

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

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CGD Brief

More than a billion people suffer from neglected diseases, and millions die each year. Effective remedies have been few because of low investment, but with a surge in funding in the past decade, dozens of candidate drugs and vaccines are now in the pipeline. Before these products can reach the people who need them, they must be tested in large-scale clinical trials that are expensive, time-consuming, and risky. These trials must be conducted with highly vulnerable patients in resource- and infrastructure-poor countries where the neglected disease burden exists. There is not enough funding to support the costs and regulatory oversight of these clinical trials. A two-pronged approach to improve the quality and lower the cost of clinical trials in the developing world is needed:

1. Establish regional regulatory pathways for the oversight of clinical trials.
2. Build quality and cost-efficiency into trial planning and design.

A Renewed Pipeline for Neglected Disease

More than a billion people suffer from neglected diseases. These include malaria and tuberculosis and lesser-known diseases such as chagas and dengue fever. Each year, neglected diseases kill millions of people and disable and deform many more, exacting a devastating toll in the world's poorest communities. Because these diseases have attracted little investment, effective remedies are few.

But over the past decade, private philanthropy, government intervention, and hard work by product development partnerships have produced dozens of candidate technologies to treat, prevent, or diagnose neglected diseases. For many diseases, the drug and vaccine candidates now in the pipeline are the first new therapies and prevention tools in a generation; for others, they are simply the first ever.

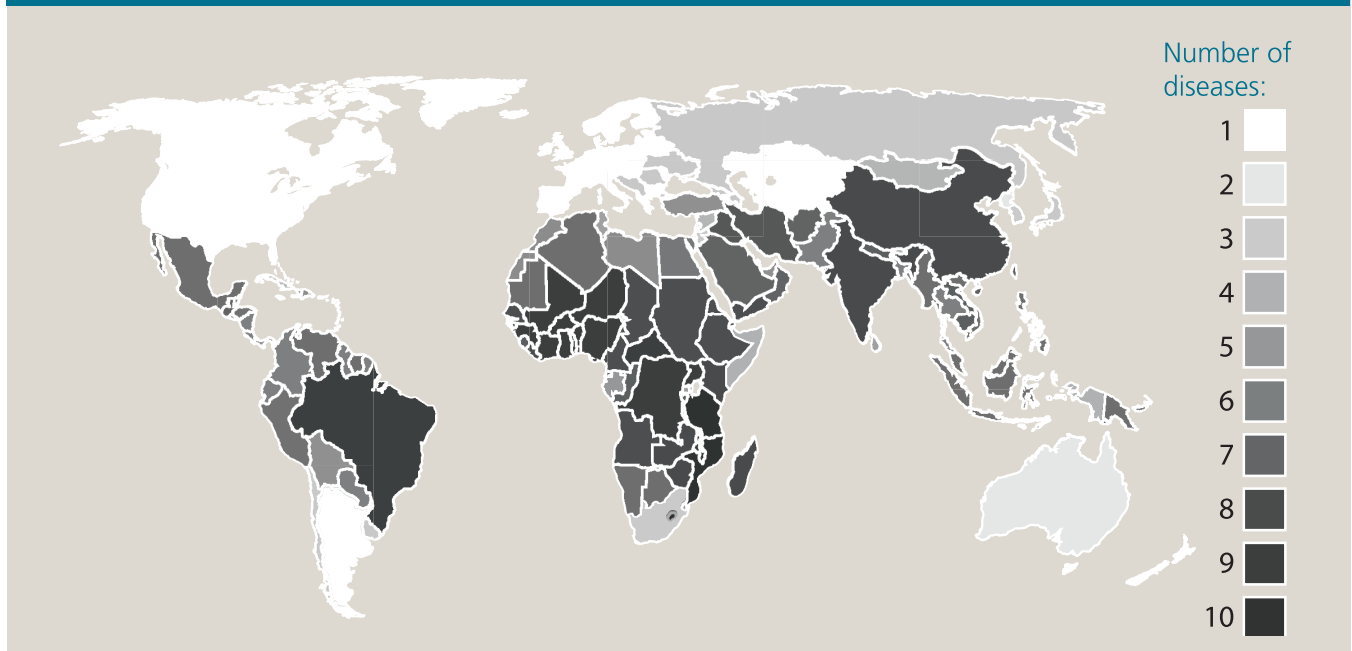
Clinical Development and the Challenges Ahead

Before these products can reach the people who need them, they must be tested in large-scale clinical trials, with highly vulnerable patients in poor countries where the disease burden exists. These include countries where few, if any, clinical trials have been conducted before (see figure 1). Moreover, many therapies must be tested in several countries, each with its own complex and often uncertain procedures. The time-consuming, risky, and expensive process is a major impediment to delivering life-saving therapies.

There is not enough funding to support trials for all the candidate drugs and vaccines in the neglected disease pipeline under current cost assumptions. Clinical trials can consume as much as 70 percent of cost and most of the time required to develop a drug or vaccine. A

CGD is grateful for contributions from the Bill & Melinda Gates Foundation in support of this work.

Figure 1. The Geographic Overlap of Neglected Diseases



single, late-stage trial requires years to complete and can cost tens and even hundreds of millions of dollars. This absence of financing risks undermining recent successes in filling the pipeline.

In the current economic environment, securing more funding for large-scale clinical trials and capacity building is unlikely. Part of the solution must include reductions in clinical trial costs and better use of the existing regulatory capacity.

Improving Clinical Trials and Regulatory Pathways

Safer, Faster, Cheaper: Improving Clinical Trials and Regulatory Pathways to Fight Neglected Diseases, the report of CGD's Clinical Trials and Regulatory Pathways working group, recommends a two-pronged approach to help fight neglected diseases: (1) establish regional regulatory pathways and (2) develop safer, faster, and cheaper clinical trials.

Establish Regional Regulatory Pathways

A unified approach through which multiple countries can work together to approve and oversee clinical trials would improve the coordination and capacity of participating ethics committees and national regulatory authorities (NRAs), provide a more attractive platform for technical assistance

and donor support, and speed product development and delivery to patients.

The report proposes a centralized procedure model in which participating NRAs and ethics committees jointly approve and oversee clinical trials for neglected disease technologies (see figure 2). The specific design must reflect the needs and interests of the participating governments and institutions but should incorporate the following objectives and parameters, and others listed in the report:

- **Capacity through cooperation.** Cooperation should proceed in the context of joint reviews of actual clinical trial applications rather than harmonization of laws and regulations in the abstract.
- **Voluntary and, at least initially, nonbinding.** Governments should have the opportunity to participate and gain confidence in regional regulation before being bound by its results. Voluntary participation for NRAs and trial sponsors is sufficient provided there are adequate incentives.
- **Broad in function, limited eligibility, and scalable.** Regional cooperation should encompass the full range of clinical trial oversight (applications, amendments, inspections, and monitoring). Initially, the pathway should be limited to high-priority countries and technologies, but expand 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.
- **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 become self-supporting. A streamlined, regional regulatory pathway with more certain regulatory timelines would offer substantial value, justifying additional fees.
- **Early investigator input and independent advisory committees.** Solicit input from local investigators and experienced, independent stakeholders early in study and protocol design to spot problems and help keep trials simple, feasible, and focused.
- **Pressure test protocols.** Multinational pharmaceutical companies often “pressure test” protocols using dummy subjects and study products prior to enrolling patients. This improves the efficiency of design and reduces protocol amendments. A similar approach ought to be adopted for neglected disease product development.
- **Simpler trials for licensure, more support for policy research in phase IV studies.** Embedding neglected disease epidemiological and policy research into clinical trials focused on safety and efficacy is an expensive way to obtain that research. Focusing on the research necessary to support licensure would reduce costs, expedite registration, and lower site and investigator demands. Separately, donors should increase funding for the policy and epidemiological studies.
- **Electronic Data Capture (EDC) and centralized monitoring.** Monitoring often accounts for a substantial portion of clinical trial costs. 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 this approach even more economical.

Safer, Faster, Cheaper Clinical Trials

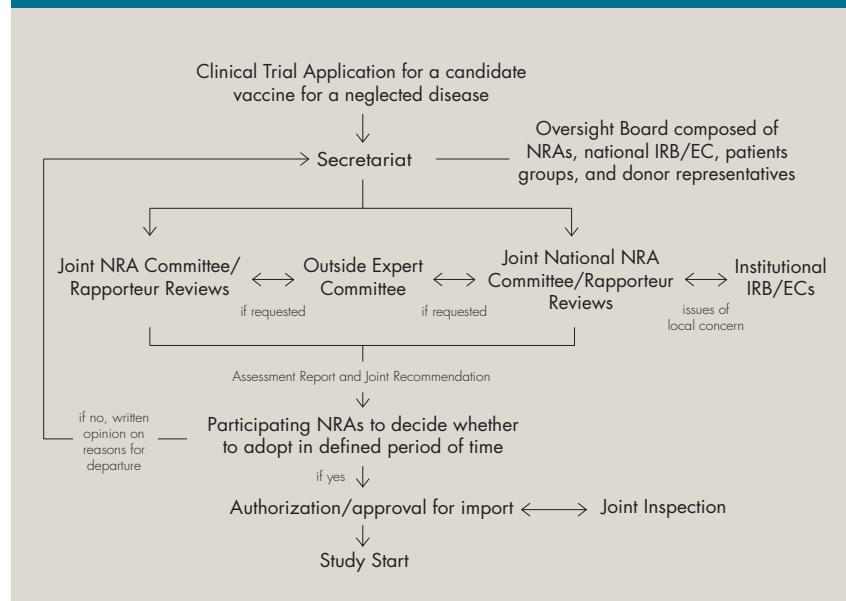
Better regulatory pathways alone will not achieve the cost and time savings required to sustain clinical development of lifesaving therapies for neglected disease. Clinical trials themselves must be improved to be safer, faster, and cheaper.

Clinical trial design and practice tend to be precedent-driven. Sponsors and investigators design studies to look like those previously approved. Regulators approve studies that resemble the studies that have succeeded in the past. This approach has contributed to the skyrocketing costs, increasing duration, and growing complexity of clinical trials. It is a particular problem in low-income countries where there is little relevant precedent from which to draw.

The limited expertise and experience of NRAs, ethics committees, and investigators in these countries further hinders the adoption of the newest and emerging approaches to reducing clinical trial costs and delays. Accordingly, the same cost and infrastructure-intensive regulatory and clinical development practices used commercially in rich countries are often imported into poor countries for highly cost-sensitive neglected disease projects.

The report recommends the following strategies to break the cycle of inertia and waste in clinical trial design and practice:

Figure 2. Potential Pathway for Regional, Integrated Regulatory and Ethics Oversight of Clinical Trials



The Center for Global Development works to reduce global poverty and inequality through rigorous research and active engagement with the policy community to make the world a more prosperous, just, and safe place for us all. The policies and practices of the United States and other rich countries, the emerging powers, and international institutions and corporations have significant impacts on the developing world's poor people. We aim to improve these policies and practices through research and policy engagement to expand opportunities, reduce inequalities, and improve lives everywhere.

Toward Implementation

Regional regulatory platforms and cooperation strategies offer practical and scalable ways to address the urgent challenges presented by the neglected disease product pipeline. These systems could be expanded over time to support other critical regulatory functions such as product registration and post-market safety surveillance in low- and middle-income countries.

Moving forward will require collaboration and investment from all key stakeholders—developing countries, clinical trial sponsors, donors and funding agencies, academic institutions, and international technical agencies. Examples include the following:

- **Developing country NRAs, ethics committees, and their governments** must demonstrate political commitment to engage in regulatory cooperation including, where possible, a contribution of funding and dedicated personnel.
- **Clinical trial sponsors** must use the regional regulatory pathway, and in doing so, agree to allow

participating NRAs to share confidential data and to demonstrate a willingness to pay additional fees.

- **Donors and funding agencies** should provide seed funding to support regional approaches to regulatory and ethics oversight of clinical trials at regional economic communities and the WHO, making use of multilateral funding platforms like the new World Bank trust fund.
- **Developed country NRAs, academic institutions, international technical agencies, and WHO** should ramp up their technical support and continue to lend their credibility and convening power, as these contributions have been critical to the success of the African Vaccine Regulatory Forum and the other regional approaches to clinical trial regulation.

Vision, strategic investments, and hard work built the current pipeline of potential new products for neglected diseases. Improving clinical trial practices and building regulatory pathways more favorable to trial subjects and innovation are critical to realizing the promise of that pipeline for patients and ensuring its future vitality.