransformation.org/>.
  175. <http://www.ctsu.ox.ac.uk/projects/sg>.

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