Pooled Funds: Assessing New Models for Financing Global Health R&D

Technical Background Paper

Cheri Grace
Mark Pearson
with Janis Lazdins

Results for Development Institute

The Results for Development Institute (R4D) is a nonprofit organization dedicated to accelerating social and economic progress in low and middle income countries. We provide policy analysis, critical information, decision-making tools, and policy advice to governments, civil society organizations, and international funders in order to stimulate positive change. With expertise in many areas—including specialties in economics and finance, health policy, education, and governance—R4D works with leaders, globally and at the country level, to design and test solutions to some of the world's biggest development challenges.

R4D's **Center for Global Health R&D Policy Assessment** provides objective and rigorous assessments of new ideas to advance research and development for global health. Launched in late 2009 with support from the Bill & Melinda Gates Foundation, the Center evaluates proposed policy innovations aimed at accelerating R&D for global health technologies including drugs, vaccines, and diagnostics. The Center convenes funders, policy makers, product developers, and advocacy organizations to discuss its findings and stimulate action. For more information, visit **www.healthresearchpolicy.org**.

Results for Development Institute
1875 Connecticut Avenue, Suite 1210, Washington, DC 20009

For additional information, please contact policyassessment@resultsfordevelopment.org.

TABLE OF CONTENTS

Acronyms

ACT	artemisinin-based combination therapy
AfDF	African Development Fund
AIDS	acquired immune deficiency syndrome
ANDI	African Network for Drugs and Diagnostics Innovation
ARV	antiretroviral
AS+AQ	artesunate + amodiaquine
BMGF	Bill and Melinda Gates Foundation
BRIC	Brazil Russia India China
CAVD	Collaboration for AIDS Vaccine Discovery
CFO	Chief Financial Officer
CHAVI	Center for HIV-AIDS Vaccine Immunology
CPTR	Critical Path to TB Drug Regimen
CRO	contract research organization
DAC	Development Assistance Committee
DALY	disability-adjusted life year
DFID	Department for International Development
DNDi	Drugs for Neglected Disease Initiative
EC	European Commission
EMVI	European Malaria Vaccine Initiative
FRIND	Fund for Research in Neglected Diseases
GATB	Global Alliance for Tuberculosis Drug Development
GEF	Global Environmental Facility
GSK	GlaxoSmithKline
HAT	human African trypanosomiasis
HSS	health system strengthening
IAVI	International AIDS Vaccine Initiative
IDA	International Development Association
IDCs	innovative developing countries
IFFIm	International Finance Facility for Immunisation
iOWH	Institute for One World Health
IPM	International Partnership for Microbicides
IRFF	Industry R&D Facilitation Fund
IVI	International Vaccine Institute
LDC	less developed country
M&E	monitoring and evaluation
MMV	Medicines for Malaria Venture
MRC	UK Medical Research Council
MSF	Médecins Sans Frontières
MVI	Malaria Vaccine Initiative
NCE	new chemical entity
NGO	nongovernmental organizations

NIH	National Institutes for Health
NPV	net present value
NTD	neglected tropical disease
OECD	Organization for Economic Cooperation and Development
PATH	Program for Appropriate Technology in Health
PDP-FF	Product Development Partnership Financing Facility
PM	portfolio management
PPPs	public–private partnerships
R&D	research and development
SAC	Scientific Advisory Committee
SBIR	small business innovation research
SWAp	sector-wide approach
TB	tuberculosis
TC	transaction cost
TDR	Special Program for Research and Training in Tropical Diseases
TPP	target product profile
UNAIDS	Joint United Nations Program on HIV/AIDS
UNDP	United Nations Development Program
UNECE	United Nations Economic Commission for Europe
UNFPA	United Nations Population Fund
UNICEF	United Nations Children's Fund
VL	visceral leishmaniasis
WFP	World Food Program
WHO TDR	World Health Organization Special Program for Research & Training in Tropical Diseases

Acknowledgments

The Center for Global Health R&D Policy Assessment would like to thank the stakeholders who agreed to be interviewed for this report. In order to maintain confidentiality, in appendix B, we have listed the institutions but not the individual names of those interviewed.

We are grateful to the members of the Expert Group for their valuable guidance and feedback throughout the assessment process: Adrian Towse, Ok Pannenborg, Rachel Nugent, Saul Walker, and Richard Skolnik.

The Center also wishes to thank the proponents of the three pooled funding proposals for their openness in sharing information and for reviewing the early findings and the consultation draft of the report.

Finally, the Center acknowledges the following individuals for their feedback on the consultation draft: Jonas Ahlén, Kevin Callahan, Wouter Deedler, Chris Dippel, Marja Esveld, Heather Ignatius, Nancy Katz, Rachel Lenington, Josh Michaud, Zafar Mirza, Carol Nacy, Leonor Pacheco, Anne-Marie Sevcsik, Peter Small, Wendy Taylor, and Regine Webster.

Introduction

There is growing interest in innovative tools and policies to accelerate the development of drugs, vaccines, and diagnostics for neglected diseases, including the list of World Health Organization (WHO) tropical diseases and other major infectious diseases, like HIV/AIDS, tuberculosis (TB), and malaria. Product development partnerships (PDPs), nonprofit research institutes, and private sector groups are working individually and in collaborations to conduct research and development (R&D) on these new global health technologies. However, some argue that their efforts are disjointed and that funding flows inefficiently to individual research projects, resulting in inadequate resources, funding volatility, and poor resource allocation. In response, several mechanisms for pooling funds for neglected-disease R&D have been proposed to address what proponents see as the key problems in the current system.

Three pooled funding proposals in particular have attracted considerable notice: the Product Development Partnership-Financing Facility (PDP-FF) put forward by the International AIDS Vaccine Initiative (IAVI), the Industry R&D Facilitation Fund (IRFF) originally proposed by the George Institute, and the Fund for Research in Neglected Diseases (FRIND) advanced by Novartis.

This paper assesses whether these three proposed mechanisms would help to accelerate R&D for neglected diseases, focusing on how the proposals are likely to perform against two central criteria: their ability to raise additional money for neglected-disease R&D and their capacity to make the allocation of those funds more efficient.

Proposals to pool research and development funding for global health

What IRFF, FRIND, and PDP-FF share in common is that they would draw on contributions from multiple public sector and private funders to establish an R&D fund. This pool of money would then be distributed across a range of R&D projects at different stages of the product development continuum. All three proposals would require some sort of governance structure—a board or committee—to deliberate on and approve resource allocation decisions.

A more detailed description of the proposals is provided in the box below and in the second part of this paper.

While they have common features, there are important differences across PDP-FF, IRFF, and FRIND:

- *How funds would be raised*—In the IRFF and FRIND, governments, foundations, and private funders would contribute grants to the common pool. With PDP-FF, government funders would offer guarantees that would allow a third party—possibly the World Bank or a regional development bank—the authority to issue bonds in capital markets. PDP-FF would repay bondholders through revenues generated from royalties from the sale of vaccines, drugs, and diagnostics in developed-country markets and "premiums" paid by the same or other donors on future product sales in low-income settings.
- *How money would be allocated to R&D projects*—In the IRFF, participating PDPs would be reimbursed for a fixed percentage of their expenditures incurred in collaboration with industry

partners, based on agreed-upon milestones. With the PDP-FF, specific PDPs would receive predetermined shares of the pool, which they could draw down over a period of many years, thus giving the PDPs a stable and predictable source of funds. In the FRIND, PDPs and private drug (and possibly vaccine) developers would compete for the available pooled funds, with a "portfolio management committee" composed of independent experts making allocation decisions for specific projects on a performance/milestone basis.

Figure 0.1. Proposal Overview

PDP-FF. The rationale for the PDP-FF is to draw on the future value of PDP products for funding today. The PDP-FF would provide stable funding to PDPs through a bond-financed pooled fund with designated shares allocated to PDPs. This guaranteed funding would allow PDPs to focus their energies on long-term product development. Once products are developed, PDP-FF would draw on two sources of revenue to repay bondholders: royalties on sales in developed countries and premiums on sales in developing countries. For donors who choose to support the mechanism by committing to pay premiums, and thereby increase the return on product sales to the fund, PDP-FF would offer the advantage of requiring payment only for success. PDP-FF would require a small staff and a board to approve bond issuances and assignment of proceeds to the product development organizations, but administrative costs would be low because most portfolio management activities would be carried out by the individual PDPs.

IRFF. The IRFF would provide predictable medium-term funding for participating PDPs so that they could operate confidently and flexibly, reducing the amount of time they would have to spend on fundraising. PDPs would be partially reimbursed for R&D expenditures that are aligned with approved business plans. In the original proposal, only expenditures for industry partnerships would qualify, but the proponents have discussed revising this provision. Donors would thus invest in a portfolio of PDPs and would not have to carry out due diligence on individual R&D organizations.

FRIND. FRIND would apply to neglected-disease research the portfolio management techniques used by private pharmaceutical firms. FRIND proposes that available funding be pooled and then allocated by a board that represents developing countries, major funders, and other international health stakeholders. As a project meets milestone targets, additional payments would be released from the fund. PDPs, university-based research institutes, and biopharma companies could submit proposals to FRIND. Participating organizations would agree to donate the intellectual property (IP) for successful products to the fund's license pool, although the proponents are reconsidering the IP requirements for the fund.

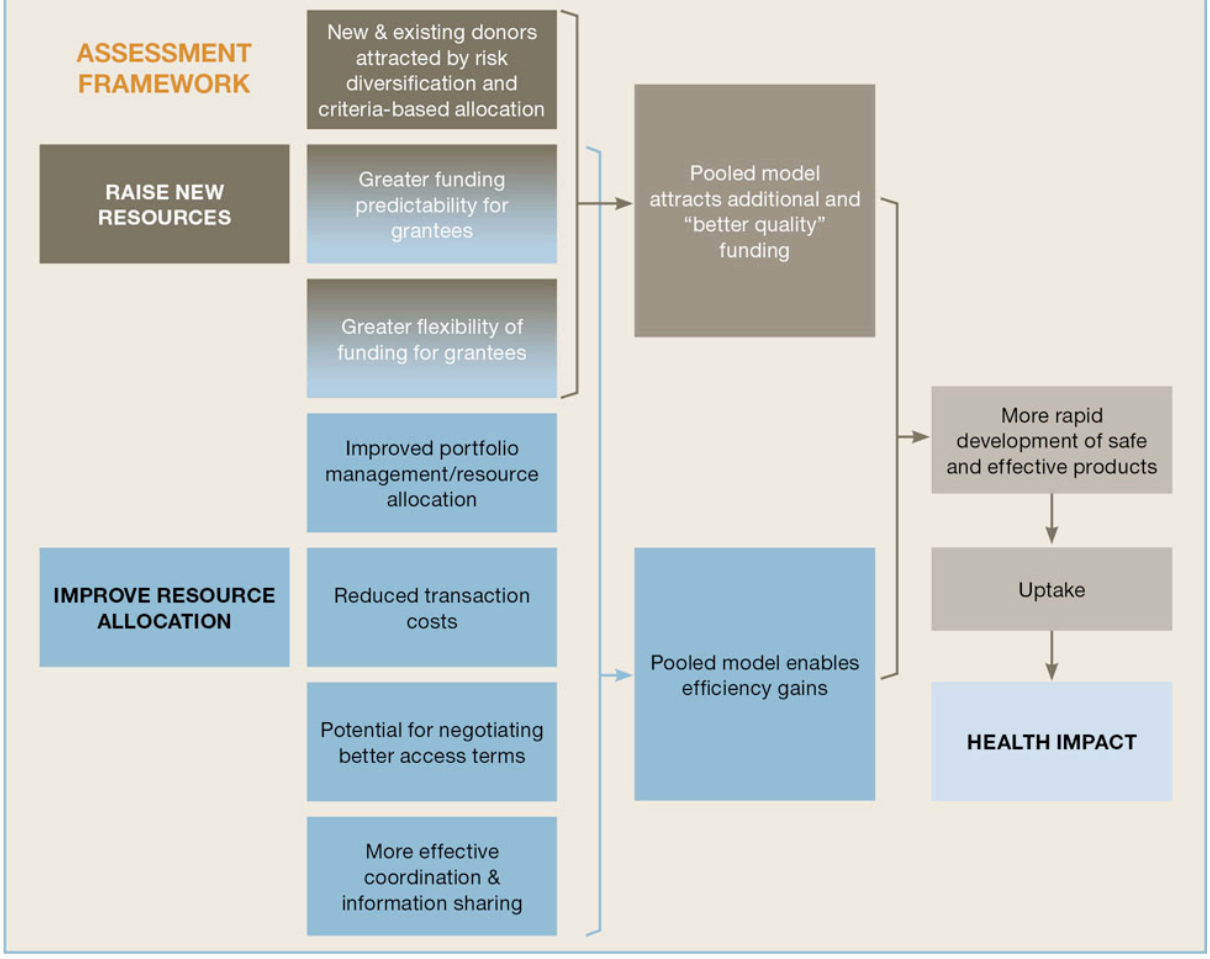
- *Eligibility for the Fund*—PDP-FF and IRFF would extend funding only to PDPs (although IRFF would reimburse spending through partnerships with industry); FRIND, on the other hand, would be open to all product developers, including industry. IRFF and PDP-FF both aim to fund a diverse portfolio of projects ranging from early- to late-stage development. PDP-FF might have a bias in favor of products with more lucrative markets and larger revenue streams in order to improve the chances for bond repayment. The scope of FRIND has yet to be finalized, but recent discussions suggest two potential approaches. In the first, FRIND would cover a wide range of early- and late-stage products, requiring several billions of dollars to achieve critical mass and operate effectively. In the second model, FRIND would focus on late-stage clinical trials. This would increase the cost per project (since efficacy trials are inherently expensive), but lower the overall financial requirement for the fund to several hundred million dollars while improving the chances of success.

Assessment methodology and approach

This report assesses the potential of the three pooled fund proposals against dimensions of the two main criteria described above—new resource generation and more efficient resource allocation. The generic expected "causal pathway" hypothesized for each pooled funding proposal to achieve health gains for the poor is shown in Figure 2. The key questions we posed for each proposal are as follows:

- *Resource Mobilization*: Is the pooled fund likely to draw *more resources* into neglected-disease R&D from existing or new donors, or from other sources such as capital markets?
- *Predictability:* Would the fund create a more *secure and predictable* stream of financing, both for neglected-disease R&D as a whole and for individual PDPs?
- *Flexibility:* Would the fund give PDPs more *flexibility* to spend their budgets, with fewer restrictions and earmarks than at present?

Figure 0.2. Expected Causal Pathway



- *Transaction and Operating Costs:* How large would the initial setup and ongoing administrative costs of the fund be?
- *Portfolio Management:* Would the fund improve *resource allocation* across neglected-disease R&D so that only the most promising projects are supported?
- *Intellectual Property Policies:* Do the fund's policies on IP strike the right balance between *fostering access* to the technologies it supports and giving product developers incentives to invest in neglected-disease R&D?
- *Improving Coordination and Information Sharing:* Would the fund improve coordination and information sharing among product developers?

The proposals assume that there is some underlying obstacle or inefficiency along one or more of these dimensions in the current R&D system. We examine the extent of the problems in each area and the potential of the proposed pooled fund to address them.

Our work was based on a review of existing literature, a mapping of current opportunities and obstacles in global health R&D, interviews with over 50 experts in the field, and modelling of the estimated size of the different pooled funds.

Key results

New resource generation

All three pooled funding proponents claim that these mechanisms raise new financial resources, both from new funders and from current donors who wish to increase their contributions to global health R&D. While the scope of this assessment did not permit us to conduct a systematic survey of donors, we did speak with a large number of public sector donors, private foundations, and the major research institutes in emerging economies and the United States. Although we did hear positive responses from a few organizations, including certain private foundations interested in entering the global health arena, the majority of donors who already support neglected-disease R&D showed limited interest in pooled funding proposals and expressed scepticism regarding the added value of such a mechanism.

When probed more deeply, it turned out that some donors were hesitant to back pooled funding arrangements because they feared the loss of control that they currently enjoy with their direct bilateral financial support to PDPs. Others liked the pooling concept but were not convinced that it would solve existing problems with portfolio management, security, and predictability of financing, etc. Indeed, several donors were not even sure that the key constraints in the current neglected-disease R&D space had been well defined, so it was hard for them to judge if the new mechanisms would be able to make a difference. Still other donors said that their budgets were already fully committed and were not growing, so they did not see how they could make a contribution to a pooled fund at this stage even if they wished to do so.

Among the three proposals that we analyzed, interviewees acknowledged that the PDP-FF had the potential to leverage fresh funding for R&D via loan guarantees, offered donors a choice of "backloading" their financing through guarantees or future premiums on product sales, and could potentially attract new and existing donors who are interested in innovative financing options. At the same time, some donors said that the PDP-FF created some presentational issues—it could appear that the funders who agree to pay the premiums are simply covering the liabilities of other donors who provide the loan guarantees. Donors also expressed concern that the design of the PDP-FF could raise suspicions among their politicians and electorates, especially given that the recent global financial crisis was caused in part by exotic financial engineering.

While PDP-FF is particularly suited to public sector donors able to offer financial guarantees, FRIND and IRFF could be backed by a wider range of funders, including those philanthropic organizations interested in supporting R&D on new drugs and vaccines for neglected diseases but lacking expertise to conduct their own due diligence. Several people from private banks that either operate their own foundations or advise clients who practice philanthropy said that FRIND and IRFF might be mechanisms they could back, but it was difficult to tell whether these groups could offer enough money to justify setting up a new fund. It could be worth exploring further whether there is sufficient appetite among these potential donors to achieve a

minimum size—IRFF's proponents suggest that $100–200 million per year over five years, or a half billion to a billion dollars, would be adequate to establish the fund as per the original proposal.

Improved predictability and efficiency

Our interviews and independent assessment of the three pooled funding proposals suggested that each idea has important strengths but also significant questionable features regarding their ability to improve efficiency and quality of R&D.

On the positive side, the ***PDP-FF*** model would provide more predictable long-term funding to individual PDPs. It would frontload financing, alleviating cash flow difficulties for PDPs over the next few years. It would also offer the possibility of self-financing through revenue streams from royalties and premiums (if drugs and vaccines are successfully developed), thus enabling donors to recoup their investments and avoiding actual calls on their loan guarantees.

On the negative side, the design of PDP-FF locks donors into a pattern of resource allocation to the PDPs that is largely agreed upon at the outset—if certain PDPs perform poorly, it would be difficult to move financing away from them to other drug and vaccine development efforts. The existing portfolio management systems of the individual PDPs would determine how PDP-FF resources are spent, with a limited role for the Financing Facility's board. In addition, given the high scientific risks associated with new vaccines for AIDS, TB, and malaria, we question the likelihood that the organizations financed through PDP-FF would create enough licensed products or generate significant revenues via sales in rich and poor country markets. The costs of setting up and running PDP-FF could be high. There is also some danger of creating incentives to preferentially pursue vaccine or drug candidates with revenue potential, which may not necessarily be the candidates with the highest public health value.

IRFF would also give stable and predictable funding for five years (but not longer, as under PDP-FF) to PDPs that have been "certified" by the IRFF board as having sound performance and solid portfolios. The original proposal, which aims at strengthening industry collaboration, would also give the PDPs incentives to enter into partnerships with biotechnology and larger pharmaceutical firms, since a proportion of R&D spending under these partnerships would be reimbursed from the Fund. Once certified, individual PDPs would have considerable latitude to manage their own portfolios. IRFF could also improve the sharing of information across product development efforts and reduce duplication, although this would be done through the voluntary actions of participating PDPs rather than as something dictated by the IRFF board. Given the simplicity and automaticity of IRFF financing, its operating costs could be kept low.

On the negative side, IRFF would finance expenditures against business plan targets rather than measurable progress against product development milestones. If business plans are thorough and expertly crafted, then expenditure would be indirectly aligned with advances toward useable drugs and vaccines to solve major neglected-disease problems. However, the link between expenditure and health impact is not guaranteed. As with PDP-FF, resources for individual PDPs, once certified, would flow virtually automatically to reimburse R&D expenditures, regardless of the quality of the underlying R&D activities. Since the time IRFF was proposed six years ago, information sharing among PDPs and private firms working on certain neglected-disease technologies (e.g., malaria medicines, TB drugs, AIDS vaccines) has improved considerably, so the case for IRFF having a role in this may be less compelling than it was earlier. Moreover, if IRFF only subsidizes collaborations with firms, then it could bias PDP decisions on partnerships.

FRIND would exercise stronger overall control of spending across neglected-disease R&D and would hold tight reins over individual product development projects by releasing funds on a milestone basis and (its advocates claim) swiftly killing nonperforming projects. It would open up channels for allocating donor funds directly to private sector product developers, rather than having public and philanthropic funds flow indirectly to industry via PDPs.

The underlying assumption is that FRIND could do a better job than either individual donors or the scientific advisory committees of individual PDPs at picking neglected-disease product development opportunities. This assumption is highly controversial, and we were not able to gather sufficient evidence in our assessment to reach a view on it or to find a consensus position from the experts we interviewed. However, we do note the dangers inherent in a highly centralized R&D financing strategy, especially for early-stage projects where there is considerable scientific uncertainty. We also question whether a single organization could develop and apply a clear metric for judging the expected benefits from investments in drugs and vaccines for a diverse set of diseases, such as African sleeping sickness, Chagas' disease, and malaria. The costs of setting up and operating FRIND, while not quantified by its proponents, would appear to be large.

A variant on the original FRIND proposal, in which the pooled fund would pay for only a limited number of efficacy trials, seems more compelling and feasible. Such a "Phase III" fund, which we estimate might require roughly $150 million annually or $600 million for an initial four-year period, could provide a critical mass of financing for several drugs and vaccine candidates at an advanced stage of development, where the risks of failure are lower but the size and cost of a trial would make it hard for individual donors to back it on their own.

Search for greater consensus, more solid facts on neglected-disease research and development

As our review of the strengths and weaknesses of the three proposals highlights, each one has been designed to address specific and different problems in the current neglected-disease R&D system. This begs the question: Which problems, if solved, would give us the most leverage to accelerate R&D for neglected diseases? In our interviews with over 50 experts, we found little consensus on this point. While some experts believed that funding predictability was important for PDPs, there was no agreement as to whether greater predictability would result in better decision making and resource allocation within a PDP; a number of interviewees felt it would have the opposite effect, making the PDPs too complacent. Some experts claimed that because PDPs already have robust portfolio management processes, increased central oversight via a pooled fund's portfolio management committee was not necessary; others maintained that PDPs make poor spending decisions and that the current system needs to be radically reformed.

This finding from our work suggests that much more needs to be done to evaluate the performance of PDPs and other product developers. The financing gaps that need to be filled in the coming years must be better quantified (the Bill and Melinda Gates Foundation [BMGF] has commissioned a study in this area, to be released in 2011). The portfolio practices and the efficiency of PDPs, both in allocating resources and in running their organizations, should also be more widely evaluated and the results collected and shared systematically with donors and experts on R&D policy. Even if all of this is done, however, we acknowledge that in the end, views about the efficiency of nonprofit and commercial R&D organizations—and about the virtues and drawbacks of centralized versus decentralized management of R&D portfolios—will still be subjective and open to interpretation. In such circumstances, the debate over pooled funding arrangements for neglected-disease R&D requires more active involvement of

product development organizations, funders, and advocates so that different views can be aired and consensus sought.

Conclusion

Based on our analysis of the three pooled funding ideas—PDP-FF, IRFF, and FRIND—and our assessment of the current environment and the mood of the donors, we are fairly pessimistic about the prospects of seeing one or several of these ideas launched in the next few years. The case for investing time and resources in establishing any of the three funds, in their current form, is weak at present.

Even though all three pooled funding ideas face significant technical and practical barriers at this time, the work that has been done by their proponents to develop these ideas is still useful and could be leveraged, in one form or another, going forward. The innovative concept behind PDP-FF—especially its attempt to tap capital markets through public sector guarantees—may be worth further study, even if such a fund does not materialize any time soon. In the same vein, a scaled-down version of FRIND that focuses on financing a subset of high-priority efficacy trials has some technical merit and might stand a better chance of being embraced by the donors; it could be worthwhile to take another look at such a reduced version of FRIND. IRFF's relative simplicity could also be worth testing through a pilot, if and when a critical mass of new and existing donors decides that it is ready to experiment with the Fund's concept of channelling a pool of extra resources to product development through "automatic" reimbursement of certain PDPs, a concept that has proven highly effective in independent assessments.

1. INTRODUCTION

1.1 Role of this study

This study is an independent assessment of three policy ideas aimed at accelerating the development of drugs, vaccines, diagnostics, and other health technologies for neglected diseases:

- The Fund for Research in Neglected Diseases, or FRIND, first proposed by Professor Paul Herrling of Novartis in 2007
- The Product Development Partnership Financing Facility, or PDP-FF, a proposal presented in February 2009 by IAVI, working in partnership with Aeras and the Malaria Vaccine Initiative (MVI)
- The Industry R&D Facilitation Fund, or IRFF, proposed in a 2005 report by the Pharmaceutical R&D Policy Project (PRPP, which subsequently became a research unit housed in the George Institute)

The three proposals share the common feature of allowing donors to invest in a portfolio of research projects within and across diseases and capturing central information of activity and progress across research portfolios. However, the proposals vary in the emphasis placed on, and mechanics of how they would achieve, expansion of the neglected-disease R&D resource base or improved resource allocation towards the most promising or most critical research areas.

1.2 Overview of the study

Section 1 introduces the study and sets out the approach. **Section 2** provides an overview of the proposals—describing what the proponents suggest the proposals will deliver. **Section 3** presents our analysis of the mechanisms and our assessment of whether they are likely to deliver what they say they will. **Section 4** presents our overall conclusions.

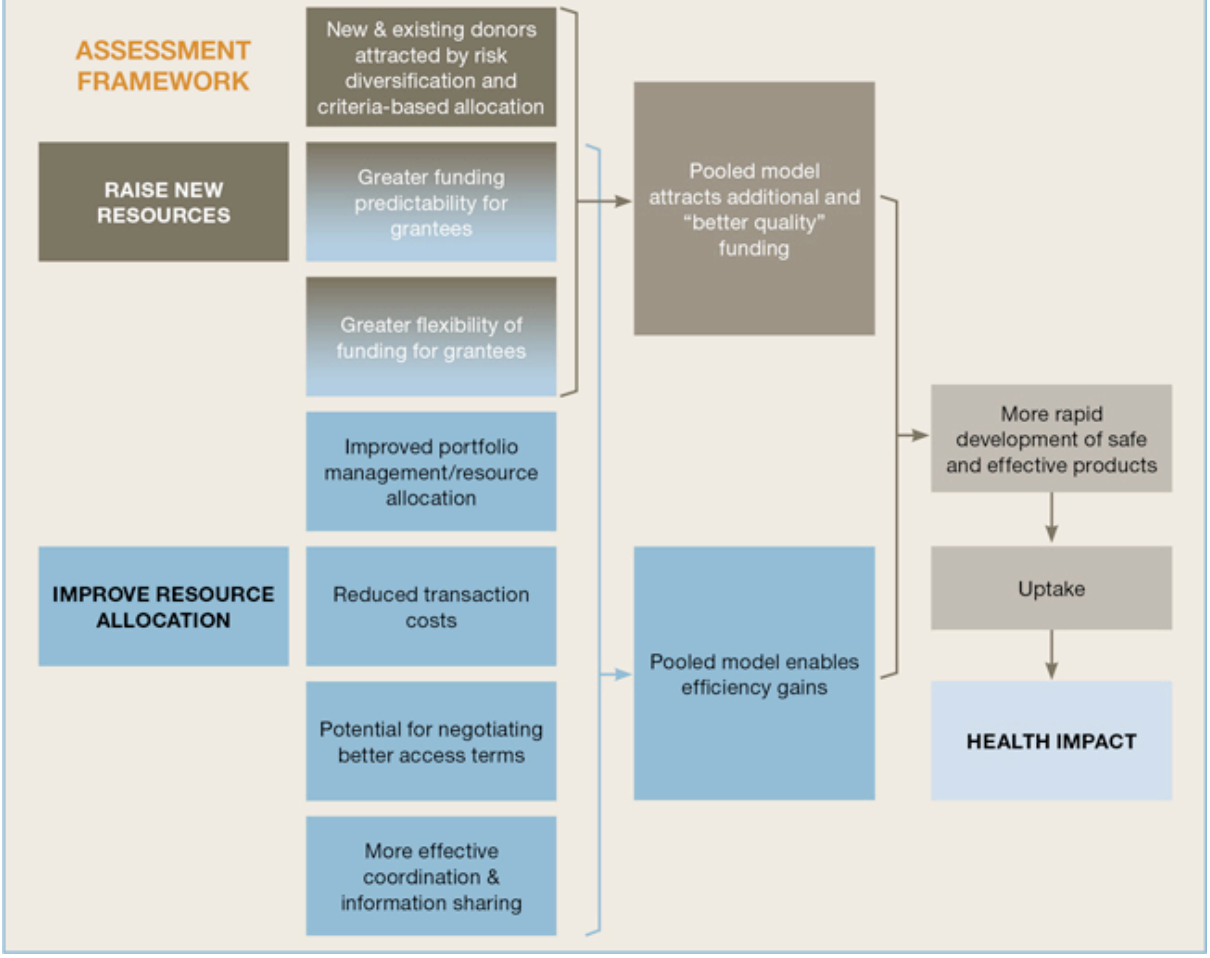
1.3 Key assessment criteria and expected causal pathway

The three pooled funding proposals are assessed against their expected ability to achieve two principal objectives:

- Capacity to raise additional R&D finance for neglected diseases
- Capacity to improve the allocation of that expenditure – improved outputs and impact relative to the investment

We identify a number of ways in which the proposals might be expected to deliver against these principal objectives. These criteria are mapped out in the figure below, which sets out the causal pathway through which the proposals are ultimately expected to result in improved health outcomes. The underlying assumption of each proposal is that the current system of neglected-disease R&D funding is suboptimal along one or more of these dimensions.

Figure 1.1. Expected Causal Pathway



1.4 Methodology

We adopted the following approach to analyzing the proposals against the criteria:

- Review of the literature (bibliography in **appendix A**)
- Interviews with more than 50 stakeholders (institutions listed in **appendix B**)
- Illustrative modelling of the possible effects of pooled funding mechanisms (**appendix C**)
- Context setting (a mapping of current challenges and emerging opportunities in the neglected-disease R&D landscape is provided in **appendix D**)
- Mapping what each proposal aims to do (section 2)
- Our assessment of what we think the proposal actually would achieve (section 3) on the basis of stakeholder interviews and our analysis

We present stakeholder views, against each of the seven criteria, and then we present our analysis of the pooled funding proposals in relation to the criteria. It should be noted that stakeholder imagination was captured most by the topics of portfolio management and financial resource needs and,

consequently, by the prospects of the proposals to address challenges within these areas. Therefore, there are more stakeholder quotes presented on those two subjects than on the other criteria.

1.5 Rationale for a new fund

The case for a new mechanism rests heavily on the assumption that there are significant problems with the current situation and that there is little likelihood that the problems will be resolved through existing mechanisms or approaches. Thus, for each criteria, we discuss the evidence for the extent of the problem, identify alternative options for resolving problems, and present our assessment of whether the proposal would be a superior method to resolving the problem, relative to the alternatives identified.

2.1 Introduction

This section provides a broad overview of the proposals. We describe the rationale for each proposal and how the mechanism is designed to work. The focus is on the question of what the proponents claim their proposed mechanism will do and how. We summarize this section with a table matching up each proposal's intentions to our assessment criteria. Section 3 lays our assessment of whether the proposed mechanisms are likely to deliver on their intentions and whether they best meet the key outstanding issues. It is worth noting that the proposals are fluid—they have been evolving over time and continue to evolve. It is also important to recognize that some features of the proposals are seen as fundamental, while others are more flexible (e.g., designed for vaccines but could be extended to drugs as well). These two points—fluidity and flexibility—are not fully reflected in the written proposals but become apparent as one talks verbally with proponents. In this section, we have tried to reflect the most up-to-date thinking, while also explaining the options and iterations that have been considered with each proposal.

2.2 Product Development Partnership–Financing Facility (PDP-FF)

Rationale

The PDP-FF proposal—championed by IAVI working in partnership with Aeras and MVI—sees the main current challenges in neglected-disease R&D as

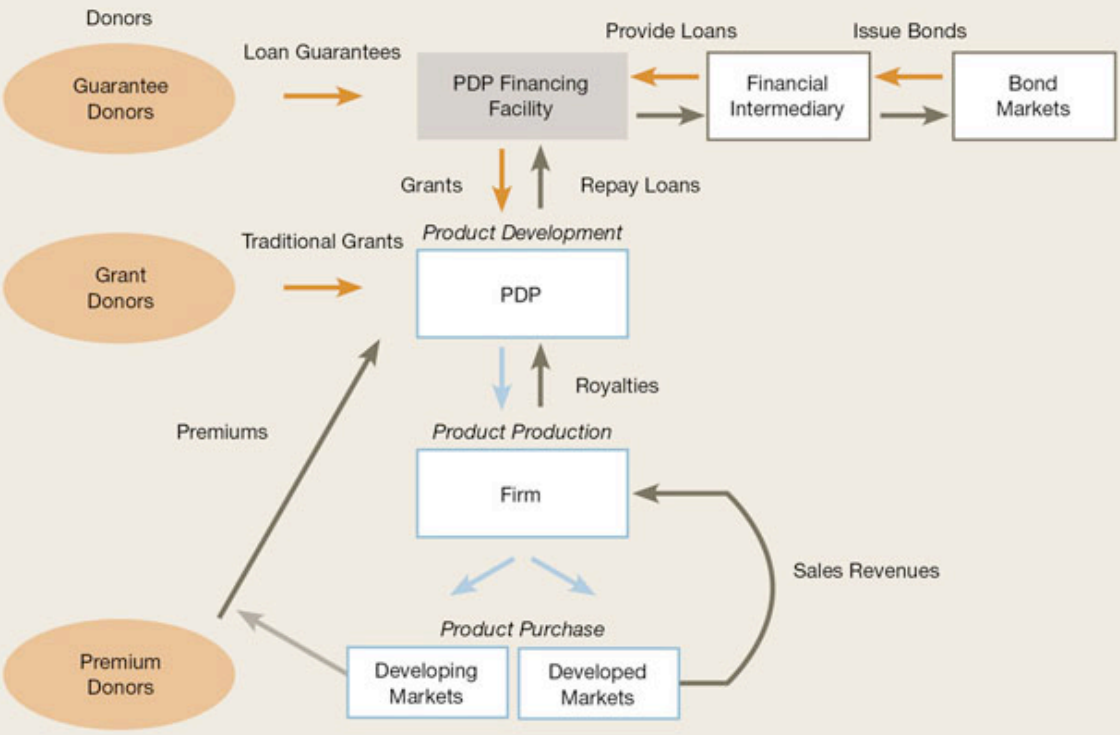
- the lack of PDP resources (in comparison to projected needs);
- insecurity in funding (with most grants typically lasting for three to five years or less compared to approximately10 to 15 years of funding needed to develop an AIDS vaccine);
- fragmentation of funding and/or excessive reliance on an individual donor;
- inflexibility in funding (with much of the potential funding available only for drug development, when that might not be the top priority).

The Facility aims to deliver a "substantial new source of secure and long-term funding" and, in doing so, provide the greater security of funding necessary to allow the PDPs and their partners to plan activities, including staffing arrangements and investments, with more confidence. It would allow investments to be made by vaccine PDPs "quickly and nimbly." The approach would also deliver value for money by "reduc[ing] the financial burden of vaccine development on donors" through royalties derived from product sales in industrialized countries and allowing donors to pay "only for success" through the premium mechanism. The approach requires, and therefore creates incentives for, greater collaboration between the three PDPs (IAVI, Aeras, and MVI) the proposals are based on (though it does not set out how this will take place). Risks to donors would be reduced through the portfolio effect achieved by the Facility and would be particularly attractive to donors "who lack the expertise or appetite for managing the allocation of funding." These advantages are believed to outweigh the somewhat higher transaction costs and concerns PDPs may have about any loss of direct control over allocation and funding decisions, as well as difficulties of provisioning support to allow for possible shortfalls in revenue. The

proposal is based on vaccines and the focus on three PDPs, but the proponents argue that this is purely illustrative and could be expanded to a wider range of products.[1]

How would it work?

Figure 2.1. PDP-FF



Source: Adapted from IAVI PDP-FF Concept Note (unpublished)

The PDP-FF is built on legally binding commitments made by donor countries to repay bondholders in the event of any financial shortfall. (Only entities with a credit rating can provide such guarantees, which effectively narrows potential funders to sovereign nations and some private sector entities. Other donors would have to provide support in different ways.) On the basis of these commitments, bonds can be issued on international capital markets, and the proceeds used to finance the PDPs' activities. Preliminary discussions have taken place with a number of organizations, including the World Bank, to identify an institution that might assume the responsibility for issuing the bonds. The proposal builds on the lessons from the GAVI Alliance's International Finance Facility for Immunization (IFFIm) experience (in which the establishment of an independent borrowing facility was seen as costly in terms of set up and additional financing costs) by proposing to work through an existing structure, such as the World Bank or a Regional Development Bank. Responsibility for repaying bondholders ultimately rests with the donors providing the guarantees. However, the approach is designed to be self-financing in the sense that bond repayments are designed to be fully covered through three revenue streams. These streams are as follows:

[1] Under normal accounting rules, donors would have to account for support when the commitment is made rather than when funds are actually spent. In theory, under the PDP-FF plan, there would be no need to make any provision as no calls on the guarantees are expected. A case would have to be made to the relevant regulatory authority—e.g., Eurostat in the case of European donors.

- *Royalties:* These will be negotiated with manufacturers of products with commercial prospects and applied to sales in high- and middle-income countries. The proposal outlines a range of possible approaches, while acknowledging that each participating PDP would need to negotiate its own royalty agreements with partners.
- *Premiums:* These are paid by a donor based on sales for a certain period after launch in low-income (or GAVI-eligible) countries once products are introduced. Funds would be channelled to the PDP-FF—either directly or through suppliers. (Premiums are in many ways similar to advance market commitments, where a donor agrees to supplement the affordable price paid by purchasers in low-income countries to offset R&D costs.)
- *Grants:* Donors would be welcome to provide grants at any point. These would be separate from PDP-FF but considered alongside PDP-FF as part of the PDPs' long-term financing needs.

Royalty payments would depend on the PDPs' contribution to the IP and could take several forms. Premium payments could be built into contracts with industrial partners (to focus on a particular product) or could be paid directly to the PDP-FF (and effectively pooled) if agreed upon afterwards.

Resources would be allocated on the basis of the initial long-term expenditure plan submitted by PDPs and agreed upon by the donors providing the guarantees. The proposal provides little detail on the criteria that might be used for assessing needs and rationing resources if demand exceeds the supply of funds. This would have to be decided by donors once the scope of any facility is established. Clear rules and a decision-making process would be established to allow for subsequent reallocations both within and between PDP programs to allow for changing priorities and circumstances. Some restrictions would be placed on the types of expenditure eligible for funding. For example, there would be a limit (to be defined) on the share of funding that could be spent on discovery and early-stage R&D, with the bulk of spending assumed to be on late-stage R&D. There would also be some ceilings on the share of resources individual PDPs could receive to ensure an equitable allocation. Factors used to determine ceilings would include the availability of promising investments, sources of other funding and the chances these might decline, and contribution to PDP-FF revenue. (The last of these raises some possibility that the Fund might focus unduly on projects with commercial prospects rather than ones that most benefit the poor.)

In terms of governance, it is envisaged that the Facility would have a small secretariat. There would be a full-time CFO and an audit capacity, but the majority of staffing would be provided in kind by PDPs. There would be a small board (PDPs, donors, experts)—possibly with an independent technical committee—to approve allocations and adjust disbursements. The proposal notes that reallocations between PDPs are more difficult, which suggests that unanimity will be required to make changes and that a large majority might be needed to reallocate between R&D stages. This raises the possibility that the very types of reallocations most likely to have an impact are the least likely to occur, though this would depend on how the Board functions. Criteria for determining priorities would include scientific merit, interests of PDPs, and interests of donors (including interest in ensuring repayments).

The PDP-FF is designed to provide additional funds (e.g., through royalties), but the potential for donors to substitute resources and thus offset, at least in part, such gains is seen as a risk. The projections suggest that this mechanism—as applied to the three PDPs—could raise some $2.2–6.9 billion over the period 2010 to 2040 ($0.9–2.3 billion in present value terms), with premiums accounting for between 66% and 89% of the total. This could provide each PDP $29–73 million annually for 15 years.

The approach assumes that, as a stakeholder articulated, "an unprecedented degree of coordination in their financial planning, fundraising processes and negotiations with industrial partners" will take place to ensure that initial allocations can be agreed upon and implementation can proceed.

Key risks identified in the proposal by its designers include:

- possible shortfalls in revenue streams (the prospects of which may make donors reluctant to provide guarantees);
- possible problems in agreeing on appropriate royalty rates (it is difficult to do this both retrospectively for products that are well advanced and for those at early stages, where commercial prospects are highly uncertain);
- possible unwillingness of the World Bank to act as a financing intermediary for problems in agreeing upon allocation and governance arrangements;
- a potential reduction in other donor-financed core funding for the respective PDPs.

2.3 Industry R&D Facilitation Fund (IRFF)

Rationale

The IRFF was originally proposed in the 2005 Wellcome Trust funded report written by the Pharmaceutical R&D Policy Project.[2] This report assessed the landscape of, and performance of, selected drug PDPs. The report concludes that industry participation in PDPs is associated with more successful and cost-effective outcomes and that the extent of PDP/industry partnerships was suboptimal prior to 2005, partly as a result of lack of funding predictability. Consequently, the aim of the IRFF is to increase predictability of funding and to enable PDPs to attract more industry participation in the neglected-disease R&D space. Furthermore, the IRFF would allow donors to diversify risk by allowing them to invest in a large portfolio of PDPs.

How would it work?

The IRFF would define strict eligibility criteria. All eligible entities would be registered non-profit health entities with the following:

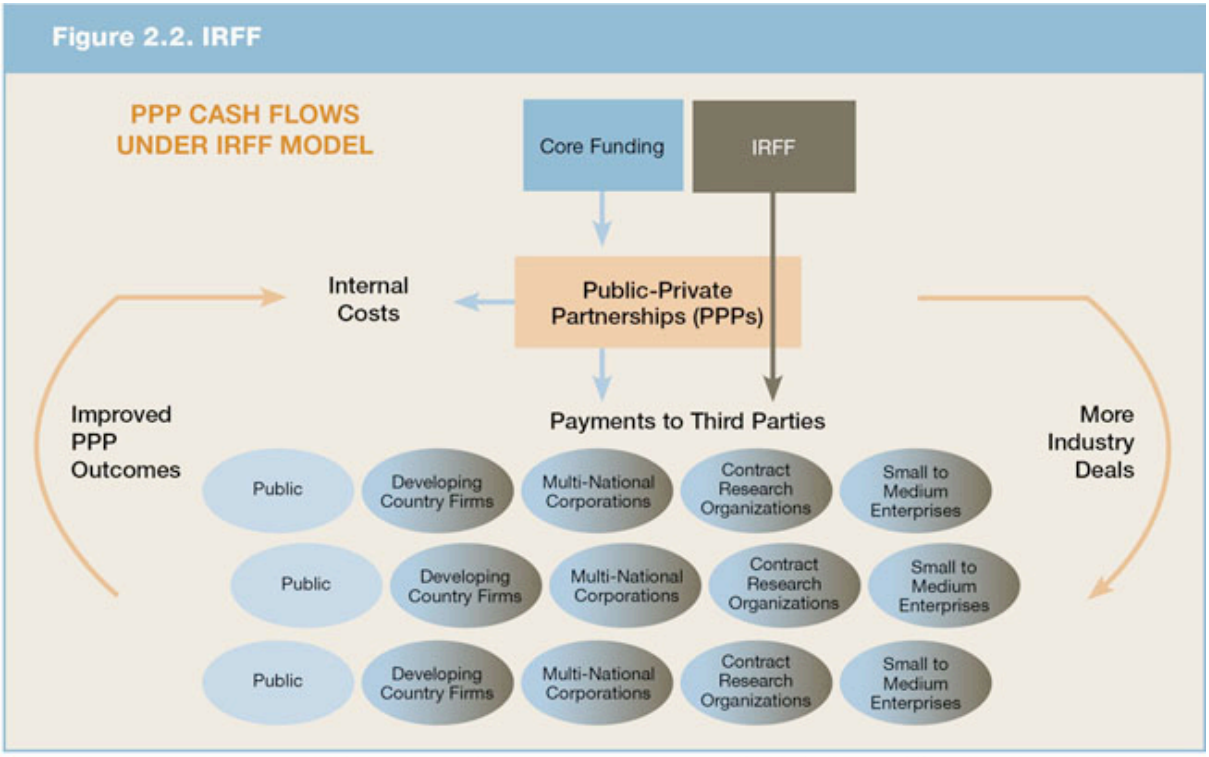
- a primary focus on drug development for neglected diseases;
- a charter that includes access to final products for developing-country patients (for example, affordability and appropriateness);
- a solid portfolio, which is non-redundant with that of other public–private partnerships (PPPs);
- scientific and management teams with drug-making experience;
- a detailed forward budget;
- an operating track record of two years or more; and
- an ability to produce yearly audited accounts.

[2] Pharmaceutical R&D Policy Project, The New Landscape of Neglected Disease Drug Development (London: London School of Economics and Political Science and the Wellcome Trust, 2005). Available online at http://www.policycures.org/downloads/The_new_landscape_of_neglected_disease_drug_development.pdf.

The IRFF would require eligible PDPs to develop multi-year financing plans and to agree to an on-going process of progress review against these financing plans. Flexibility of funding would be restricted to contracts with industry (this has been verbally revised) but funding would otherwise be unrestricted and provided on a per portfolio basis allowing PDPs to retain control of the selection, implementation, and termination of projects. PPPs would continue their current practice of establishing R&D funding contracts with industry third parties, including commercial contracts with small companies, competitive subcontracts with contract research organizations, and co-payments to large pharmaceutical companies. The idea of the IRFF facilitating better resource allocation would come about indirectly: "IRFF favors optimal performers, as those who move the most projects most quickly will draw more from the fund."

The IRFF would commit to a PDP ceiling of funding for five years, based on donor commitments of five years. Accredited PDPs would be automatically reimbursed for a portion (e.g., 80%) of their expenditures on industry contracts. (Partial reimbursement limits the risk of potential overuse by PPPs.) The replenished PPPs could then take on additional neglected-disease projects in their portfolio, including further industry contracts. Paying in arrears would provide stronger incentives for PDPs to provide the necessary information to the IRFF to allow them to develop central oversight. There would be an option for the IRFF to also act as a hub providing shared or centralized services, such as legal services, human resources, regulatory support, etc. IP negotiations would remain the responsibility of the PDPs.

Figure 2.2. IRFF



Source: Adapted from Pharmaceutical R&D Policy Project, "The New Landscape of Neglected Disease Drug Development," 2005

A small management team and advisory board would be responsible for:

- accrediting PPPs;
- reviewing R&D portfolios of funded PPPs and managing the global cross-PPP portfolio (e.g., ensuring no duplication of efforts);

- reviewing and advising on yearly PDP budgets;
- ensuring streamlined disbursement of funds;
- providing PPPs with financial/portfolio planning advice and support where needed;
- reporting to donors; and
- managing any unspent donor-committed funds.

Advantages for donors are proposed to be

- simplified policy choices by providing a single mechanism to fund all industry partners of all drug PPPs across all neglected diseases (including those beyond malaria and TB);
- rapid and measurable R&D pipeline progress achieved in the same financial year, rather than long delays to see successes, which might otherwise be the case when donors have a more limited pool of grantees;
- access to accurate real-time information on donors' expenditure and its impact—thus allowing donors to review the mechanism within a short period;
- funding of only proven organizations and companies;
- diversification of funder risk, since donors would now fund a global PPP-industry portfolio, rather than single groups or projects.

Funding is additional to core funding and was intended to cover estimated funding gaps to bring the PDP to its "optimal portfolio" (definition not elaborated). At the time of the proposal, this funding gap was estimated to be some $130–190 million per year. It was proposed that new donors could be attracted to this mechanism. European Commission (EC) member states were mentioned specifically, as well as smaller donors lacking the capacity for due diligence to choose which PDP to fund.

2.4 The Fund for Research in Neglected Diseases (FRIND)

Rationale

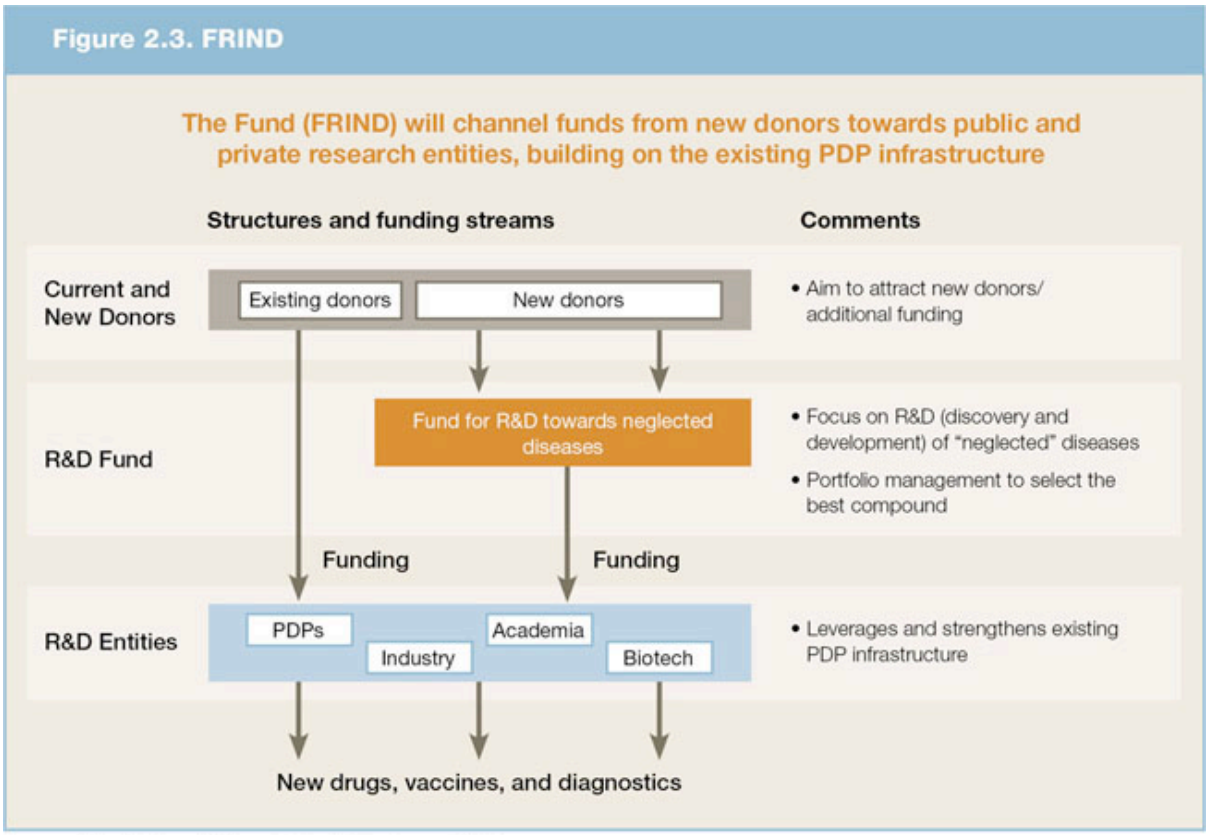
The rationale for FRIND is the recognition that pipelines are maturing, and resources are insufficient to bring the existing pipeline candidates through to registration. FRIND is focused on getting those candidates already in the pipelines through to registration at the least cost/avoiding waste. The FRIND proposal discusses the need to attract additional resources from traditional donors as well as developing-country governments. (While the pooling feature has the potential to attract small donors whose needs may not be well served by the current system and where the time spent per grant value equation does not work well for PDPs, FRIND does not focus on this.)

How would it work?

Eligible diseases in the FRIND proposal include the ten on the Special Program for Research & Training in Tropical Diseases (TDR) list—including malaria, TB, and neglected tropical diseases—and eligible technologies include drugs and diagnostics. The FRIND proposal assumes that all neglected-disease R&D donors—existing and new—wanting to fund this subgroup of diseases and technologies would agree to pool their funds into a common fund. This fund would have a Board and a portfolio management team with not only central oversight of the relevant neglected-disease R&D space but also leverage to make resource-allocation changes within that space, in pursuit of improved efficiency. The proposal discusses

the need to avoid political influences in resource-allocation decision making, and instead focus on medical and scientific criteria. Funding would be provided in arrears, milestone to milestone, with the goal of bringing increased rigor into portfolio management and ensuring that suboptimal projects are killed early. Some potential for revenue generation is acknowledged but not quantified.

Figure 2.3. FRIND



Source: Adapted from Dalberg Global Development Advisors

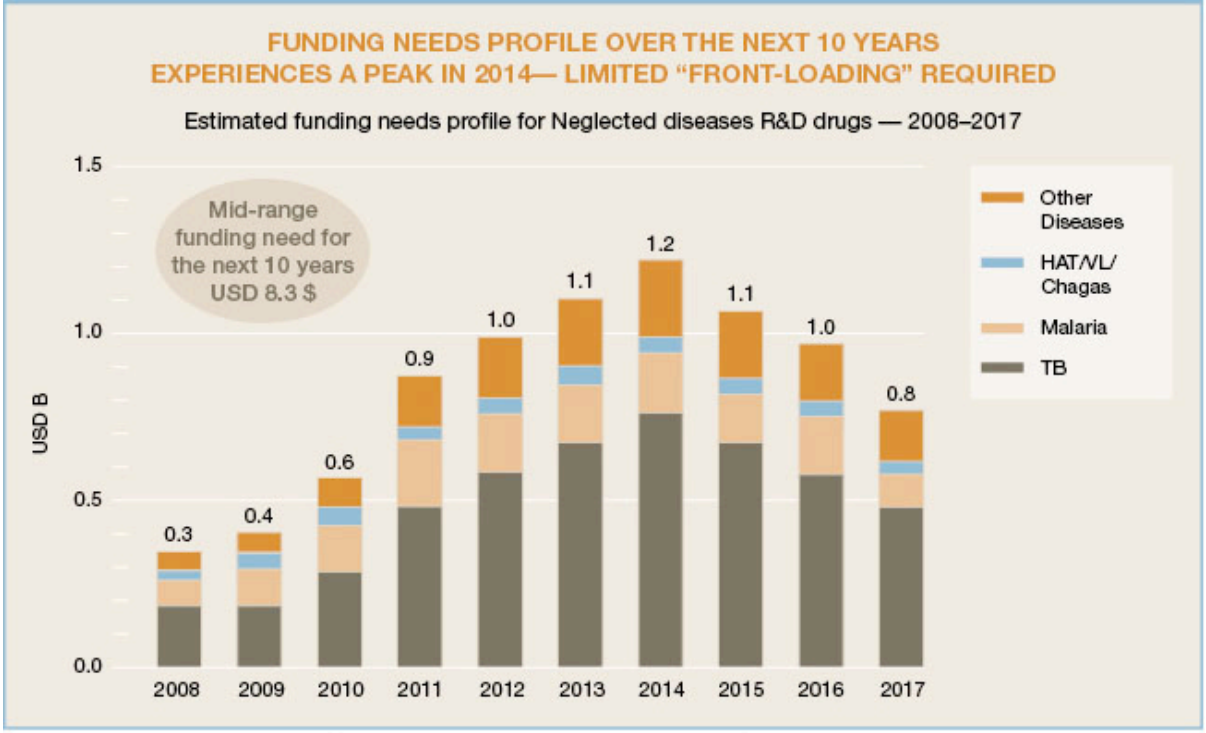
Originally, the proposal assumed that late-stage work would be funded in malaria and TB; that all stages of R&D for visceral leishmaniasis (VL), Chagas' disease, and human African trypanosomiasis (HAT) would be funded; and that discovery work would be funded for smaller diseases. FRIND proponents projected a resource need of $6–10 billion over the next ten years to fund R&D needs within the ten TDR diseases. An allocation formula was not developed, but early modelling suggested that 75% of the funding might go to TB and malaria late-stage work, based on funding needs at the time of the modelling.

Subsequent written iterations of the proposal have looked at the option of "partial portfolio management," whereby only a partial subset of the disease and technology space is funded. More recent verbal discussions with proponents have revealed an even narrower option, in which FRIND would fund only the "strongest compounds in late-stage development." Verbally, the proponents clarified that a focus on late-stage work recognizes the potential innovative benefits of "chaos" during earlier phases of R&D and the need to focus rationing on the expensive late stages of R&D.

Eligibility for funding is wider than PDPs; any product developer could apply. In the written proposal and also during subsequent due diligence work conducted by advisors, it was proposed that FRIND would own exclusive license to the technology—although only for the indication that had been funded by FRIND. It was explained that the goal is to create an IP pool, with the Fund being the owner of technologies, controlling where the technology is produced and registered and at what price it is made

available. Subsequent to publication of the consultation draft of this report, we were informed that the IP policies FRIND would institute are not yet set in stone and there is current rethinking on the issue.

Figure 2.4. Funding Needs Profile



Source: Dalberg Initiative for Sustainable Funding for Neglected Disease R&D. Final Report 2007.
Data source: Global plan to stop TB 2006; MMV financial plan 2008–2017; DnDi Busijess Plan 2007–2014; Dalberg interviews and ananlysis.

FRIND's Executive Board would provide overall governance and oversight on behalf of the donors, the Health Economic Expert Committee would propose funding allocation across diseases and technology type, and the Fund's Scientific Advisory Committee would perform due diligence on portfolio funding requests from PDPs and project funding requests from other entities—and maintain an overview across all portfolios. The Scientific Advisory Committees of the PDPs would continue to manage the PDPs' portfolios—but would be strengthened with FRIND advice and support. In the full portfolio management option, FRIND management would have central oversight and leverage with which to compel grantees to share information and coordinate resources. There is also mention of housing the N2D2 research platform within the Fund, supporting discovery activities for all diseases.[3]

[3] The N2D2 proposal, or the idea to create a Network for Neglected Disease Discovery, which was originally conceived by Paul Herrling and Trevor Jones, aims to facilitate collaboration between pharmaceutical firms and PDPs on, especially, compound library screening.

Table 2.1. Summary of what the proposals say they will do

Critria	PDP-FF	IRFF	FRIND
More resources	Yes – choice of routes—guarantees, grants, premiums… and royalties…	Aims to attract donors unwilling/unable to undertake due diligence, EC member states mentioned specifically	Recognizes need to attract new donors, as well as existing donors, into the Fund
Improved predictability of funding for grantees	Yes – in terms of raising $ for PDP-FF, donors legally bound	Yes – in terms of a committed PDP ceiling of five years and automatic reimbursement to accredited PDPs	Not a focus – milestone payments according to clear success criteria; emphasis more on using funds as carrot to drive performance, not on providing predictability of funding
Improved flexibility of funding for grantees	Yes – core funding for long-term plans, but with certain conditions (restricted share to early stage) No – restricted to PDPs	Yes – flexible funding in support of business plans; funding ceiling is for entire portfolio, not by project	No – implication of milestone payments is that funding is per project (Note: if late-stage funder, then first point less restrictive) Yes – in the sense that institutional eligibility is wider
Reduced transaction costs (TCs)	No – seen as additional funds with limited additional costs	PDPs spend less time engaged in fund-raising	Yes – would reduce TCs for donors and PDPs in the full PM option but increase TCs in the partial PM option No – implication of milestone-based funding is increased TCs
Improved portfolio management (PM)	Not a focus of the proposal	Within PDP PM: PDPs retain full responsibility for accelerating and terminating projects Across PDP PM: IRFF "favors optimal performers," as those who move the most projects most quickly will draw more from the Fund	Within PDPs – a major focus of the proposal is the role of the milestone payments and FRIND portfolio review committee in killing suboptimal projects Between PDPs – a major focus of the proposal is the advantage of central oversight of comparative data generated, allowing improved allocation
Better coordination	Yes – agreeing on allocation will require coordination; otherwise, not a major feature of the proposal	Sees a potential Fund role in providing platform services to PDPs or acting as an information clearinghouse for industry and PDPs	FRIND's central oversight role and leverage (in the full PM version) is seen as an enabler of better coordination and sharing of lessons learned; N2D2 could be housed in the fund
Governance and management	Joint Board to which PDPs will subjugate decisions (concerning the allocation of funds from PDP-FF)	Small management team with a focus on pharmaceutical portfolio and fund management, supported and directed by an advisory board with a mix of neglected-disease experience and financial knowledge (for accountability purposes)	Envisages a Governance Board with donors and a PM Board making allocation decisions based on scientific, economic, etc., criteria (not political criteria)
IP	Participating PDPs would retain full responsibility for IP negotiations	PDPs would retain full responsibility for IP negotiations	FRIND would own exclusive license to technology – only for the indication funded

This section contains our summary of findings of how the three proposals fare against the key criteria, summarized in text and then in table format. In the subsequent section, we define and clarify the criteria, discuss the degree to which challenges have been identified within that dimension, discuss alternative means of addressing any identified challenges (i.e., the counterfactual), and explain the detail behind our assessment of the proposals against the criteria.

Ideally, any new mechanism should be able to provide strong evidence on the weaknesses of current approaches, address at least some of the most important constraints, and do so in ways that are proven to work. An initial finding—which is worth stating up front—is that **the evidence base in terms of the performance of the current system against a number of crucial dimensions is weak.** The implication of this is that **if we do not know the extent of the current problems, it becomes extremely difficult to assess the extent to which the proposals can address them.**

For instance, stakeholders interviewed had widely divergent views about the importance of revenue mobilization; some felt the scientific challenges in their sector were more substantial than the funding challenges, while others were already keenly aware of the impact of funding constraints and were altering their decision making because of it. BMGF has made public statements indicating that there will be a funding shortfall before fully funding its current portfolio, but as of yet, we have no evidence on the magnitude and timing of the shortfall. Hence, we conclude that the evidence base is weak on this important dimension.

Similarly, while stakeholders agreed with the principle that resources should be used efficiently and that portfolio management is an important means to achieving this goal, there was less agreement on whether an actual problem with portfolio management exists. Many stakeholders (particularly from industry) opined that there is scope for improvement in within-PDP portfolio management, while many others (particularly from PDPs) believed that portfolio management is fairly sound and that the examples of fragmentation and duplication often discussed are now out of date and irrelevant. Empirical data to make an informed decision are scarce and lacking scientific validity, as discussed further in the portfolio management chapter of this paper.

3.1 PDP-FF

Resource mobilization: Is the Fund likely to draw more resources into neglected-disease research and development from existing or new donors?

Of the three proposals, PDP-FF is the one that focuses most on resource generation. PDP-FF is attractive in the sense that it provides a choice of funding modalities—donor guarantees, royalties, and premiums. The whole approach is dependent on having sufficient donors willing to provide legally binding guarantees. The pool of such donors is rather limited (to entities with a credit rating); further, some donors' public finance rules prevent them from entering into multi-year agreements. For others it is simply a matter of choice—they are not comfortable making long-term commitments. However, if sufficient guarantees to establish the model have been secured, the Fund is then open to contributions from donors who are keen to reward success or be associated with successful products through the provision of premiums. The overall scheme is also intended to attract those interested in sustainability,

as the intention is that the approach would be self-financing in that revenue from royalties and premiums would be designed to cover R&D investment costs and that the guarantees would not, ultimately, need to be called. Some donors have an interest in innovative financing more generally and might be willing to support PDP-FF for this reason. The approach would also offer flexibility for donors to make grants, on a more opportunistic basis, should they have funds available. On the downside, the complexity of the approach may make it difficult to sell the approach to donors' tax payers, especially given widespread concerns about financial engineering following the financial crisis. Incentive/presentational issues would also need to be resolved. (For example, a donor paying a premium would effectively be bailing out a donor providing a guarantee. For donors who wish to see their support as directly supporting R&D, this may be a drawback.) It is also possible that the approach will be more attractive where the R&D efforts are likely to be successful imminently, rather than in areas that are most important and where immediate wins are not possible. Similarly, it also creates incentives to focus efforts on products that are likely to have some commercial market and royalties might be possible, rather than on products likely to be used only by the very poor. There is a further risk that front-loaded funding will increase long-term sustainability challenges, through the establishment of an unsustainable pipeline and/or postponing an even larger financial crunch in part by giving donors the (misleading) impression that funding issues have been resolved.

Predictability: Would the Fund be more likely to increase predictable revenue mobilization in the long term and disburse funding more predictably to research groups?

This is a major strength of PDP-FF. The model provides entirely predictable resources as support (the donor guarantees) that are legally binding, and bond issues can be timed to fit with any fund's needs. The intention is for funds to be allocated up front on the basis of agreed upon 10 to 15 year plans with PDPs (covering all funding sources), with clear rules on reallocations that should allow PDPs to engage in long-term planning. However, while the model provides predictable money for the fund, the extent to which this leads to more predictable funding for individual PDPs—and promotes better decision making as a result—depends on the ability of the Fund to channel funds in a timely and predictable manner. It also assumes that institutional arrangements (e.g., governance structure, capacity) allow for better decision making. The risk is that more predictable funding could lead to reduced incentives to perform or to kill suboptimal projects, if arrangements are not structured to manage this risk. (This relates more to the basis for disbursement than to the predictable nature of the funding.)

Flexibility: What restrictions does the Fund have in terms of disease area, technology type, research and development stage, and institutional eligibility, and are these restrictions sensible?

The degree of flexibility depends on how any fund would be designed and which diseases, technologies, pipeline stage, or types of activities would be eligible for reimbursement by the Fund. The risk is that the focus on self-financing and the ability to negotiate royalties will restrict choice of products to those that have commercial prospects and where the IP holder is willing to agree to royalty arrangements. As the proposal stands now, there are a number of key restrictions (though this does not necessarily imply that they are not valid). For example, only certain types of activities will be eligible; for example, a ceiling would be set on the share of funds that could be allocated to discovery and early-stage trials. In addition, the proposed rules for reallocating resources between PDPs (which, it is suggested, would require unanimity) make such changes unlikely. The funding is also restricted to PDPs, so is likely to leverage new opportunities in the neglected-disease sphere only to the degree that PDPs leverage these opportunities.

Portfolio management: **Is the Fund likely to improve the effectiveness of resource allocation or portfolio decision making across development efforts where donors are making the decisions and, secondly, portfolio management within PDPs?**

This is not a major focus of PDP-FF. As mentioned above, within PDPs there is a concern that the focus will be on products with potential commercial markets, which may not coincide with products having the best potential for health impact. Across PDPs, there is the possibility of reallocating resources, with clear rules and processes set out for such reallocations.

Transaction costs: **How intensive are the initial setup and ongoing transaction costs of the Fund, and to what extent are they necessary and/or justified?**

Experience from IFFIm suggests that up-front establishment costs are likely to be substantial. Given that new allocations are set once, up front, ongoing transaction costs would be low to modest in the long run but would depend upon the nature of the check-in at periodic intervals and ongoing bond issuance costs. Many PDPs are already exploring innovative financing options independently, in recognition of the coordination and time-lag costs associated with a collective approach.

Intellectual property policies: **Do the Fund's policies on intellectual property strike the right balance between fostering access to the technologies it supports and offering the Fund the best choice of partners for research and development activity?**

This is not a feature of the proposal—PDPs would continue to manage IP, as is the case currently. As noted above, the revenue-generation goal carries the risk that PDPs will aim for projects where they can extract favorable IP terms, which may limit partnering options

Improving coordination and information sharing: **Would the Fund be likely to improve coordination and information/resource sharing amongst product development partnerships and across research and development efforts more generally?**

The proposal accepts that agreeing on allocations will require coordination but does not specify how this will take place.

3.2 FRIND

Resource mobilization: **Is the fund likely to draw more resources into neglected-disease research and development from existing or new donors?**

FRIND's greatest fund mobilization potential theoretically comes from donors who are lacking in due diligence capacity. In the Phase III variation of FRIND, a pooled fund would also fit well with the needs of donors who require more immediate results. Interviews with potential donors revealed that traditional donors who are heavily invested in neglected-disease R&D, with strong due diligence capacity, are not attracted to pooled funding models. However, some existing PDP donors with less due diligence capacity were lukewarm to the idea, and the most positive response came from donors who would be entirely new to the sector.

Predictability: Would the Fund be more likely to increase predictable revenue mobilization in the long term and disburse funding more predictably to research groups?

FRIND would seek to increase predictability of the overall neglected-disease funding envelope available for successful compounds (i.e., predictability of resource mobilization) but not predictability for individual compounds (predictability of resource disbursement). In case of failure and lack of results with an individual compound, funding would be stopped immediately. This milestone-by-milestone disbursement approach contrasts with a core funding approach and is focused on rectifying perceived inefficiencies in the current grant-funding system, providing increased performance incentives. In the Phase III FRIND variation, funding is secure for the duration of the phase so the disbursement predictability point becomes less relevant. As for the revenue mobilization criteria, whether FRIND could actually achieve predictability in resource mobilization depends on the length and nature of donor commitments; this makes FRIND relatively less predictable compared with PDP-FF on this parameter.

Flexibility: What restrictions does the Fund have in terms of disease area, technology type, research and development stage, and institutional eligibility, and are these restrictions sensible?

The due diligence work on FRIND has included consideration of several different options for the scope of the Fund, and no firm decisions have yet been made with regard to the technology types, disease areas, R&D stages, and types of activities/investment that would be eligible for support. In the earliest iterations of the FRIND proposal, potential disease areas, technology types, R&D stages, and activities eligible for support were very wide—we suggest too wide to achieve the technical oversight goals envisaged. With regard to eligibility of institution type, FRIND uniquely would fund non-PDP groups, which has the potential to pull in innovators who might not otherwise participate in neglected-disease R&D but may carry additional cost implications for the Fund to assess and manage non-PDP-housed projects. The IP requirements, as stated in written versions of FRIND proposals, would reduce flexibility of partner/grantee choice, and we understand that the IP policy is currently being reconsidered. The milestone-to-milestone/project-by-project funding approach would reduce flexibility of funding from the perspective of the grantee product developer.

Portfolio management: Is the Fund likely to improve the effectiveness of resource allocation or portfolio decision making across development efforts where donors are making the decisions and, secondly, portfolio management within PDPs?

The FRIND proposal has different variants and they each would have likely different effects on these questions. In terms of aggregate portfolio management controlled by donors, the original full portfolio management variant of FRIND would offer the theoretical potential to serve as a channel for agreeing to a rational and evidence-based approach to resource allocation across the space (though it would not be the only way to achieve this). However, stakeholders are skeptical about the political and technical feasibility of achieving such an agreement. Also, since a pooled fund is unlikely to receive support from the largest funders within the neglected-disease R&D space, we think the full portfolio management option will be unable to find the level of resource input required to give it leverage within the R&D space.

The partial portfolio management option is viewed as more technical and politically feasible, and we think it has more potential to fit with the reality of the likely size of the fund. Partial portfolio management would not bring the same degree of rigor, rationing, and central oversight into the system that was a principle objective of the original FRIND; however, we think this objective was unrealistic in the first place.

In the Phase III variant of FRIND, technical feasibility of central oversight, joint decision making, and rationing would improve, and the option seems to be more politically feasible as well.

With regard to portfolio management within PDPs, FRIND assumes that there is unnecessary duplication of R&D efforts and that there are ongoing portfolio management challenges within PDPs. The evidence base is too weak to assess whether these assumptions are valid. However, even if they are valid, we are not convinced that ever greater central oversight and monitoring will provide better results than the status quo situation with BMGF as a dominant and well-informed funder. If there are indeed agency and information problems, then more of the same is probably not the answer; rather, splicing on different incentives through different forms of funding might be a better route.

Transaction costs: How intensive are the initial setup and ongoing transaction costs of the Fund and to what extent are they necessary and/or justified?

The larger and more diverse the space FRIND would control, the more complicated the decision making and coordination would be. So, in the full portfolio management option, setup and ongoing costs would be intensive, while a fund with reduced scale and complexity would require less intensive inputs. Similarly, the wider the flexibility (of diseases covered, technology types, and, especially, types of institutions funded), the more intensive would be the assessment and monitoring requirements. But regardless of the choices made about funding eligibility, a central FRIND premise is the milestone-to-milestone funding approach and heavy emphasis on central oversight and technical monitoring. This makes FRIND inevitably more transaction intensive versus the IRFF and PDP-FF, which take a lighter-touch management approach. In the Phase III variant of FRIND, the transaction cost problem lessens, as the grant application, fund, and monitoring cycle is reduced to a single phase.

If FRIND were to substitute for numerous existing donors, each separately undertaking due diligence and monitoring activities, then overall transaction costs in the system would decline. However, our interviews revealed that the most prominent donors to neglected-disease R&D are unlikely to participate in pooled funds. Thus, their due diligence and monitoring will carry on, and the pooled fund would likely become an additional funding channel adding to the grant application and monitoring and evaluation (M&E) burden of PDPs. But if FRIND became a central channel through which numerous smaller donors could collectively fund R&D work, this would be transaction cost reducing.

Intellectual property policies: Do the Fund's policies on intellectual property strike the right balance between fostering access to the technologies it supports and offering the Fund the best choice of partners for research and development activity?

In the written proposal of FRIND, and throughout subsequent due diligence work done by advisors, it was stated that FRIND would own exclusive license to the technology—but only for the indication that had been funded. We suggest that this requirement may be too restrictive for some technology categories and likely to limit the Fund's partnering options. We understand that the IP policy is currently being reconsidered.

Improving coordination and information sharing: Would the Fund be likely to improve coordination and information/resource sharing amongst product development partnerships and across research and development efforts more generally?

In the full portfolio management option of FRIND, central oversight would facilitate better coordination and information sharing. In the partial portfolio management option, the sharing would be limited to the sectors covered by the fund, which could be quite valuable within disease areas (across technology types). We can see good potential for housing initiatives to support and facilitate across sector and across disease work, such as N2D2, though there are other means to achieve the same ends.

3.3 IRFF

Resource mobilization: Is the Fund likely to draw more resources into neglected-disease research and development from existing or new donors?

IRFF assumes that existing donors to PDPs would be attracted by the risk diversification potential of a pooled fund, as well as the potential to share due diligence with other donors. In reality, donors already feel they are investing in a diversified portfolio when they invest in several PDPs (who are themselves seen as miniportfolios). Interviews revealed that most existing donors in this space are not keen to divorce themselves from the control and decision making of how their funds are allocated. As with FRIND, the best potential match to an IRFF-type pooled fund would seem to come from fragmented, small potential donors who are entirely new to this space and lacking in due diligence capacity and where the small grant size-to-time invested ratio does not work well for PDPs; interviews yielded some positive signals from this group.

Predictability: Would the Fund be more likely to increase predictable revenue mobilization in the long term and disburse funding more predictably to research groups?

IRFF would seek to increase predictability of the overall neglected-disease funding envelope available for successful compounds (i.e., predictability of resource mobilization), as well as predictability for individual compounds (predictability of resource disbursement from the Fund to the PDP). Predictability of funding is a central feature of IRFF, as it has been opined that industry deals (in 2004 when the IRFF concept was developed) were suboptimal due to lack of funding predictability. Accredited PDPs funded by IRFF would be given a five-year budget ceiling against agreed upon business plans, and the PDP would be automatically reimbursed for 80% of R&D expenditure, upon realization of targets in the business plan. With regard to revenue mobilization, IRFF would require donors to make legally binding commitments for five years. This would be an improvement in predictability, relative to the status quo of a three- to five-year grant cycle, however, still not as predictable as the PDP-FF.

Flexibility: What restrictions does the Fund have in terms of disease area, technology type, research and development stage, and institutional eligibility, and are these restrictions sensible?

IRFF restricts funding to accredited PDPs only. This keeps things relatively simple but only leverages new opportunities in neglected-disease R&D to the degree that PDPs are able to leverage these opportunities. The detailed design issues regarding eligibility of disease area, technology type, pipeline stage, and activities were not fully fleshed out in the proposal. The original proposal restricted eligibility of fund reimbursement to industry partnerships only, which may create perverse incentives. This aspect has subsequently been verbally revised by the proponent. IRFF funds from the PDP perspective would be relatively flexible, though it would depend on how detailed the business plan is and the nature of the check-in and monitoring done by IRFF. The upfront, between PDP allocation feature of IRFF could actually increase overall system rigidity if funding cannot be flexibly reallocated to other PDPs experiencing greater success within the five-year period.

Portfolio management: Is the Fund likely to improve the effectiveness of resource allocation or portfolio decision making across development efforts where donors are making the decisions and, secondly, portfolio management within PDPs?

Like FRIND, IRFF would have central oversight and information with which to enable donors to agree on a rational and evidence-based approach to resource allocation across the space; however, this was not

an objective of the proposal. Nor does the IRFF proposal seek to manage or enable better portfolio management within PDPs; the underlying assumption is that PDPs have the correct systems, structures, and incentives to manage their portfolios well.

The intention of IRFF is to provide more predictable funding, but the risk of predictability would be to reduce incentives to perform or to kill suboptimal projects, though the PDP copayment of 20% would help offset this risk. A further concern is the apparent relationship between expenditure and performance in the proposal. This reinforces the activity focus of the grant-funding model and may not be aligned with results: expenditure does not necessarily equate to products with large health impact, or products getting to patients faster. What effect IRFF would have on portfolio management could really only be determined through more detailed design, in particular, the degree of rigor required of the PDP business plan, the nature of the check-in with IRFF at periodic intervals, and the ease with which funding would be released. If the milestones in the business plan are solid, then the risk of funding activity rather than results could be reduced.

Transaction costs: How intensive are the initial setup and ongoing transaction costs of the Fund, and to what extent are they necessary and/or justified?

IRFF would entail up-front establishment costs; at a minimum, donors would need to agree on priorities, an allocation mechanism, and a common reporting mechanism. Transaction costs between the IRFF and PDPs would be relatively modest compared to IRFF, though it would depend on a more detailed design and the nature of the business plan and M&E procedures.

If IRFF were to substitute for numerous existing donors, each separately undertaking due diligence and monitoring activities, then overall transaction costs in the system would decline. However, this is not likely to happen (there was limited interest in IRFF from existing donors); nor was substitution seen as an objective by IRFF proponents. IRFF proponents saw IRFF as an additional funding channel, so it would add to the grant application and M&E burden of PDPs. However, this may be a welcome thing if IRFF could serve as a channel though which to consolidate many small donors from whom PDPs would not otherwise find it economic to approach on a disaggregated basis.

Intellectual property policies: Do the Fund's policies on intellectual property strike the right balance between fostering access to the technologies it supports and offering the Fund the best choice of partners for research and development activity?

IRFF would work only though PDPs, so the status quo situation would be maintained with regard to IP.

Improving coordination and information sharing: Would the Fund be likely to improve coordination and information/resource sharing amongst product development partnerships and across research and development efforts more generally?

As with FRIND, central oversight could be used to facilitate better coordination and information sharing. The IRFF proposal specifically mentions a potential IRFF role in serving as an information clearinghouse and providing platform services to PDPs. (Note: There are other ways to achieve these objectives, and such work is already in progress.)

Table 3.1. Analysis of proposals against dimensions

PDP-FF

Criteria	What the proposals say they will do	Summary of our assessment
More resources	Yes –choice of routes—guarantees, grants, premiums… and royalties…	**Pro:** Provides donors with a choice of funding modalities. More likely to be attractive to results-focused donors (i.e., those willing to pay premiums), donors interested in being seen to support innovative approaches, and those interested in leveraging additional resources and getting a bigger bang for their buck (through royalties and cost-recovery element). Flexibility to translate guarantees to grants. **Con:** Complexity may make it difficult to sell the approach to donors' taxpayers. Guarantee component restricted to entities with a credit rating. Incentive/presentational issues will need to be resolved (i.e., a donor paying a premium would effectively be bailing out a donor providing a guarantee). Likely to be more attractive where the R&D will be successful imminently. Risk that frontloaded funding will increase long-term risks (potentially postponing an even larger financial crunch in part by giving donors the (misleading) impression that funding issues have been resolved).
Improved predictability of funding for grantees	Yes – in terms of raising $ for PDP-FF, donors legally bound	Mobilization: More predictable resource mobilization as support is legally binding and bond issues can be timed to fit with need. Funds are allocated upfront on the basis of agreed upon 10- to 15-year plans with PDPs (covering all funding sources), with clear rules on reallocations. Disbursement: The extent to which this leads to more predictable funding and better decision making depends on the ability of the Fund to channel funds in a timely and predictable manner (in ways that have not always been possible under IFFIm) and institutional arrangements (governance structure, capacity) that allow better decision making to take place. Risk is that more predictable funding could lead to reduced incentives to perform or to kill suboptimal projects, if not structured to manage this risk. (This relates more to the basis for disbursement than the predictable nature of the funding.)
Improved flexibility of funding for grantees	Yes – core funding for long-term plans, but with certain conditions (restricted share to early stage) No – restricted to PDPs	Depends on detailed design issues regarding which diseases, technologies, pipeline stages, or types of activities can be reimbursed with the Fund. Risk that design for self-financing and ability to negotiate royalties will restrict choice of products to those that have both commercial prospects and where IP holder is willing to agree on royalty arrangements. Only certain types of activities will be eligible (e.g., a ceiling would be set on the share of funds that could be allocated to discovery, early-stage trials). Proposed rules for reallocating resources between PDPs (unanimity) make such changes unlikely. Funding restricted to PDPs, so the Fund leverages new opportunities in the neglected-disease sphere only to the degree that PDPs leverage these opportunities.
Reduced TCs	No – seen as additional funds with limited additional costs	Upfront establishment costs likely to be substantial. Given that allocation is set once, upfront, transaction costs would be low in the long run but would depend upon nature of the check-in at periodic intervals. Many PDPs are already exploring innovative financing options independently, in recognition of the coordination and time-lag costs associated with a collective approach.
Improved PM	Not a focus of the proposal	Within PDPs: Concern that focus will be on products with potential commercial market, which may not coincide with products having the best potential for health impact. Across PDPs: Yes, with clear rules and processes for reallocation.
Better coordination	Not a focus of the proposal	Agreeing on allocation will require coordination.
IP	Participating PDPs would retain full responsibility for IP negotiations	Not a feature of the proposal. PDPs continue to manage as is the case currently. Revenue-generation goal carries risk that PDPs will aim for projects where they can extract favorable IP terms, which may limit partnering options.

IRFF

Criteria	What the proposals say they will do	Summary of our assessment
More resources	Aims to attract donors unable to undertake due diligence, wanting to pool risks in this manner; EC member states mentioned specifically as new donors potentially attracted	Theoretically, we acknowledge the potential to attract donors who would not otherwise participate in this space due to (a) lack of capacity to make evidence-based decisions about which technology efforts to back (would apply to consumers, such as MASSIVEGOOD, as well as donors with little knowledge of science or development, e.g., charity funds of banks); (b) need to show results and, therefore, attractions offered by a pooled fund, where chances of backing a winner are increased (this point exaggerated if the Fund focuses only on relatively de-risked late-stage projects); (c) desire to back something bigger/more sexy than a single disease area (would apply to same groups as in point a). Actual potential: Most existing donors believe they are already diversifying risks/investing in a pool of projects. There was no great appetite or expressed need from donors for the benefits IRFF proposed to offer. Corporate charitable giving was interested in the idea, but it is unclear how much money is available through this channel.
Improved predictability of funding for grantees	Yes – in terms of a committed PDP ceiling of five years and automatic reimbursement to accredited PDPs	Mobilization: Less predictable than PDP-FF in terms of revenue mobilization. Depends on length and nature of donor commitments. Disbursement: Funding is linked to PDP spending against approved business plans and should, therefore, be as predictable as PDP spending. Funding is automatic so should be predictable. Proposal originally restricted reimbursement to industry deals only, creating incentives to choose partners based on who will be funded rather than on who has the best candidate.
Improved flexibility of funding for grantees	Yes – flexible funding in support of business plans; funding ceiling is for entire portfolio, not by project	Depends on detailed design issues regarding which diseases, technologies, pipeline stages, or types of activities can be reimbursed with the Fund. Original proposal restricted reimbursement to type of partner. This has now been revised. The upfront, between PDP allocation feature—which offers the benefit of increased security to individual PDPs—could actually make the overall flexibility of the system more rigid if funding cannot be reallocated to its most productive use (based on changes in science and individual candidate prospects). Restricted to PDPs, so the Fund leverages new opportunities in the neglected-disease sphere only to the degree that PDPs leverage these opportunities.
Reduced TCs	PDPs spend less time engaged in fund-raising	Upfront establishment costs: Agreeing on a common approach to reporting, in itself, is likely to require significant time and effort. If Fund substitutes for existing funding channels, then overall TCs would decrease, but the vision is that the Fund would be additional, not a substitution. IRFF implies modest transaction costs at the PDP level, as funds are paid automatically according to PDP spending against approved business plans, but it would depend on nature of the check-in at periodic intervals.
Improved PM	Within PDP PM: PDPs retain full responsibility for accelerating and terminating projects Across PDP PM: IRFF "favors optimal performers," as those who move the most projects most quickly will draw more from the Fund	Across PDP PM: Concern that expenditure seems to be equated with performance, reinforcing the activity focus of the grant-funding model. Expenditure does not necessarily equate to products with large health impact, or products getting to market faster. If the milestones in the business plan are solid, then the risk (of funding activity rather than results) is lessened. Within PDP: Risk that more predictable funding could lead to reduced incentives to perform or to kill suboptimal projects, if not structured to manage this risk. Copayment of 20% helps to manage this risk.
Better coordination	Fund could provide platform services to PDPs or act as an information clearinghouse	Good potential to leverage information position of the Fund towards better coordination and resource sharing, especially needed within disease areas, though there may be other ways to achieve this.
IP	PDPs would retain full responsibility for IP negotiations	Fund access would depend on having access-friendly IP policies in place. PDPs continue to manage IP, as is the case currently.

FRIND

Criteria	What the proposals say they will do	Summary of our assessment
More resources	Recognizes need to attract new donors, as well as existing donors, into the Fund	As with IRFF, there is the theoretical potential to attract donors who would not otherwise participate in this space. Actual potential: Most existing donors believe they are already diversifying risks/investing in a pool of projects. There was no great appetite or expressed need from donors for the benefits FRIND proposed to offer. Corporate charitable giving was interested in the idea, but it is unclear how much money is available through this channel.
Improved predictability of funding for grantees	Not a focus – milestone payments according to clear success criteria; emphasis more on using funds as carrot to drive performance vs. providing predictability of funding	Mobilization: Less predictable than PDP-FF in terms of revenue mobilization. As with IRFF, depends on length and nature of donor commitments. Disbursement: At the individual grantee level, volatility higher relative to core funding, as funding is only offered milestone to milestone. The goal is to increase incentives to perform and to ensure that suboptimal projects are killed. If FRIND is limited to Phase III, then lack of predictability problem lessened, as the funding is secure during that phase of work.
Improved flexibility of funding for grantees	No – implication of milestone payments is that funding is per project (Note: if late-stage funder, then first point less restrictive) Yes – in the sense that institutional eligibility is wider	Depends on choices made by fund regarding institutional eligibility, technology type, disease area, pipeline phase, and activities. There is a risk that IP stipulations would reduce applicants to those willing to hand over exclusive license. Eligibility wider than PDPs so is more flexible than the other proposals and relative to status quo (though work outside PDPs is funded as well, e.g., Grand Challenges, but non-PDP funding tends to be discovery focused).
Reduced TCs	Yes – would reduce TCs for donors and PDPs in the full PM option but increase TCs in the partial PM option No – implication of milestone-based funding is increased TCs	In the full portfolio management option, TCs would decline as the fund substitutes for disparate funding channels. In partial PM option, TCs increase because the fund becomes additional. There would be significant upfront establishment costs. Agreeing on a common approach to reporting, in itself, is likely to require significant time and effort. FRIND implies fairly substantial ongoing TCs because M&E increases from current three- to five-year grant cycle to a milestone-funding approach. Also increased TCs because of the portfolio review committee micromanaging PDP portfolios. In the Phase III FRIND variation, TC problem lessens.
Improved PM	Within PDPs – milestone payments and FRIND portfolio review committee aid in killing suboptimal projects Between PDPs – central oversight of comparative data generated, allowing improved resource allocation across R&D efforts	Leverage limited in the partial portfolio management option. Concern about operational feasibility and effectiveness of attempting to gain oversight and control of a larger, more diverse space. If fund limited to Phase III, operational feasibility is enhanced, therefore, more likely to find a common metric and have a less theoretical discussion comparing candidates. Could provide a channel for joint donor agreement on priorities and criteria for decision making, but would not be the only means to achieve this.
Better coordination	Central oversight and leverage (in the full PM version) is seen as an enabler of better coordination and sharing of lessons learned; N2D2 option	In the full PM option, central oversight would facilitate better coordination and information sharing. Less so in the partial PM option. Good potential for housing initiatives to support and facilitate across sector and across disease work, such as N2D2, though there may be other ways to achieve this.
IP	FRIND would own exclusive license to technology – only for the indication funded	Requirement to own exclusive license too restrictive and likely to deter partners, limiting the Fund's choice/options.

4.1 Raising resources

In this section we discuss stakeholders' views about whether there is a resource gap in neglected-disease R&D and stakeholder opinion about the potential of these proposals to raise additional resources. We subsequently discuss the evidence base for the existing resource gap and other ways to raise additional resources and offer our assessment of the proposals' potential to bring additional resources into neglected-disease R&D.

What stakeholders said

There was a particular lack of consensus on the subject of whether there is a looming funding shortfall in the neglected-disease R&D space. On the one hand we heard:

- "If a good quality candidate makes it to Phase III, the funding will be there."
- "The problem isn't Phase III funding—it's getting money for discovery."
- "I may be wrong but I don't believe funding is the major issue. I'm convinced that if we had clinical trial results demonstrating a vaccine with real potential, we'd get the funding... Funding constraints are more for early-stage work."
- "[In the microbicides and HIV vaccine field], the rate-limiting factor isn't money—it's science and scientific decision making."
- "IPM [International Partnership for Microbicides] has repeatedly underspent against its budgets (consistent with other PDPs, e.g., DNDi [Drugs for Neglected Disease Initiative] operates at 15% surplus). Money not spent will go towards the Phase III trial." (IPM Evaluation)

On the other hand, one stakeholder noted, "Everybody wants to fund discovery work, because it's cheap. What's missing is the late-stage funding, where costs really creep up." Similarly, another said, "We need new money, not an idea for rearranging deckchairs on the Titanic," referring to the FRIND idea to bring efficiencies through better portfolio management.

There are already examples where resource constraints are being felt and are affecting decision making:

- Aeras slowed down work with Crucell on its TB vaccine candidate.
- Example of suboptimal decisions being made based on suboptimal funding: [X PDP] took molecules 1, 2, and 6 (of 6 molecules offered) into their early-stage research portfolio. One company said, "You can't choose which molecules at THIS stage—we don't know enough yet. You would never terminate molecules at such an early stage in industry. It's not a scientifically valid way to conduct research." But the PDP was cognizant of its funding restrictions and felt it needed to ration portfolio entry.

- It is likely that two microbicide candidates will be ready for Phase III trials by 2011; as reported by stakeholders and in the New York Times, donors may choose to ration resources and fund the candidates sequentially rather than simultaneously.[4]
- "Many PDPs are slowing down activities… as an industry partner to several PDPs, you have expectations of timelines and resources and we're seeing these come under pressure—PDP work with us is being slowed down."
- "Who are these new donors the proposals talk about? The government of France wrote us a check, and we thought they left a zero off. Pharma won't fund us—we've tried. We've looked under every rock."

In general, people in the vaccine field felt that science was a larger constraint than funding, whereas people in the drug development sector were more aware of an impending funding crisis, though there was not uniform opinion within either of these groups.

In order to assess stakeholder views about the potential of the proposals to raise additional resources, we carried out a rapid assessment of a sample of existing and potential donors. These included bilateral, national research institutes, including selected emerging economies; the philanthropic sector; and the corporate-giving sector. We found relatively little evidence of untapped resources. Key barriers expressed included major constraints on current budgets and uncertainty in future policy directions (given changes in government) but also the lack of evidence that the approaches would yield value for money (compared to other potential investments). However, there were some positive signals from some less resource-constrained donors.

Revenue mobilization

In terms of the potential for additional funding, while some donors have scaled back interest in innovative financing approaches, some donors do see the potential for increasing aid budgets in the coming years. It is clear that donors face differing resource pressures. One suggested that "given scaling up there was a reasonable chance of putting more funds into R&D." Some argued there were missed opportunities from countries currently not contributing. One argued that "many western countries like Germany have not stepped up to the R&D space. There is potential to attract funding from these countries." In other cases, there was considerable uncertainty about the future, with one donor suggesting that "given the new government, it is not clear whether or not we can initiate any more PDP funding." Some donors, though, were extremely pessimistic. One interviewee argued that this is "not a good time to be doing this. Other initiatives have fallen flat. The UN Secretary General's initiative for MNCH [maternal, newborn, and child health] attracted only $5 billion of the $30 billion needed. Global Fund will be lucky to achieve low scenario; GAVI in trouble. US $60 billion Global Health Initiative looks promising but only $700 million this year, and this is still not approved. Donors won't be lining up to fund this (especially PDP-FF)." Declining or heavily constrained aid budgets were seen as a major problem. One suggested that "aid funding is directly linked to GDP—so has gone down." Timing was also seen as an issue given current budgeting cycles. One pointed out that "aid budgets are extremely constrained—budgets already committed for coming years, e.g., UK, Netherlands—so any pool could only kick in around 2015."

[4] See Why Won't AIDS Donors Confirm Their Best New Hope for Avoiding Future Treatment Costs, September 10, 2010, by Mead Over

Some donors felt that a more compelling case needed to be made: "We need to be really clear on the problems the funds were trying to solve." One donor said that they need "more information on value for money compared to access," though another did suggest that "the PDP funders group has arranged joint donor evaluations of IPM and MMV [Medicines for Malaria Venture]" and that these were "quite useful" but that "a further 'hard-nosed' look at the science of PDPs (not necessarily linked to funding) would be helpful as well." Some said they were concerned about the complexity of PDP-FF and whether that complexity would make it a difficult sell to politicians and the public: "Bond financing is easier to get for more tangible things. It's an easier political sell. But I can see the logical progression these PDPs are trying to make—people might accept that if it makes sense for existing vaccines, then it makes sense for vaccines in development."

The philanthropic sector tends to focus on small-scale activities with clear and immediate benefits—especially where those benefits take place in the donor's country. Advice received suggested securing resources from such sources would be challenging, although not impossible.

Potential for, and willingness to, pool funds

Pooling is seen to be acceptable but only under certain conditions. One interviewee suggested that they had "no problem in pooling"; another that it saw "pooling as potentially quite attractive but surprised no one 'bit on the hook.'" Another made the point that it would be particularly helpful for donors lacking the capacity for due diligence, though they did express fears that they would have little say in the big decisions: "Smaller government donors or donors who are managing large PDP portfolios with limited staff would be happy to pool funding. [We] would certainly be interested in pooling, but we are not confident that donors like Gates would be willing to give up their control." Another suggested, along similar lines, that "pooling would be helpful as it would make our work easier. I am invited to PDP scientific meetings but have nothing to offer. Only Gates is really able to do this." Others saw a new fund as an opportunity to make efficiency savings: "It would be great if a pooled fund could help PDPs share resources. For example, perhaps PDPs could share HR or regulatory departments. Is it necessary for all of them to have these offices independently?" Finally, it became apparent that donors who support sector-wide approaches (SWAps[5]) would not necessarily support the types of pools proposed here—the issues are seen as rather different in the sense that the ultimate fund recipient is often a for-profit private entity.

Many expressed some dissatisfaction with the current status quo and the need to take some action: "It would be an improvement on the current situation, which is a 'bit of a dog's breakfast'"—with no one (e.g., WHO) taking the lead. However, some raised serious concerns about the appetite for taking forward an initiative such as this—not because of its lack of merit but because of antipathy towards any new global health initiative. One pointed out that "you also have to keep absorption capacity in mind. There has been a proliferation of proposed financing mechanisms, but you will soon face donor fatigue. There's a limit to what funders can absorb. At some point, the pot is limited, and investing in new mechanisms means spreading the money more thinly among existing ones, which may be functioning well to begin with." Another suggested that "a pooled fund will only succeed if it brings in additional funding. The transaction costs of change are quite high, so only additional resources would compensate for this," while noting the current challenges in securing additional funding. Another argued for the need to start small and demonstrate effectiveness before scaling up: "It is more likely to build this up over time

[5] Donor-funded support to national health systems is often supported through SWAps, which may involve pooled funding and other common procedures in support of a government-owned health strategy.

as the Fund demonstrates a track record. The Fund would have to establish a results-oriented track record, and then it will attract new money."

Some interviewees were extremely pessimistic, concerned that their own priorities might not be reflected in decision-making criteria for the pool (suggesting the possible case for subfunds within a pooled fund, which, while reducing flexibility, might make the approach more attractive to some donors), or saying that a pooled approach would not be compatible with their organization's approach to accountability, which requires a more direct link between donor funding and the activities of a specific PDP. Indeed, this lack of direct link and control was seen as the principal limitation to donors who were more actively involved in the neglected-disease R&D space, a representative comment being, "No matter how sophisticated and efficient these mechanisms are, funders lose control of their research priorities. They also don't get credit for what they fund." For organizations such as the UK Medical Research Council (MRC) and research ministries, they saw little potential for pooling, though there were some prospects for "funding local contractors' broader PDP/other contracts." Even smaller donors to PDPs were concerned that a pool might adopt priorities at odds with their own: "A key disadvantage of a pool is that choices may not reflect political priorities – what if sexual and reproductive health left out?" Similarly, "There are few new donors with no capacity to decide investment and likely are willing to have it taken out of their hands." Smaller donors were similarly concerned that their views would be ignored in a pool dominated by the larger funders: "We risk being lost in the pool, but that is life." Another was concerned that "Gates is driving the process—picking and choosing. They don't like advisory committees, so why would they support another?"

There were further concerns about possible governance arrangements. One interviewee was worried that "any governance structure would be unlikely to deliver a rational approach—in fact quite likely to do the opposite. We need to think through role of recipient countries. Currently, they are thought of as passive recipients. They often don't want these things even if they are told they are good for them." Another saw "oversight by committee" as "a risk to the quality and speed of decisions." They pointed out that "if we have one committee and it doesn't work we are in trouble, compared to eight committees where maybe six work." Another suggested that the whole focus on new models—and attracting extra resources—failed to address the key challenge facing the PDP arena: the question of how to make difficult choices between competing uses with limited funds available. One interviewee suggested that "PDPs have good scientific expertise, but demand for funds exceeds supply. Setting out criteria and a process for resource allocation is not a 'power grab'—it needs to happen. We need to know if compound A from one PDP is better than compound B from another. A lot of players in this space shy away from the allocation discussion and avoid the idea that funding allocation decisions need to be made at all." In practical terms, one interviewee highlighted the difficulties likely to be faced to make a new fund work, arguing that "the PDP-funders group have been trying to come up with a common reporting format but it's a challenge and very time consuming." Some suggested that more limited approaches might be needed: "I can only see a case for pooling for similar products—easier to make decisions. Otherwise, we are comparing apples with oranges."

The most positive responses interestingly came from the banking sector; the concept of a diversified portfolio of relatively late-stage de-risked compounds, promising quantifiable disability-adjusted life year (DALY) returns across a range of diseases, was understandable and interesting to this audience. One pharmaceutical equity analyst said, "If you build a credible enough allocation system, then I think you could attract new donors to the system. I think that's your challenge. You build the system first and then you announce it to potential donors as a done deal. 'We guarantee x return in DALYs if you invest with us.'" He continued, "Frankly, I'm surprised something like this doesn't already exist. You often see smaller charities banding together (for maximum impact) in other sectors. Donors believe there's better control if they give

to one charity with better capacity for decisions versus a small charity with no capacity for due diligence. Better governance with big charities—they're more accountable." And a pharmaceutical equity analyst from another major investment bank said, "My firm's charity fund would not fund an individual disease PDP but it might fund something bigger, like this. [A previous investment banking employer] couldn't give money to health-related charities because you can't measure the outcome—it's a key criteria to be able to measure outcomes. The chances of one small group are low. If you make a donation into a basket, you have a higher chance of success—that could be an attractive proposition." The advice given was to set up a robust allocation system and governance "beyond reproach."

What alternatives exist to raise additional resources?

The three proposals are only a subset of many potential ways of raising more resources and allocating resources in more effective ways. WHO convened an Expert Working Group on Research and Development Financing "to examine current financing and coordination of research and development, as well as proposals for new and innovative sources of funding to stimulate research and development related to Type II and Type III diseases and the specific research and development needs of developing countries in relation to Type I diseases."[6]

It should also be noted that many PDPs are already exploring innovative financing options individually, and several PDPs opined that the benefits of a collective approach may be outweighed by the costs of coordinating with other PDPs. The Global Alliance for Tuberculosis Drug Development (GATB) is looking into spinoffs of for-profit entities and venture capital, based on its own IP (and possible indications outside TB); Aeras is looking to monetize its manufacturing facility or generate revenues from its one proprietary product; royalties collected on private sales of DNDi's artesunate + amodiaquine (AS+AQ) antimalarial are retained and rolled back into subsidizing further price reductions in the public price of AS+AQ; IAVI has started approaching individual donors to ascertain interest in bond financing (though in this case, the intention is for the funds to support a group of PDPs participating in the PDP-FF rather than only IAVI); the Program for Appropriate Technology in Health (PATH) is working on getting interest of global impact investors who invest for social and financial returns.

Our analysis

BMGF has commissioned work to examine the magnitude and timing of resource gaps for funding full development of its own portfolio of candidates, taking into consideration assumptions about co-funding from others. This work is in draft form and not yet available outside the Foundation, however the Foundation has offered the following information in public meetings:

- Without any backfilling and investment in additional projects, and assuming normal attrition rates, BMGF could support development of its current pipeline [that's not including all the projects outside its current pipeline].
- However, there is a need to continue to fill the pipelines from the early stage, so BMGF will continue to backfill and take on new projects. Therefore, there will not be enough funding to support full development of its current pipeline.

The general consensus among stakeholders interviewed was that the new funds would have to bring in new resources to be viable. We would question this—if the potential efficiency gains from pooling are

[6] Final report is at http://www.who.int/phi/documents/RDFinancingEN.pdf.

significant enough, such an approach could still be justified. The proposals are all based on the assumption that there will be a funding gap. Our assessment, based on interviews with a number of potential and existing donors, is that the prospects for attracting additional resources for any new mechanism are generally poor, at least in the short to medium term.

None of the proposals result in more resources per se. Although PDP-FF is relatively more focused on resource mobilization versus the other two proposals, its main benefit would be changing the time profile of funding. Increasing overall funding would still require additional contributions in the form of guarantees. This, in turn, opens the possibility of raising additional funds through premiums and/or royalties. (FRIND also talks about raising revenue from products with commercial potential where feasible, and some PDPs are already starting to benefit from royalty generation, quite apart from any pooled funding proposal.)

Our assessment is that the prospects for attracting additional resources are poor, as summarized below.

Table 4.1. Current status of potential funding sources

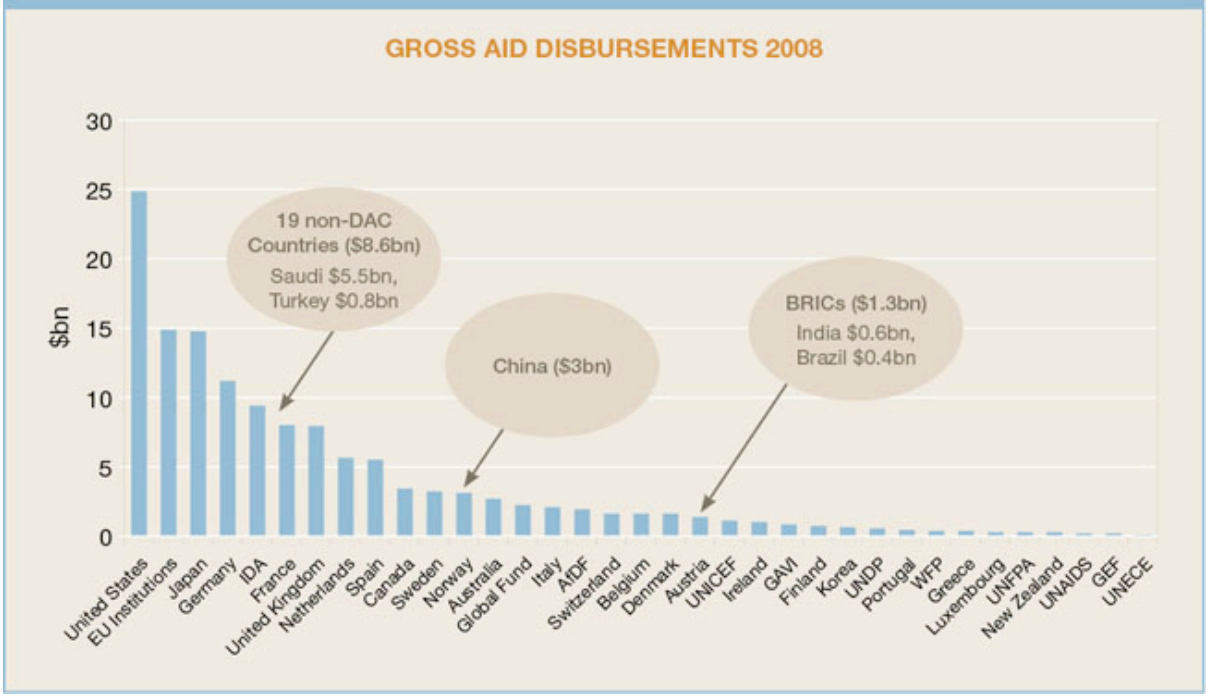
TRADITIONAL AID DONORS	NONTRADITIONAL AID DONORS
Significant decline in overall traditional aid flows ~20% 2008–2010 (Source – OECD DAC) Diverse picture – aid flows are holding up well in some countries but not others Some major donors are not contributing to neglected-disease R&D Global health initiatives are "not flavor of the month"; e.g., Global Fund, GAVI, Maternal Health Initiative, all struggling for resources	Small but growing Typically tied to domestic use Developing-country product developers beginning to play a role in the neglected-disease R&D space; potential for domestic funding to cover such costs
INDIVIDUAL GIVING	**CORPORATE CHARITABLE GIVING**
Remittances • Huge in volume —much is south-south—but very little takes the form of charitable donations Philanthropy • North and south, some cross-border but most domestic • Happening earlier (i.e., not bequeathed) • $ + other things (i.e., tied) • Results focused, but focus often on short-term gains and on investments that benefit the country in question	Modest (except for banks) Often domestic and tied (pro bono) Often related to reducing carbon footprint/community development (exception: UBS support for neglected-disease R&D and new Goldman Sachs fund) More likely to pool, but may have strings attached

As mentioned, there were positive signals from people knowledgeable about corporate giving of investment banks, but based on our rapid review of the resources available from such sources, there does not seem to be massive potential, though there may be scope for further due diligence in this area by foundation/corporate charitable giving specialists. It should be noted that contributions from the corporate-giving sector apply potentially to FRIND and IRFF but not to PDP-FF. PDP-FF limits the pool of guarantee donors only to those who have the balance sheets or the credit ratings to guarantee bonds. Foundations, corporate charitable giving, and family trusts would not be eligible. Unless sufficient donors can be identified to provide such guarantees, the approach would be unviable, irrespective of those willing to pay premiums for royalties.

Although the aid programs of nontraditional donors are growing, often rapidly, they remain small by global standards. The chart below uses Development Assistance Committee (DAC) data to show trends

in aid flows for traditional donors and compares it to estimated funding from nontraditional donors. The programs of the BRICs, for example, amount to roughly the same size as the current Austrian aid budget. China currently disburses roughly the same amount as Norway. Although these economies also disburse substantial amounts through their research ministries, such funding is likely to remain tied to local recipients and thus not available for any form of global pooling. At the same time, such tied funding could release funds for other uses—such amounts could be quite considerable should developing-country firms take on a larger role, as many respondents advocate.

Figure 4.1. Gross Aid Disbursements



4.2 More predictable resources leading to better decision making

Increasing the predictability of funding is a stated goal of the PDP-FF and IRFF proposals. It is important to distinguish between predictability in revenue mobilization (i.e., the nature and timing of receipts into the pooled fund) versus the predictability in resource allocation and disbursement from the pooled fund to PDPs. PDP-FF seeks to achieve increased predictability in revenue mobilization through bond financing, and IRFF similarly seeks to obligate donors to commit grants for five years. Both PDP-FF and IRFF would predetermine PDP-funding allocations based on an approved formula, with the goal of increasing predictability of disbursement from the Fund to PDPs as well. The assumption behind increased predictability is that efficient decision making would be enhanced; long-term investment decisions can be made, and the industry will be more attracted to seek partnerships where funding is pre-secured.

What stakeholders said

Some PDPs do see predictability of funding as an important constraint to efficient decision making in neglected-disease R&D, the issue being a mismatch between what is fundamentally a long-term endeavor—R&D—and the nature of the donor grant-funding cycles—one to five years, depending on the donor. “DFID [Department for International Development] and Gates fund for five years. USAID also does

five-year cooperative agreements, but actual funding is subject to congressional appropriation. GATB was supposed to get $40 million over five years from USAID, but they're getting only $3 million per year, which is having serious repercussions."

Stakeholders also recognized that the benefits from predictable funding vary according to the stage of the pipeline. Predictability is particularly important for Phase III trials because regulatory authorities will only authorize a trial once they see evidence that full funding is available to see the trial through to completion.

Despite the felt need of predictability, some donor respondents suggested that the proposals were "putting the cart before the horse" in that they would want to see results before they would provide predictable funding. Similarly, several questioned why some PDPs should be cushioned from the normal fund-raising process and thought enhanced predictability could reduce incentives to perform. Another opined that "the governance and review structure could address the performance incentive problem. I believe it can be structured so there is accountability, while sheltering a little bit from the funding variability." Some stakeholders also questioned whether the three PDPs who are leading the PDP-FF work would actually be best placed to benefit from it (although the PDP-FF proponents have explained that the Fund could certainly be expanded to include other technologies and/or disease areas).

"If you knew a product development effort would be successful in a limited amount of time, bond financing would be OK. In the case of AIDS, TB, and malaria, we'll be doing research for some time because the first vaccine may not be as effective. So there needs to be a constant stream of finance for R&D."

"I am not keen on the PDP-FF. As we know from IFFIm, it's costly to put together. IFFIm has not been attractive enough for donors, so they'd expand the model beyond immunization. I don't think the cost is justified by the benefit of reducing the pain of fundraising for these three organizations, who already have wealthy donors and good funding prospects anyway. If we were going to bear those costs, better to do it for PDPs who aren't as successful in raising funds."

Our analysis

Mobilization

PDP-FF's relative strength is that it removes all unpredictability in revenue mobilization as long as donor guarantees are provided (and assuming donors will honor these commitments). For FRIND and IRFF, ongoing funding will depend upon the continued goodwill of their donors. They may well provide long-term, predictable funding, but there is no guarantee this will be the case.

PDPs emphasize the importance of stable and assured long-term funding. Against these criteria, only PDP-FF provides virtually assured funding. We would question the importance of stable funding. This implies some constant level of funding. Our understanding is that funding needs might actually need to be quite volatile (i.e., unstable) as they respond to progress in the product pipeline, which involves considerable uncertainty. Indeed, a smooth expenditure pattern might even suggest that poor decisions are being made and that the focus is on spending the money rather than efficient progression of the pipeline. The key issue, therefore, is not to provide stable funding but to provide funds when they are needed (but only where it is warranted).

We also need to ask, "Predictability for whom?" Results-based funding approaches can cause problems for traditional donors who have fixed annual budgets and want to spend their funds. Failure to do so is often frowned upon and may result in future budget reductions.

Disbursement

Predictability does not necessarily mean that resources will be released under any circumstances. Releases are linked to some form of criteria in all three proposals. If these criteria are clear and unambiguous, then it could be argued that funding is still predictable as the recipient is fully aware of what needs to be delivered to access resources. As such, funding can be predictable but still be volatile, or vice versa. Problems typically arise when the expected results are not clearly defined, cannot be measured, or where factors outside the control of the recipients affect performance.

The IRFF and PDP-FF proposals talk about approving long-term expenditures against business plans, which would form the basis for support. We agree with the concept of long-term expenditure plans as a concept but would question its feasibility. Funding needs at the PDP level are, and will remain, highly uncertain, given scientific and other risk. Secondly, even if the proposed mechanisms are supported, they are seen as additional to existing funding. Much of the existing funding is likely to come from a wide range of donors and often be short term in nature, which also makes long-term financial planning extremely challenging.

None of the proposals ensure predictability in the actual disbursement of funds. This depends on how efficient management systems are at disbursing funds efficiently. (The recent GAVI health system strengthening [HSS] evaluation found a number of cases of unpredictability despite the use of IFFIm funds.) Disbursement of funds under IRFF and PDP-FF should be relatively straightforward as the process is automatic, based purely on PDP spending against business plans (whether that is a good indicator of performance is another matter). As FRIND adopts a milestone-funding approach this could potentially cause delays in disbursement—as difficult decisions are made—even if sufficient funds are available.

Finally, it is important to note that predictable funding may provide opportunities for different types of decisions than would otherwise be the case, but management may not necessarily act on those opportunities. For example, predictable IFFIm funding would have allowed GAVI to change the nature of contracting with industry, but it does not appear that such opportunities were taken (GAVI Phase 2 evaluation, 2010). There is also a risk that providing funds predictably, upfront rather than according to milestones, leaves less scope for making disbursements performance related.

The different proposals place different emphases on the balance between predictability and performance. For FRIND, the focus is on incentivizing performance so the funding mechanism is intended to directly drive performance. For PDP-FF and IRFF, the funding creates a platform on which better decisions can be made, but the funding method itself does little to drive this. The guaranteed nature of its funding base would put PDP-FF in a better position to make sound, long-term decisions in ways not open to the other mechanisms. Whether this potential is realized would depend on the effectiveness of its management and governance arrangements.

4.3 Increased flexibility of resources

Flexibility in funding allocation is a function of which diseases, technologies, R&D stages, activities, and institutional types are eligible for funding. Detailed design decisions on all these parameters have not been made for the proposals; therefore, we can only assess what has been stated in the proposals at this early stage. Generally speaking, a wider choice in eligibility of diseases, technologies, activities, etc., would imply a greater degree of risk diversification but the disadvantage of heightened complexity, risking diseconomies (as discussed further in the Portfolio Management section). On the other hand, the risk one takes with narrowing eligibility to, for example, specific partners or activities is the incentive this

creates to "work the system," causing grantees to base decisions on how and with whom to work based on what will be funded rather than necessarily on what is the best choice for furthering the project.

What stakeholders said

The majority of stakeholders were of the view that the ability to shift funds between projects and portfolios over time is the key to efficiency, whereas donor earmarking of projects is said to be one of the drivers of increased transactions costs, and it provides an incentive to continue with suboptimal projects. A surprising finding was that the majority of respondents, including some PDP staff, thought that a pooled fund's eligibility should not be limited only to PDPs:

- "Having one funding channel is never a good thing. We should avoid monopoly PDPs, as well as monopoly funders to PDPs. This ensures that multiple paths to innovation are enabled and the work doesn't stop if the funding from one channel runs out."
- "There is a problem when a PDP has a monopoly. Imagine an AIDS vaccine developer based in Europe. You can't get funding from NIH [National Institutes of Health] so you've got to get IAVI funding. What if IAVI doesn't like your technology? You're stuck."
- "A pooled fund with wider eligibility could pull people into this space. We need to create chaos."

Some interview respondents suggested that donor funding might be better routed direct to companies in certain disease areas: "I worry that the PDP discussion is based on a model that became popular five years ago. Other models may have more robust potential in some disease areas, e.g., for-profit companies working together in consortia. The PDP model should not be fixed in stone. It should be seen as an experiment; we need to understand where and why it's not working." The Portfolio Management section contains further stakeholder views on this theme.

Our analysis

More flexibility is not necessarily better—we need to ask, "Flexibility—to achieve what?" Flexibility gives the recipients of funds the potential to align their spending with overall priorities. This is clearly a good thing if their priorities are sound. Earmarking of resources to specific uses prevents this. Flexibility and priorities need to be considered at both PDP and global levels. PDPs have their own priorities, but there is no overall agreement on global priorities for neglected-disease R&D. This raises a number of questions:

- Are the priorities set by PDPs sound? If they are, then giving them greater flexibility on how they spend their resources is a good thing. If they are not, then it will do harm.
- Should there be an attempt to set out global priorities? Currently, there is little to no basis for assessing whether the allocation of resources between PDPs is optimal or not. The challenges in defining global priorities or even agreeing on any criteria on which they should be based are huge, and we do not necessarily suggest this route be pursued. However, in the absence of such an exercise, there is a risk that greater flexibility in the allocation of resources might actually make things worse.

The disadvantages of inflexibility are clear, though its impact is difficult to quantify. Excessive earmarking to individual projects runs the risk of the funds being lost if the project fails (or even worse, it creates strong incentives to maintain suboptimal projects).

None of the proposals suggests the provision of fully flexible resources. FRIND proposes a tightly earmarked milestone-by-milestone approach that is results focused but inflexible (i.e., it offers no flexibility for PDPs to move funds within their portfolio). Both PDP-FF and IRFF allow for reallocations

between PDPs and within PDP activities, though in the case of the former, the governance rules (suggesting unanimity is required for certain decisions and strong majorities for others) may make it unlikely to happen.

Both IRFF and PDP-FF restrict funding to PDPs; however, eligibility for FRIND is wider. A pooled funding mechanism that vets and prioritizes projects from industry as well as PDPs may enable funders to capitalize on emerging opportunities with regard to R&D capacity in innovative developing countries and increased interest from pharma. (See further discussion on this point in appendices D and F.)

More recent discussions around FRIND have focused on the potential to fund Phase III trials; PDP-FF and IRFF do not restrict allocation by phase. IRFF originally restricted reimbursement to private sector partners, the risk being that partners are chosen based on eligibility for funding rather than on which partner is best placed to contribute, regardless of institutional type. The industry-only restriction on funding eligibility has been rethought by IRFF proponents and verbally revised.

From a PDP perspective, while more flexibility is obviously welcome, PDPs can still manage effectively if only part of their funding is unrestricted. DNDi, for example, sets a target of 50% of its funding coming from unrestricted sources.

It is also worth pointing out that inflexibility may only be revealed by detailed design. The proposals, as they stand, have not been fully fleshed out. PDP-FF appears relatively inflexible in that it specifies in detail the possible rules for reallocating resources between PDPs. The other proposals do not go into such depth—this does not mean these issues do not have to be addressed.

Looking to the future, and based on current practices, many new donors—especially those from emerging economies—will quite possibly provide even less flexibility (e.g., through tying funds to national institutions or particular projects). Existing donors may still wish to tie their aid to specific disease categories or technologies. A pooled funding mechanism could deal with this through subfunds, although this would reduce overall flexibility of allocation based on the objective metrics developed by the Fund.

4.4 Portfolio management

Improved portfolio management is a particular focus of the FRIND proposal. The earlier versions of the FRIND proposal assumed that FRIND would become the single dominant fund through which all neglected-disease R&D financing would be channelled for the technologies under development within the neglected-disease space, as defined by the Special Program for Research and TDR. Subsequent iterations of the proposal considered the idea that FRIND could be structured for "partial portfolio management," that is, channelling only a portion of the funds towards only a portion of the neglected-disease R&D space. FRIND assumes that central oversight allowed by a pooled fund would enable better resource allocation compared to the current situation.

Like FRIND, IRFF would have oversight of all PDP activity, but the idea of using this leverage to manage PDP decisions is not a feature of the proposal. IRFF "favors optimal performers," as those who move the most projects most quickly will draw more from the Fund; the risk with this strategy is the apparent relationship between expenditure and performance, reinforcing the activity focus of the grant-funding model, and not necessarily aligned with getting products to market or with health impact.

PDP-FF would allocate each PDP's share based on preapproved ceilings to ensure an equitable allocation, but the point is not developed or seen as a major benefit to the degree it is with FRIND. There is a risk that PDP-FF creates incentives for PDPs to favor projects with commercial potential, which would be problematic if these projects do not coincide with those that have the most health impact potential.

In this section, we will analyze the potential of achieving improved resource allocation with a pooled funding mechanism, as envisaged in the FRIND model in particular. First, it may be helpful to define what we mean by improved resource allocation. If we define this as more efficient resource allocation, then this would imply that for a given amount of expenditure, there are improvements in terms of (a) outputs (such as greater quality, quantity, or speed of technology candidates produced) or, looking further down the results chain, (b) greater impact (health impact). In the neglected-disease R&D system, resource allocation is taking place at two levels:

Resource allocation levels	Decision makers
1. Across PDPs, or across development efforts outside of PDPs	Donors
2. Within PDPs	PDP management, advised by its independent Scientific Advisory Committee (SAC)

Our analysis divides the discussion about efficient resource allocation into the two levels—across PDPs (or candidate developers outside PDPs) and within PDPs—discussing the following:

- What is the current situation? Extent of problems?
- If there is a problem, what alternatives exist to improve the situation?
- Could a pooled funding mechanism be a viable means to improve the situation?

The case for supporting a new fund rests on the extent of the current problem (if it exists) and whether the pooled fund would be the best means to solve the problem relative to other means.

Efficiency of resource allocation across product development efforts, including product development partnerships: what stakeholders said

A pooled funding mechanism would bring donors together to agree on joint criteria for allocation of funds towards R&D efforts—which diseases, which technologies, and which innovators should be supported and in what proportions? We asked stakeholders for their views on this idea—what might the criteria and the allocation mechanism look like? Many stakeholders believe that neglected-disease R&D resources should be allocated first and foremost to maximize health impact/health gain for a given amount of expenditure. However, it was also recognized that other considerations are factored into decision making in reality. Donors' choices about which disease areas to support are often a reflection of political priorities or dictates from above the people at the technocratic level who might otherwise make the decisions based on purely rational criteria, such as impact on disease burden.

Other criteria were also seen as important; supporters of technologies to combat HIV argued that we must factor in the costs saved by avoiding antiretrovirals (ARVs) and the economic implications of AIDS when prioritizing R&D spending, as well as human rights and women's status considerations. The neglected tropical disease community argues that equity considerations need to be factored into global R&D prioritization because tropical diseases are preferentially affecting the poorest populations who have no access to safe water, sanitation, and health services. The diagnostics community asserts that diagnostics are much less expensive and quicker to develop versus vaccines and drugs, so relatively superior in terms of value for money.

Nearly all stakeholders doubted that it would be operationally practical and politically possible to develop appropriate metrics and to find the appropriate people "beyond reproach" to make credible, evidence-based resource allocation decisions across multiple disease areas, technologies, and pipeline stages, as envisaged in the original "full portfolio management" FRIND proposal. Interview respondents

spoke about the political wrangles, the lack of scientific consensus, and lack of common metrics for making rationing decisions:

- "If we put $100m on the table just in HIV, there's infighting...competition between therapy, testing, and treatment advocates. So I don't see how you'd ration even further to look across diseases."
- A stakeholder from industry opined: "It would be impossible to make allocation decisions in a field where there is no consensus about where the priorities should be—decision tree not possible. How does one decide which disease and then which technology within the disease? (Deciding which project to fund within a disease and technology area is easier, and where industry portfolio management tools can offer something.) There are industry portfolio management tools which facilitate management agreement on what to take forward, based on probability of success in technology development and market potential, but these tools are not sophisticated enough to allow you to select between, e.g., malaria vaccines versus malaria drugs versus nets. Imagine an expert committee with Janet Hemingway [IVCC and vector control proponent], Joe Cohen [malaria vaccine proponent], and Nick White [artemisinin combination therapy (ACT) proponent]. It would not be possible for them to agree on the relative importance of insecticides versus drugs versus vaccines."
- "In these fields, it's not as much about the money as about the challenges of the science. This is the rate-limiting factor. In the end, it's down to judgement calls, so FRIND 'objective criteria' would be useless."
- "In the AIDS vaccine field, there's scientific debate about what's the best trial to do after Sanofi.....Sanofi + protein booster? An NIH trial in South Africa? Try a follow-up in Thailand? There's not yet consensus."

However, despite the difficulties cited above, many respondents did believe that resource allocation across candidate developers including PDPs should be improved: "Decision making is too concentrated." "I just assumed Gates had robust portfolio management processes, but do they?"

When we tested the idea of a FRIND focused only on late-stage funding, there was a complete turnaround in stakeholder opinion, as revealed in these comments:

- "Now that's a pretty interesting idea. You'd have proof of concept by then. You'd have comparable immunogenicity data for vaccines. You don't want to have many failing Phase III, so by then your candidate is largely de-risked. It wouldn't work for microbicides though. There are no surrogate markers so you have to take it to Phase III to see if it's effective (similar problem with an AIDS vaccine). I'm sure you could develop some choice criteria for microbicides though. In the end, there would have to be scientific judgement about which microbicide to fund. So by Phase III, you can have a less theoretical conversation and more confidence about rationing/choosing which to fund."
- "With the modifications you described [whereby FRIND is partial portfolio management, focused on funding late-stage only, offers new funds, and eligibility is wider than current PDPs], this would be of value, provided the rules of eligibility are clear. You would need solid technical oversight and governance. As an additional channel, it could accelerate work and strengthen the field. But I don't think it would be as useful if only funding the same culprits as usual."

There were also views expressed in support as well as against the idea that working through the PDP model is the most efficient use of resources. Some stakeholders thought that it is more efficient to

develop technologies jointly with PDPs, leveraging PDP disease knowledge and clinical trial infrastructure that can be shared across multiple technology development efforts: “It would have cost us $100 million instead of $60 million if we had developed X drug without the support of Y PDP.”

On the other hand, there were many criticisms about the efficiency of PDPs. Biotech firms criticized the high cost of PDPs, citing as an example the advantageous packages PDP senior management receive relative to their biotech management equivalents. European, university-based PDPs said that the “corporate” PDP model is much more expensive than the university-based model, where salaries and packages are paid by the university rather than by the PDP. There was also a view that PDPs are not capturing the full range of opportunities: “MMV and GATB are reactive rather than proactive. They respond to proposals and don’t proactively look for low-cost BRIC firms to work with, and similarly, most BRIC firms are not aware of PDPs.”

A few stakeholders were of the view that neglected-disease R&D work should be routed in different directions. “Gates keeps thinking about the big pharma model but biotechs have a different set of needs.” Some expressed the view that the innovative capacity of biotechs is superior to that of pharma: “GSK [GlaxoSmithKline] and Novartis have 150 [full-time employees] per research center and they take up all the PDP’s time. Now that Pfizer, AstraZeneca, and Sanofi have come into the picture as well, we [biotech firm] will not get attention at all. Someone needs to analyze the productivity of these groups relative to the amount of PDP resources and PDP time they use up; neither GSK nor Novartis have put a neglected-disease technology in the clinic in the past decade.”

Conversely, pharma firms uniformly believe that the industry model of portfolio management is the gold standard and that PDPs should do more to emulate it. “In industry, when we do product development, we do an end-to-end view. We know what TPP [target product profile] we’re looking for. There’s bidirectional feedback between disease people and people on the ground happening in real time. In a single organization, you can do that. But PDPs don’t have all the stages of the process in house. Can they maintain that line of sight?”

Efficiency of resource allocation across product development efforts, including product development partnerships: our analysis

Efficient resource allocation across PDPs would imply that donors allocate resources to their most efficient use within the entire neglected-disease R&D space, including towards candidate developers outside PDPs. Theoretical benefits of improved portfolio management would be higher where

- fragmentation/duplication is more common (e.g., where commercial potential draws in industry activity outside PDPs);
- fragmentation/duplication is more expensive (e.g., vaccines and later stage pipeline);
- funding for the disease/technology area is fragmented, meaning that no single donor has overview of the field; and
- potential synergies can be realized by housing multiple development efforts under central oversight (e.g., different technologies within one disease area).

In the FRIND model, there is a focus on the cost side of the efficiency equation—making sure there is no unproductive duplication across candidate developers, ensuring everything is well coordinated, and ensuring that only the best candidates from the entire space are taken further in development. We would

argue that this is essentially the status quo situation, with BMGF having dominant funding status and oversight of the entire neglected-disease R&D space.[7] BMGF develops its portfolio strategy largely based on disease burden and then develops and publishes its strategies for each disease area, including defining relevant target product profiles. The one area where the Foundation's portfolio management processes reportedly differ from industry is in relation to risk tolerance. Relative to industry, the Foundation can take a longer-term view and can take on higher risk; this is arguably needed given the historic lack of investment in neglected diseases and the need for innovation.

At the other end of the continuum is the more procompetitive model, which arguably gets you more actors involved in the relevant R&D activity, greater efforts brought to bear, greater speed, more choice of candidates—and the higher cost that goes with this greater activity, similar R&D efforts in parallel rather than sequentially, and inevitably some duplication. Indeed, some would also argue that BMGF is supporting the features of the procompetitive model as part of its central oversight role, as it funds work outside PDPs, funds multiple PDPs in some disease/technology niches, and also sometimes funds the development of several similar candidates at once, in the interest of speeding time to market.

Where the balance should rest, between the two ends of the continuum, will differ according to the science and needs of the disease/technology sector. If concerns, as expressed by some interview respondents, about near monopolies of donors (i.e., Gates) and of routes to funding (i.e., PDPs) are valid, then the risk may be limitation of competition and innovation in the long run. The balance in some sectors may need to shift towards more fragmentation (rather than concentration, as proposed by FRIND) of routes to market and funding channels.

It is also important to recognize that some duplication in the system is necessary; parallel work on several candidates needs to be conducted early on because some might fail, and there needs to be a system that promotes several players working on the same problem but bringing different solutions and techniques to bear. Many of the examples of apparent duplication that stakeholders speak about actually turn out to be examples of complementarities or examples of previous, but now resolved, duplication:

- As mentioned, early-stage work should have some parallel efforts to ensure multiple approaches are brought to bear and considering that many will fail.
- Duplication in artemisinin-based combination therapies (ACTs) has been largely resolved with the exit of DNDi from ACT development; the Institution for One World Health (iOWH) and MMV communicate through their common partner, Sanofi; and MMV has several ACTs in late-stage development [some opine that "those horses have already left the gate"] but has now shifted resources and focus to more innovative antimalarial discovery work.
- There has been criticism of the value of some candidates being developed within the tuberculosis (TB) drugs sector; however, as with the above example, those horses have left the gate already and BMGF has been actively involved in re-engineering that sector. The Critical Path to TB Drug Regimen (CPTR) Initiative, which has just started within the TB drugs sector, will completely re-engineer that space. Every major TB drug developer is signed up, and CPTR will institutionalize comparisons and common standards, enabling the development of new TB drug combinations.

[7] Some question whether BMGF has detailed oversight of private R&D activity and activity within Europe; theoretically, all R&D activity within a given disease/technology niche is meant to be on the radar screen of the relevant PDPs.

- MVI and European Malaria Vaccine Initiative (EMVI) are focusing on different aspects of the science. MVI is focusing on a vaccine targeting the first phase, just after the mosquito bites, and also transmission-blocking vaccines; the focus is on mortality reduction and malaria elimination. EMVI is focusing on blood stage vaccines—a later phase of infection, where the focus is on reducing morbidity—and also on malaria in pregnancy. The work of these two PDPs is therefore complementary.
- TB VAC and Aeras Global TB Vaccine Foundation are focused on different stages of R&D—TB VAC on early stage and Aeras on later stage. Four of the five candidates in Aeras' portfolio originated with funding from TB VAC. So these groups are complementary, not duplicative.

Would it be possible to develop robust criteria and a credible process for making more rational allocation decisions across development efforts? It becomes less feasible as you extend the scope of the Fund to include more diversity in disease and technology areas and a wider range of R&D pipeline activities. Conversely, reducing the scope down to diseases, technologies, or R&D activities that share something in common would improve feasibility of comparison and benefits from technical oversight, especially if the scope is reduced to later-stage pipeline activities. On what basis do we make these conclusions?

- Industry recognizes the difficulty of applying quantifiable metrics to discovery funding decisions, and so the principal metrics used for portfolio management—net present value (NPV) and technological feasibility—are used for evaluating and comparing products only once they enter clinical development. Decisions on discovery-stage work are dominated by more strategic considerations and qualitative metrics. Thus, the metrics of technological feasibility and cost per DALY have a higher prospect of being useable and approved by donors, if we are talking about relatively later-stage projects.
- Empirical work within the pharmaceutical industry also supports the idea that larger firms must balance the risk of diseconomies with the potential benefits of size, which result from internal knowledge spillovers between related businesses.[8]
- Another example that strengthens our argument about the benefits of reducing the complexity and scope of development efforts funded by a pooled funding mechanism is the way the market usually prices conglomerates—at a discount to the value of the parts of the business. A classic way to create value has been to break up a conglomerate into clusters of synergistic businesses. This highlights the market's view of the diseconomies and inefficiencies that may arise with large unrelated businesses and, conversely, the benefits that can come from grouping together synergistic businesses. The implication for a pooled fund is that value is more likely to be created where oversight and control is limited to technology investments that are focused on one disease area, on one technology type, or on the same stage in the R&D pipeline.

As for the question of whether donors should support work within or outside PDPs (i.e., should FRIND's proposal to allow eligibility beyond PDPs be accepted?), this is essentially a question of the costs and

[8] Debate about firm size and R&D performance dates back to Schumpeter, and the empirical work in this area has been largely inconclusive. While some research suggests that R&D productivity increases with increasing firm size (Panzar 1989, Chandler 1990, Freeman 1982), other studies suggest that beyond a certain point, escalating coordination costs and problems of agency lead to diseconomies of size (Holmstrom 1989, Zenger 1994). One study (Cockburn and Henderson 1996), which did find a relationship between firm size and research productivity in the pharmaceutical industry, concluded that the main source of advantage was the ability to capture internal knowledge spillovers within the firm (i.e., knowledge capital accumulated in one program may be utilized as a productive input to other *related* programs, at little or no additional cost). This study also found that very significant organizational management effects in research productivity (i.e., differences in development strategy), in the pace and timing of development spending, and in the formulation of the research strategy that guides clinical development were found to be an important determinant of development productivity, regardless of firm size.

benefits of the PDP model relative to other ways of working. Neither is the evidence base showing PDP R&D productivity relative to other options very strong, nor does the evidence support the rose-tinted glasses through which some of our interview respondents viewed biotech[9] and industry R&D productivity.[10] The relative productivity and value of any particular R&D effort depends on many things; our interviews as well as empirical work (cited in footnotes) would suggest that effective organizational management is a crucial variable, regardless of whether the effort sits within pharma, biotech, or PDPs. Crucially, if a pooled fund were to accept applications from developers outside of PDPs, this may produce benefits from drawing in innovators who are not willing or able to work through PDPs.[11] However, there might also be costs if a pooled fund needed to duplicate PDP infrastructure, for example, to negotiate IP and access agreements with these new players.

In conclusion, could pooled funding mechanisms improve the efficiency of resource allocation across PDPs? It depends on several factors:

- Whether robust criteria could be developed. It is argued that this would be relatively easier to do with late-stage candidates, although it would still hold challenges.
- Whether donors could agree on the criteria and be willing to subjugate their allocation decisions to the pooled funding mechanism. The process by which decisions are made about Phase III microbicide trials—given that several parallel efforts are bearing fruit simultaneously—may be considered to be an interesting test case for the concept of joint donor decision making against rational criteria.[12]
- How much leverage the pooled fund has to redirect resources, which would be a function of the size of the fund or proportion of resources flowing through it relative to the overall space it funds. If FRIND would be one more fund added to the mix (which is more likely to be the case) rather than a super-fund, then it would not have the leverage to redirect resources within the entire space, though it could challenge the status quo if it chose to fund a project outside a PDP versus a comparable project within a PDP or it could dominate a subsector/niche.

Efficiency of within-PDP resource allocation/portfolio management: what stakeholders said

Many stakeholders compared PDP portfolio management unfavorably to that of industry. “The big difference is in the approach/mindset to making go/no go decisions. Industry’s follow-up on projects is more rigorous. They want to terminate nonpromising projects ASAP. But PDP grantees (or PDPs themselves if they work internally) will continue to spend the money they have for a three-year grant because [it is] difficult to reprogram. There’s a different mindset.”

---

[9] While some analysts have suggested that pharma could learn from biotech’s focus on limited therapeutic areas, citing biotech firms as examples of companies with core focuses that lead to greater levels of success in drug discovery, other researchers have shown that biotech is even less efficient than pharma in developing drugs (Pisano 2006).

[10] “The world pharmaceutical industry has taken a wrong turn in its choice of management techniques, with the result that creativity has been inhibited”; see Reuben et al in Pharma Insight Reports. Also see Munos 2009, Kaitin 2010, Paul 2010.

[11] See section 4.3 describing stakeholders’ concerns about the risks of monopolies of funding or of funding routes.

[12] To illustrate the sort of challenges that would need to be resolved, consider this: The microbicide field has not come to firm conclusions regarding fundamental questions on the appropriate profile of a successful microbicide, such as how antiretroviral agents should be delivered (local or systemic), whether drug-induced viral resistance will be problematic, the level of effectiveness a microbicide must demonstrate in a Phase III trial to be useful, the ideal mechanism of action, the frequency and mode of application, and the intended target population. These are clearly issues in need of resolution, and ideally, a product developer as well as funders should develop a position on each of these issues before a microbicide enters a costly late-stage efficacy trial.

When industry analyzes the candidate's net present value, it factors in expectations about how existing products or other products in the pipeline will affect sales, what disease needs will be by the time the product is registered, and how the product life cycle will evolve once registered. PDP insiders confide that PDPs are not engaging in this level of forward thinking about the product's positioning and impact; rather, the approach is let's get the product out and then we will see what we do with it. Part of the problem is the expectations of funders. Shareholders invest not because they are interested in the goods that are produced but rather the revenues they will gain. Informants argued that the focus of donors should shift from getting products registered to the "revenue" these products are delivering in terms of health impact.

Interview respondents criticized other aspects of PDP portfolio management:

- PDPs have inadequate systems, processes, or skills for portfolio management.
- PDPs have the correct portfolio management processes and systems but are not using them. Some of the more frank interview respondents criticized the independence of the SACs, suggesting that donors need to better evaluate the process, competency, and independence of the SACs.
- There is a failure to kill suboptimal projects due to an allegiance of a particular donor, due to allegiance of a particular SAC member, or due to friendships and trust developed between PDP management and a particular team working on a candidate.
- PDPs having incentives to keep suboptimal projects in their portfolios because a full pipeline makes the PDP look active and presents a clearer case for raising more money from donors: "PDPs are measured less on outcomes and more on activity, e.g., having arrived at Phase III is seen as important by donors, irrespective of the merit of the technology."
- And related to the previous point, it is believed that PDPs have an incentive to prioritize projects with high technological feasibility but with only incremental health impact, in order to show results quickly and inexpensively.

Appendix E provides further details of specific portfolio management challenges.

Efficiency of within-PDP resource allocation/portfolio management: our analysis

Despite the important contribution portfolio management makes to effective resource allocation within neglected-disease R&D, the empirical evidence on the efficiency of PDP portfolio management is scant and the validity questionable. The only publicly available information we have on this subject comes from three independent evaluations—IPM, IAVI, and MMV—and the Wellcome Trust–funded Pharmaceutical R&D Policy Project:

- The IPM evaluation found that "decision-making processes appear informal and IPM has not yet adopted formal portfolio management processes that include a portfolio management committee and project teams." The recommendations were that "IPM should adopt a formal portfolio management process such as TPPs, explicit go/no go criteria, and project team and portfolio review committees" and "IPM should provide structured comparisons with products being championed by other groups in the field" (IPM Independent Evaluation).
- MMV was faulted on portfolio management as well: "The loss on MMV's Lapdap project amounts to $5.7 million and highlights a major deficiency in communication between MMV and its downstream partners" (MMV Evaluation). "The two most expensive projects which have been terminated are the FASII (fatty acid biosynthesis) and the LDH (lactate dehydrogenase) inhibition

at a cost of $2.5 million and $2.0 million, respectively. With the benefit of hindsight, or stronger scientific direction within MMV, these projects could have been terminated earlier" (MMV Independent Evaluation).

- IAVI fared the best in this area: "IAVI has clear and appropriate go/no go criteria for determining which vaccines advance into the next stage of development…. The go/no go criteria are well thought through and appropriate for HIV vaccine development. IAVI provided evidence of using the criteria in decision making, and the number of projects terminated speak to a certain degree of discipline in applying them. The evaluation team did not, however, review each project for adherence to the criteria." Even so, room was found for improvement: "As IAVI sets the strategy for its R&D efforts, it would be valuable for IAVI to create a clear set of scientific questions that IAVI is seeking to address, describe how its portfolio can contribute to overall scientific learning, and document and monitor progress toward these higher level objectives, as well as what has been learned from each vaccine development effort" (IAVI Independent Evaluation).
- The Pharmaceutical R&D Policy Project evaluated four drug PDPs—MMV, GATB, DNDi, and TDR—and came to very positive conclusions about PDP portfolio management. R&D timelines, cost, and innovative level of PDP projects were superior to industry-alone or public-alone approaches. While this work was a welcome addition to advocacy efforts at the time of its publication, its scientific validity can be questioned on the basis of the small sample size, short timeline of observations as PDPs had only been in operation for a short time as of 2004/2005,[13] noncomparability of data (industry timelines were based on new chemical entities (NCEs), whereas PDP pipelines are characterized by incremental innovations), and inaccurate assumptions about cost of capital.[14]

What options exist for improving PDP portfolio management? Some of these challenges identified by interview respondents are easier to correct than others (e.g., putting in place the right systems and structures for effective resource allocation, changing the leadership, and so on). Donors could support strengthening of PDPs' portfolio management processes and systems as one option, including better evaluation of the PDP's SACs and processes by which their recommendations are fed into decision making.

But many of these portfolio management challenges relate to more fundamental and difficult to solve problems of information and monitoring problems between donors and PDPs and incentives that naturally derive from the form of financing (i.e., grants, which reward effort and activity, not results). To alter the incentives inherent in the grant-based system, donors could supplement the PDP system with mechanisms[15] that reward results rather than effort and activity. Finally, in order to decrease the incentives to prioritize incremental innovations and increase focus on "game changers," donors could shift their M&E focus further along in the results chain from an output focus (i.e., product registered) to an impact focus (i.e., technology uptake, or health gain/death averted).

Could FRIND improve portfolio management? While FRIND could evaluate whether the PDP has the correct processes and systems to aid in criteria-based decision making, it would be very costly to

[13] Variation in research productivity is likely to reflect differences in technological opportunity across research areas, so validity of comparisons is improved with a larger sample size of comparable projects observed over a longer period of time.

[14] For further discussion of the cost of capital point, see Grace and Kyle 2009, page 149 of *Global Forum Update on Research for Health Volume 6: Innovating for the Health of All.*

[15] Such as prizes, advanced market commitments, or more generally increased attention to linking funding to achievement of approved target product profiles.

monitor whether the systems and processes are actually used in practice. The relatively well-resourced independent evaluations referenced previously were able to do the former but acknowledged that they were not able to do the latter sufficiently. FRIND may have difficulty gaining sufficient information with which to monitor and judge the merit of PDP decisions on whether to proceed with a candidate's development; this is less true as the candidates advance through the pipeline and the candidates' properties become less theoretical and more transparent.

Also, again the Fund's influence would be proportional to its degree of leverage. Small funding would imply limited leverage, unless the Fund chose to target its resources to a small number of PDPs where it would be the dominant funder. A relevant comparator would be the way that UNITAID has taken up the pediatric and second-line ARV niches, where it dominates the funding for those sectors and achieves market impact.

BMGF, as the dominant funder, currently has the best leverage and is in the best information position to resolve portfolio management problems at the PDP level, exerting the kind of influence envisaged by FRIND. Indeed, BMGF does take an active role on Boards and starts various initiatives aimed at improving the effectiveness of portfolio management, such as the CPTR initiative in the TB drugs field. However, it is not known whether the Foundation uses this leverage and information in the same way that a venture capital fund or a pharmaceutical portfolio management team would.

The FRIND proposal does not provide a convincing argument as to why and how an alternative dominant fund would have even better information and leverage relative to BMGF. There is even less reason to believe FRIND would have better leverage and information relative to BMGF if FRIND were a smaller fund.

Assuming that FRIND would have the same or even better information and leverage as BMGF, the case would still need to be made that central control and command would be the best way to achieve improved portfolio management within PDPs. Given the nature of the challenges described above, it may be better to supplement the system with something different—a more results-focused mechanism—that would get at the problems of incentives and get around the need for ever tighter monitoring, which requires better information and can be very costly.

Conclusion

This chapter reviews some of the challenges with resource allocation and some of the ongoing work to address the challenges and presents an assessment of each proposal's relevance to addressing those challenges. The theoretical desirability of efficient resource allocation, including through better portfolio management, is accepted by all stakeholders. We suggest that feasibility and the value of achieving better portfolio management via a pooled funding mechanism would improve in line with the degree of synergies and similarities between the activities and candidates supported by the Fund. The FRIND proposal is not explicit about the nature of the current resource allocation challenges, nor is a convincing case presented as to how and why FRIND could be more successful, versus other options, in leveraging improved allocation. Given that there would be very tangible costs to implementing such a proposal, the case for incurring these costs in order to achieve improved resource allocation is not convincing.

4.5 Reducing transaction costs

Transactions costs—the costs of doing business—are rarely clearly defined, let alone costed. The issue is closely related to that of governance and it can be helpful to distinguish between

start-up costs (especially relevant here as we are talking about establishing a new mechanism) and ongoing costs (related to ongoing decision making and monitoring of performance);

internal transaction costs (those related to governance) and external transaction costs (those related to servicing the relationship between PDPs and its funders).

Transaction costs are usually perceived in a negative light—the aim is to minimize them or even eradicate them. In practice, transaction costs can add value (e.g., if you can identify poor performance, you can begin to do something about it). The aim, therefore, should be to reduce the costs that add little or no value, or unnecessary transaction costs. In terms of up-front or establishment costs, similar arguments could be made. While it might be possible to take shortcuts and rush things through, this might result in design flaws that create tension later. Thus, it will be important to balance such costs and benefits. A further issue in relation to new mechanisms is that the up-front costs might be so high that they offset any benefits a new mechanism might bring, raising the question, ”Why bother?”

What stakeholders said

Most PDPs see the current transaction costs of raising money and reporting to donors as relatively unimportant. When we asked PDPs if there was a benefit to having all of their existing donors convert to a pooled funding arrangement, a representative response was, “Minimal benefit. The bureaucratic costs of pooling existing donors would outweigh the benefits. But if they can work out a process by which smaller donors could come in (new money), this might be worth setting up the pool.”

Similarly, another PDP said, “Consolidation in itself, without a major infusion of new funds, is a low priority exercise.” Most PDP stakeholders were concerned that the FRIND approach would raise transaction costs substantially since the PDP’s SAC would essentially be duplicated in a super-fund SAC-like portfolio management committee. The words “micromanage” and “second-guessing” were used by several interviewees.

On the other hand, some stakeholders are looking realistically at what the future brings and see the benefits a central fund could bring: “The trials we did with X PDP cost about $60 million USD. It was cheap because the molecule already existed and has been used in [human populations] for other indications. It was an opportunistic/piggyback project. However, the trials of new TB combinations will cost $400-500 million USD. Where will that kind of money come from? Can you imagine having to go to 100+ donors and all their friends to raise that kind of money?” In a similar vein, one PDP said, “We’re working on a grant for 1 million Euros. A lot of work has gone into securing that small amount. There is a lot of churn for very little money.” And another PDP said, “If all the government donors pooled their funding, this would be a positive from our standpoint…..But is it really feasible given the vagaries of politics?”

Our analysis

The up-front costs of any of the proposals are likely to be substantial. All of the funds would need to establish a resource allocation mechanism, including agreeing upon criteria on which to base funding decisions. The larger the space the fund would control, the more political and protracted the process

would be. All of the funds would need to construct a governance system and select the appropriate people to manage and govern the mechanism.

PDP-FF would involve, amongst other things, securing agreement for an institution to host the Facility as well as agreements to coordinate the different revenue streams to ensure costs are covered. One respondent, based on the experience of IFFIm, suggested that "we need to guess how long it will take—then double it." Though the other mechanisms may be rather simpler, they still involve difficult decisions that cannot be made easily, if they can be made at all (e.g., initial allocation of resources between PDPs), or activities that define eligibility (e.g., accreditation of PDPs).

Ongoing transaction costs, related to ongoing decision making and monitoring of performance, would be highest in FRIND. FRIND proposes to fund milestone by milestone, implying tight monitoring of performance. Information asymmetries between PDPs and the Fund would imply high M&E costs involved to search for information with which to second-guess PDP decision making. The proposed portfolio management committee would be reviewing portfolio decisions made by PDPs, which would reduce decision-making power of PDP management and SACs and render these groups duplicative with the FRIND committees and management processes.

In terms of ongoing external transaction costs, PDPs generally recognize reporting costs as necessary. Unnecessary transaction costs might be reduced to a degree through the adoption of a common reporting framework. This is already being attempted by the PDP Funders Group, but progress towards achieving it reportedly has been slow. A general experience from attempts to pool resources and agree on common approaches in other settings (such as sector-wide approaches) has tended to find that transaction costs have increased in the short term and will not necessarily decline in the medium to long term unless specific actions are taken to reduce them. In short—it simply doesn't happen by itself.

The crucial issue from the perspective of the proposals is whether donors transfer funds from existing mechanisms to a pooled funding mechanism. This is separate from the issue of additional funding. For example, if Sweden and Norway each provided IPM £10 million directly but then decided to increase their support to £15 million each using a pooled funding mechanism, the impact on transaction costs would depend on

- whether they transferred all of their funding through the pooled funding mechanism and not just the additional funding; and
- whether the transaction costs associated with the pooled fund are higher or lower than those related to the Swedish of Norwegian support.

If all funds are channelled through a pooled fund, the number of mechanisms would fall from two to one; if only the additional funds are channelled through a pooled fund, the number of mechanisms would increase from two to three. Under the former, overall transaction costs would probably decline. Under the latter, they would likely increase. The extent to which this would be the case would depend on the extent to which the individual donors made different demands in terms of reporting requirements on the PDPs.

Experience suggests it should not be assumed that donors will disburse support through a single channel (e.g., in the Bangladesh SWAp, DFID provides support both inside and outside the pool). This can help reduce risks, especially when there are some concerns about the effectiveness of a pooled mechanism.

Experience (from SWAps) also suggests that transaction costs are unlikely to reduce in the short term. Indeed up-front costs associated with agreeing on the rules of the game are often substantial. Costs may decline in the medium term if an increasing share of funding is channelled through a pool (and possibly if other donors are willing to use a pool's processes, even if they will not pool funds). There is

the potential to have greater impact on PDPs who have particularly diverse funding sources (i.e., IAVI, IPM, DNDi and not Sabin, International Vaccine Institute [IVI], iOWH).

Assuming PDPs have a single application to the Fund and a single reporting mechanism for expenditures, the pooled fund would be particularly attractive to PDPs in situations where the transactions costs for applying for, and accounting for, grants is high relative to the grant size. Transaction costs for donors would also be reduced to the degree that they accept a joint application and reporting process and accept the decision-making metrics and choices of the decision-making body. IRFF and PDP-FF are likely to be least transaction cost intensive as they assume portfolio management arrangements are sound and that any efforts to improve these would add to costs without adding value.

It could also be expected that different PDPs would be affected differently. Some are already used to multiple donor reporting requirements and might find few problems generating a new report; others less used to doing so might struggle.

4.6 Intellectual property

All of the pooled funding proposals require public health access as a criterion for funding. In PDP-FF and IRFF, PDPs retain responsibility for negotiating access with partners. In FRIND, developers inside or outside PDPs would be eligible for funding and FRIND would require exclusive license to the technology for the indication funded with FRIND money. Proponents of FRIND have explained that exclusive license is sought because "it's simple, NGOs [nongovernmental organizations] like it, and it allows the fund to decide where the product is manufactured, registered, and what its price will be…. The goal is to create an IP pool."[16]

What stakeholders said

The overwhelming stakeholder view of the FRIND policy of requiring exclusive license was that it is too restrictive and may reduce the Fund's choice of industrial partners.

- "The FRIND idea won't work in HIV. Partners are expecting revenues from wealthy markets."
- "The FRIND proposal would not fly in vaccines. Why should a newcomer get to own everything when others have developed it up to that point? There is a particular problem in vaccines where ownership can be fragmented and manufacturing is based on know-how."
- "Leishmaniasis has a commercial market–private market in Indian, Arab, and Mediterranean populations. So companies would not be willing to give an exclusive license."
- "Products are often mixes of things, some of which have commercial relevance. If FRIND controls where the adjuvant is manufactured, to whom the technology is transferred, etc., then the company will lose control. In the end, you'd have less participation in the space, so such a strict policy is a bad thing."
- "I don't understand how that would work. FRIND would own the license and then they would out-license back to us for manufacturing? Surely FRIND would not have its own manufacturing

[16] In response to the consultation draft of November 2010, Novartis clarified the current FRIND position on IP: "The FRIND proposal on IP should be seen as a means to an end, the end being affordable access for all in need of the drugs / diagnostics / vaccines developed. The FRIND proposal is able and willing to incorporate any structure / mechanism that can provide this."

facility. The manufacturing site [to which they license] would still be able to negotiate terms, e.g., what capacity they will make available when, so I don't see what advantage FRIND gets by owning the exclusive license."

- "You can't divorce ownership from distribution, marketing, and sales. This would be ripe for inefficiencies."
- "If a project in ND [neglected diseases] is not colliding in any way with other, more commercial, IP interests, then FRIND's proposal is fine. But in many areas, there is potential collision, and companies will not want to make the IP vulnerable. Especially the case wherever a molecule has potential to kill cells, e.g., Chagas. This makes it potentially relevant to oncology. The bottom line is that such a policy may deter participation, and therefore, the ND area will suffer from lack of projects."
- "If we give the license to the PDP, we need to be sure they can develop the drug and manufacture it. We do that in a capital- and resource-efficient manner. We would hesitate to hand over our licenses because PDPs don't know how to make the drug."
- "This IP idea is politically inept. It's a big pharma model. IP deals need to be concluded case by case. GATB tried this and they missed out on opportunities the first few years."
- "I am not a fan of IP pools. There is always reluctance among developers to give up their IP, and asking them to do so will scare people away. The Alliance had this experience. In the beginning, collaborators were asked to give up their IP, but since we've stopped that practice, collaboration has actually increased. IP pools work when you have fragmented IP like in software. This is more comparable for vaccines (where one firm has patent on the vector and another on the adjuvant and another on the antigen and another on the manufacturing process) than drugs."

Our analysis

The ability the Fund would have to extract exclusive license terms would vary according to disease area (relatively easier where there is zero commercial benefit,[17)] technology type (IP in vaccines is notoriously fragmented,[18)] type of partner (other things being equal, stakeholders opine that pharma would hand over IP more easily than small firms), and the magnitude of technical or monetary contribution the Fund has made (influenced by size of the fund). Thus, if the Fund wants to have a maximum choice of technologies from which to support, it would be better to negotiate IP case by case, perhaps according to a preapproved algorithm or policy. The key to such an algorithm would be balancing incentives for industry to participate with the donors' goals to achieve affordability and access in the sectors and countries where public health objectives will be maximized.

In PDP-FF, the proposal recognizes the difficulty of negotiating royalty payments for candidates already in the PDP's pipeline and for which IP negotiations have already been concluded, as this would be seen as a retrospective attempt to change terms. It may also be challenging to negotiate royalty payment terms for early-stage products, given uncertainties about the technology's benefits and commercial

[17] Increasingly unlikely as firms even see the brand-building potential of products with limited commercial market as having spinoff benefits towards other, more commercial products having sales potential in emerging markets or wealthy segments of developing countries.

[18] For an illustrative example, see the IP map for a malaria vaccine in development: http://www.who.int/intellectualproperty/events/en/Patricia.Roberts.pdf.

potential. A potential disadvantage of the objective to earn revenue via royalties would be the incentives it creates to extract maximum IP from partners, which may limit technology/partner choice, as with FRIND. Such an objective might also create an incentive to preferentially treat the PDP's own candidates, or candidates where the PDP owns relatively more IP, relative to candidates where the IP is owned by others. If the latter were actually the superior candidate, there would be a disadvantage from a public health perspective. Is this just a theoretical possibility? Some stakeholders opine that we are already seeing examples where PDPs preferentially treat in-house candidates relative to other candidates in their pipeline.

4.7 Coordination and information sharing

It is well recognized that coordination has been problematic and information and resource sharing less than ideal in the neglected-disease R&D space. The challenges and the opportunities to improve the situation may be different as one looks at the various disease and technology categories.

What stakeholders said

An area of particular weakness felt by stakeholders is the lack of strategic operational alignment between product (drugs, vaccines, diagnostics) PDPs acting in the same disease area, where competition arises for resources, especially clinical trial sites, investigators, and patients. Ideally, PDPs working in the same disease area should look for opportunities to jointly build and share such resources and to jointly think about combinations of drugs, diagnostics, and preventative technologies in order to have maximum disease impact.

There are also common types of expertise needed by PDPs and common types of activities conducted by PDPs, and efficiency of resource use could be improved if PDPs could share resources and lessons learned, as has been the case at PATH: "PATH is a 'supra' PDP in a way. Depending on how you define a PDP, we have 10 or 20 product development efforts at PATH. There are significant cost efficiencies to this, as confirmed in our recent independent evaluation, which concluded that if some of PATH's PDPs went outside of the PATH umbrella, their overheads would go up by 50–100%. PDPs under PATH share services such as legal and HR. Many PDPs are undersized organizations so these things cost them a lot. However, we're not a FRIND in the sense that we're not taking portfolio management decisions. Each PDP has its own scientific review process for each portfolio. So the advantage is that you maintain the innovation while capturing efficiencies of scale and knowledge exchange between PDPs—e.g., what kind of partnership works best."

Duplication of scientific approaches has also been a concern, most pronounced within the AIDS vaccine field, though there have been changes to remedy this: "Now that we have these mechanisms to drive sharing and collaboration, we have a new challenge of how to preserve competition and avoid group think, i.e., how do you get an effective balance between collaboration and competition?" Another respondent similarly said, "Some duplication makes sense. Candidates can address different variations of the disease problem, e.g., cutaneous leishmaniasis versus other types of leishmaniasis. And some candidates might fail. What you need to avoid is multiple groups working in the same space without sharing information." One stakeholder spoke to the challenging balance between competition and waste from duplication: "I think it is particularly interesting that Novartis is concerned with duplication. The International Vaccine Institute in Seoul, Korea, was on the verge of developing a typhoid conjugate vaccine when the Sienna Novartis vaccine institute stepped in and developed it, completely duplicating work that had been done." Another stakeholder spoke of a systemic problem in vaccine R&D work in Europe: "With the flu epidemic, no single body had the power to decide what was appropriate, and as a

result, unnecessary vaccines were purchased and money wasted. Now five groups are developing a dengue vaccine: French, British, German, Swiss, German. They don't collaborate at all. We would like to do what we did in malaria. Malaria scientists now will talk to each other—agree on a standard assay, agree on the decision-making criteria for when a candidate should go to clinical trial. A more rational decision-making approach is needed."

A few stakeholders spoke to the strong incentives working against sharing of information amongst scientists: "The FRIND proposal sounds logical and efficient, but I don't think it would work in practice. It's true that there are projects duplicating each other. It's true there are people continuing to try things that are likely to fail. It would help if players shared information, especially on failures. There is information sharing in the precompetitive space, but once you get to clinical trials, it's not easy for the sponsor of a study to share negative results. And 90% of research output is negative results." Many respondents described already concluded or ongoing work to increase collaboration and information sharing, for example, "TB drug developers are sharing information and data in the precompetitive space: creating new regulatory science as they work to develop the endpoints used in TB drug trials; lab standardization, when instead of eight companies developing lab manuals, all eight developed one together; groups allowing their compounds to be tested as combinations in animal experiments; companies are sharing information on successful compounds. There are generally data-sharing agreements governing these arrangements." In addition, one stakeholder said that there are ongoing discussions about possible mergers between PDPs.

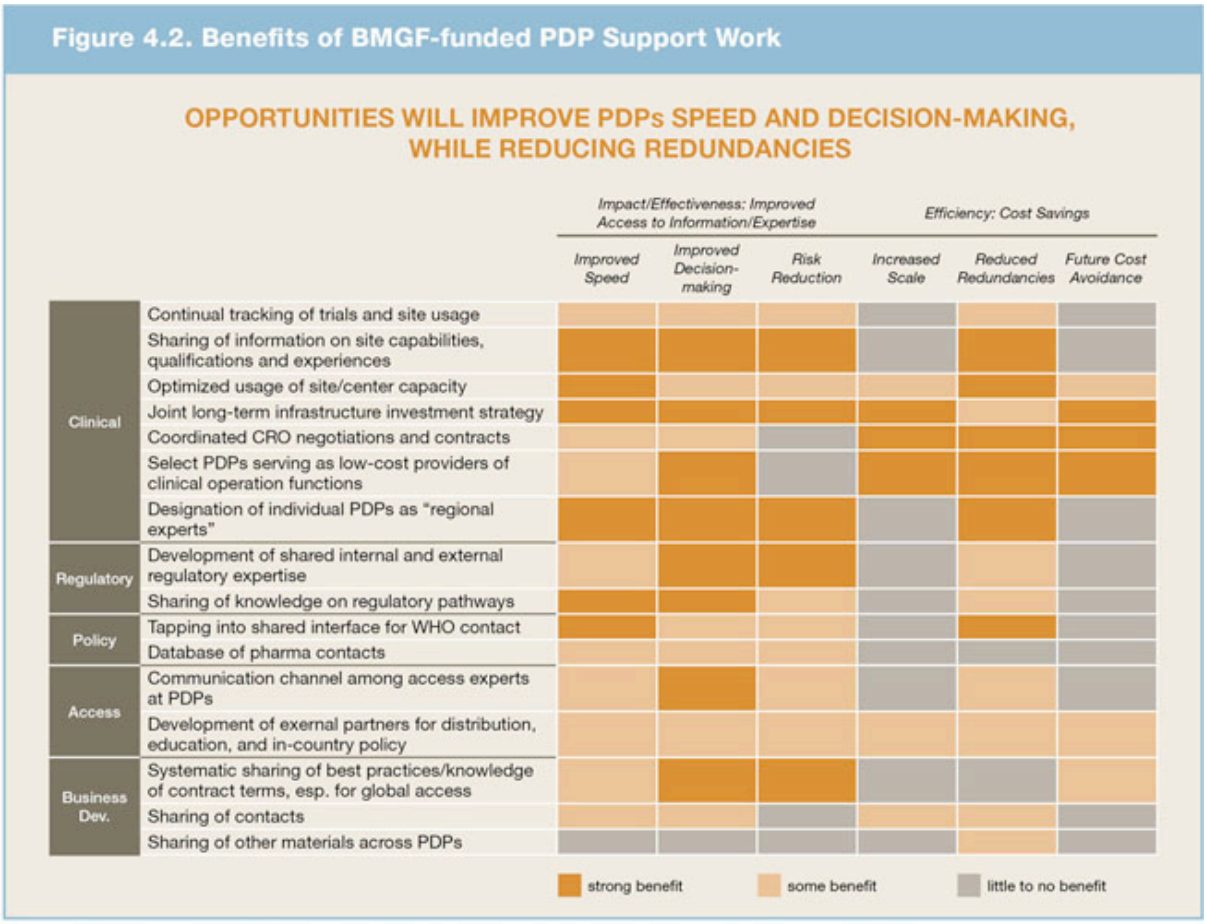
Our analysis

What is being done to remedy the challenges, that is, the counterfactual to a pooled funding mechanism? In an attempt to improve collaboration and information sharing, BMGF has been funding what is called the PDP Collaboration Initiative, which aims to map areas where ad hoc collaboration is already taking place between PDPs, identify areas where more systematic collaboration could produce benefits, build scale where it makes sense, and produce efficiency gains, as detailed in the slide below.

One specific example of work under this umbrella is the CRO preferred provider initiative, which is helping PDPs access preferred provider agreements with contract research organizations. The goal is to allow PDPs to achieve better pricing and choice of CROs, through the scale effects of approaching CROs collectively.

BMGF is funding work in specific disease niches as well. In the TB space, a recent development is the CPTR initiative already mentioned. There is a view that this kind of model may have applications for malaria and some of the tropical diseases where resistance emerges and cooperation is needed in order to find the best combinations.

Figure 4.2. Benefits of BMGF-funded PDP Support Work



Source: BMGF-funded "PDP Collaboration Initiative." Presented by Boston Consulting Group, July 2010.

In the HIV vaccine space, BMGF started an initiative called the Enterprise, which was intended to encourage collaboration and information sharing amongst all R&D actors. More recently, Gates and NIH began programs that contractually require grantees to share information and establish common standards. The Collaboration for AIDS Vaccine Discovery (CAVD) is the BMGF-sponsored collaboration within the AIDS vaccine field requiring all Gates-sponsored centers to share information, data, and reagents. The intent is to share lessons learned and avoid repeating errors. The Center for HIV-AIDS Vaccine Immunology (CHAVI) is its NIH equivalent (a $300 million initiative) started around 2005, with specific contractual requirements for data sharing and storage.

A lesson within the AIDS vaccine field is that it is not enough to set up the systems for engaging in collaborative work—as was the case with the Enterprise—one needs to be a dominant funder requiring collaboration via contractual means. And even though CAVD and CHAVI are requiring collaboration and information sharing in their contracts with grantees, there is not complete confidence that CAVD and CHAVI have been successful, so it may be beneficial to add on other incentive mechanisms, rather than rely on command and control of a benevolent funder.

Would the pooled funding initiatives enable better information sharing and coordination? The IRFF proposal's idea to provide platform services to PDPs or to act as an information clearinghouse for industry and PDPs is an interesting one, which would address some of the needs expressed by PDPs and implicitly by donors, given that they are already funding work in this area. The benefits could include spreading the costs of common PDP activities over a larger activity base (returns to scale = efficiency

gains) as we have seen in industry, where specialized expertise—expertise in biostatistics, expertise in dealing with regulatory agencies across the world—is shared across a wide variety of disease areas. Whether these platform services and shared activities would need to be routed through a financing mechanism is a question.

Similarly, FRIND's proposal to house the N2D2 proposal is an interesting one. N2D2 aims to facilitate collaboration between pharmaceutical firms and PDPs on compound library screening. The FRIND proposal also focuses on the information sharing that would be enabled by its central oversight role; it is assumed that FRIND's dominant funding position, in the full portfolio management option, would give it the leverage to require cross-fertilization of ideas/knowledge spillovers between PDPs (returns to scope = efficiency gains), which would prevent repeating mistakes. The merits of the idea are acknowledged, but whether scientists can be compelled by a dominant funder to share their ideas and failures is questioned.

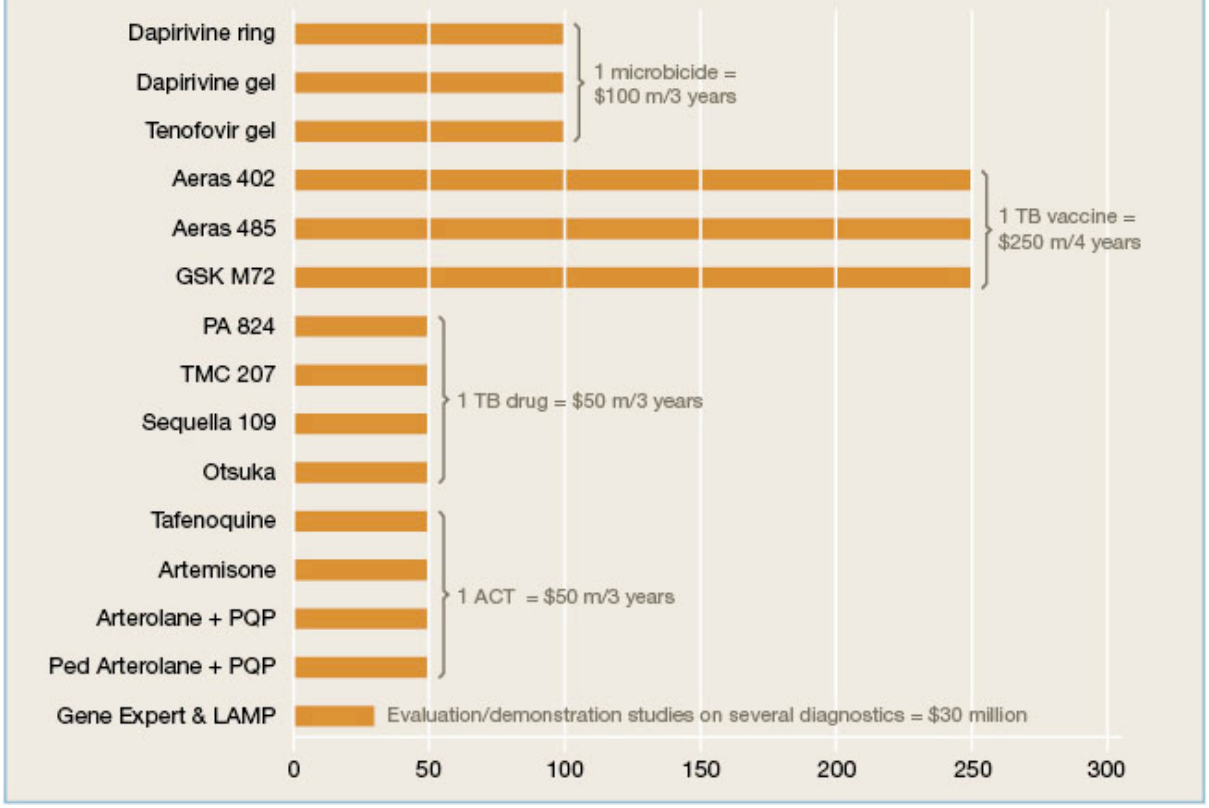
As far as the pooled funding mechanism's ability to exert leverage towards enhancing collaboration, this would be related to the size of the Fund relative to the space it funds. Assuming that the Fund was large and had significant leverage, the situation would be similar to what we have now, where BMGF is a dominant funder, with the best information across portfolios and ability to exert its leverage where it thinks there needs to be better information sharing and collaboration. If the Fund were smaller, then it is questionable whether the Fund would have such leverage to require grantees to work together and share information. If the Fund were limited to Phase III funding, then potential to achieve benefits in this area would probably be limited, as the need for coordination and information sharing is a felt need throughout the entire R&D value chain.

5. MINIMUM SIZE OF THE FUNDS

IRFF is specifically designed to fund the gap between the PDP's current portfolio and their "optimum portfolio." When the original proposal was written in 2005, the funding gap was calculated for the four drug PDPs of focus in the Wellcome Trust–funded study, and this was estimated to be $130-190 million per year. The definition of "optimal portfolio" and the method for calculating the $130-190 million figure was not elaborated. To calculate the size required for IRFF today, we would need to know (a) the number of PDPs participating; (b) the cost-share percentage (80% was recommended as a "reasonable proportion" in the IRFF proposal); (c) the demand for funds, based on the difference between the current and the optimal portfolio; and (d) the number of years of funding required.

What would be the size of funding required by FRIND in the partial portfolio management option? This would depend upon which diseases, technologies, stages of the pipeline/activities, and types of institutions were deemed to be eligible for funding. We modelled what we thought was the most operationally feasible option, and also an option that would meet some of the current resource and rationing needs—a fund that funds Phase III candidates only. The slide below is meant to illustrate what kinds of applications a call for proposals might receive if this fund were to focus on Phase III. Assuming (for simplicity) that the criteria in this round were approved between donors, and the choice was made to fund one candidate each under the categories of ACT, TB drug, TB vaccine, microbicide, and evaluation/demonstration work on several diagnostics, then the fund would need to raise a total of $480 million to fund these candidates over the next three to four years, or about $140 million per year, assuming three- to four-year trials (diagnostics = shorter cycle, vaccines = longer cycle). This assumes that all current Phase II candidates would apply to the Fund, including PDP and private sector developers. Even with the degree of transparency and availability of metrics allowed because the focus is on later-stage candidates, such choices would still be quite difficult to make for reasons earlier elaborated. For example, donors would need to agree between the balance of speed to registration (i.e., funding several microbicide candidates in parallel, in case one fails) versus prudence in resource allocation. TB drug developers would argue that you need drugs of different classes for TB because of resistance so you would not want to ration between classes, only (possibly) within classes. ACT developers would argue that the different ACTs in Phase II currently meet the needs of different populations so are not really duplicative, and so on. The counter-arguments could be that because resources are scarce decisions had been made to fund candidates according to approved prioritization criteria sequentially instead of in parallel. Others would be free to fund trials of the candidates not selected by the fund. Whether this would be accepted politically is unknown.

Figure 5.1. Current Phase II Candidates and Illustrative Costs for Phase III



*In the case of diagnostics, we use the same language as with drugs and vaccines for simplicity. The most relevant comparator in the case of FRIND's portfolio would be the evaluation studies (to get regulatory approval) and demonstration studies (demonstration of effectiveness/relevance in resource-limited settings, sufficient to warrant global endorsement by WHO) for developing additional assays on GeneXpert, and on LAMP platforms.

How do these assumptions compare to the original FRIND size estimates? FRIND assumed that all neglected-disease R&D funding for the ten TDR diseases would be routed through FRIND. FRIND proponents projected a resource need of $6-10 billion over the next ten years; approximately 75% of the funding would go to TB and malaria late-stage funding. The detailed assumptions behind the $6–10 billion figure have never been shared so it is not possible to validate them. However, the estimates do appear to be on the high side relative to our estimates of the size required if FRIND were a Phase III fund (see below). Our estimates did not include the discovery- and early-stage work for the TDR neglected tropical diseases (NTDs) outside TB and malaria, but they did include Phase III funding of a vaccine and a microbicide and were still considerably lower. The range of $6–10 billion over ten years is also on the high side if you compare it to the current PDP funding in aggregate—about $600 million per year (G-Finder). While it is true that FRIND proposes to fund work outside PDPs (which would be additional to the $600 million), the fund would be limited to the drug and diagnostic space for the ten TDR diseases. The majority of the current $600 million spend is directed towards vaccines and HIV—not included in FRIND. In the absence of further detail about how the $6–10 billion was calculated, we cannot assess the validity of the projections.

In terms of the size required to issue bonds, size would not be an issue if PDP-FF were routed through an existing organization such as the World Bank. The World Bank does regular bond issues and funds

are co-mingled; World Bank would allocate PDP-FF its share. In the case of IFFIm, where a stand-alone facility was established (although with key functions outsourced to GAVI and the World Bank) and funds were raised purely for GAVI, there were significant up-front establishment costs. We were advised that the minimum efficient size for such an independent facility would need to be of the order of $15–20 billion to offset such initial costs.

The other side of the scale question is how many PDPs would need to participate in order to have sufficient pooling of risks on the revenue-raising side. As argued elsewhere, donors may be more interested in funding worthwhile candidates than in avoiding paying off their guarantees, so one could view the revenue-raising aspect of PDP-FF as a bonus, not a requirement. If revenues are seen as important, then calculating a minimum size requirement for PDP-FF would require studying portfolios for all the PDPs, determining which candidates have revenue potential, studying likely timing of registration and uptake, determining likely private pricing and donor financing, and determining likelihood of extracting sufficient IP to retain revenues. IAVI modelled this for eight products in the major classes of potential products and found a three-fold difference between the highest and lowest revenue projections. This clearly suggests considerable uncertainty on the revenue mobilization side, reflecting risk as to whether successful products will be developed and, if they are, what revenue can be derived from them.

It should be noted that many PDPs are already pursuing innovative financing options independently, reportedly in recognition of the coordination and time-lag costs associated with a joint approach: "The more the risk can be diversified, the more attractive to donors.[19] But the downside is that the broader the base, the harder it is to get things done. We would like to close our deals within the next 6 to 12 months. If you build in two years of talks with other PDPs, it slows things down."

[19] Examples we uncovered (there may be others) include the following: GATB is looking into spinoffs of for-profit entities and venture capital, based on its own IP (and possible indications outside TB); Aeras is looking to monetize its manufacturing facility or revenues on its one proprietary product; royalties on private sales of DNDi's AS+AQ antimalarial are retained and rolled back into subsidizing further price reductions on the public price of AS+AQ; IAVI is approaching individual donors to ascertain interest in bond financing; PATH is working on getting the interest of global impact investors who invest for social and financial returns.

6. OPTIONS FOR FUND SCOPE, GOVERNANCE, AND MANAGEMENT

The key challenges to making a pooled funding mechanism work would be agreeing on resource allocation metrics and designing governance and decision-making structures beyond reproach. The PDP-FF proposes a small secretariat, with a full-time CFO, and an audit function. There would be a small board (PDPs, donors, experts), possibly with an independent technical committee to approve allocations and adjust disbursements. The rules for allocations and disbursements are not defined in the proposal but unanimity would be required for changes in allocation. FRIND envisages a Board and a separate portfolio management committee; the latter would be engaged in milestone monitoring and technical oversight of the portfolios. If IRFF is only a banking function, releasing payment upon expenditure, then a small number of people would be required and costs would be minimal. If IRFF becomes involved in performance monitoring, or providing shared services, then more people and different expertise would be required.

In the portfolio management section, possible metrics for making resource allocation decisions were discussed—cost per DALY and technological feasibility being principal ones for later-stage projects. The difficulty of coming to an agreement on appropriate metrics for resource allocation was voiced during stakeholder interviews as the single most difficult challenge to the implementation of a pooled fund.

The fundamental tension is between the diversification of risk—enabled by larger fund scope—and the complexity and cost that comes with wider scope. The range of expertise and complexity of decision metrics increases as criteria expand to include wider technology types, disease types, and grant recipient types (i.e., PDP or non-PDP). However, wider scope offers wider risk pooling. The exception would be a Phase III-focused fund; in this case, chances of success are heightened at the same time that complexity is reduced. Illustrative modelling included in appendix C is intended to shed some light on the potential impact of pooling on risk.

Interestingly, a Phase III-focused fund would become rather like a pull commitment—an advanced trial commitment if you will—in that it would reward the *result* of getting a candidate accepted for a Phase III trial. One of the disadvantages of the current push/grant-oriented system is its focus on rewarding *activity* and the difficulty of specifying and defining the value of that activity due to information asymmetry between funders and implementers. These information and (with that comes) monitoring difficulties would suggest that the system might benefit from splicing in mechanisms that would prioritize results over activity, so that developers would become more focused on achieving the end result and less focused on justifying activity. A Phase III fund could even take the results focus a step further and, rather than passively accepting Phase III applications, it could define the target product profile it intended to fund for each disease/technology niche. One stakeholder interviewed opined, “A potential benefit the pooling initiative could bring would be to make sure it’s crystal clear what kind of therapeutic you’re looking for. Some TPPs are overly prescriptive, while others are vague. As a drug discoverer, you can follow your own agenda and end up being completely inappropriate,” highlighting the need for clear TPPs so resources are not wasted.

It should be acknowledged what a Phase III-focused fund would not achieve. It would not enable early-stage work, nor would it engage the interest of capital-constrained firms, who need to be compensated for work as it incurs, such as biotechs and firms in innovative developing countries. It would not help in fields where there are no late-stage candidates (e.g., AIDS vaccines), but this is not to say it would need to focus on treatments and diagnostics (as envisioned in FRIND) over preventative technologies. There are microbicide and TB vaccine candidates that are expected to enter Phase III trials within the next year or two, so these have the potential to be prime beneficiaries. Finally, a Phase III-focused fund would not

necessarily be the best location in the R&D pipeline for rationing for all technology types. For instance, decisions about which TB drug combinations to support need to be taken much earlier in the R&D pipeline.

Decisions about how active or passive the fund would be would obviously factor into the kind of governance structure and expertise required to manage the fund. Would the fund make recommendations about possible partner configurations, the way Wellcome Trust does, or would it simply assess proposals for merit, as submitted? [20] Would the fund passively react to proposals or conduct due diligence to identify needs and bottlenecks in the space and then issue more proactive requests for proposals based on its research? Given likely limited funding at first, would the fund target specific niche opportunities where its impact could be demonstrated and where BMGF cannot or does not want to take a role?[21] The balance between proactive and reactive obviously would be key to determining the size and expertise required of the secretariat and board.

Another key decision would be the role of BMGF. If the main goal is new money at minimum cost, then BMGF could incubate a subfund, offering investors an opportunity to fund the late-stage Gates portfolio. BMGF already actively searches for high net worth individuals willing to coinvest into opportunities, so it would seem there is already a similar concept brewing at the Foundation. The Gates team could provide oversight and due diligence like FRIND, and new investors would get the advantage of diversified and reduced risk and Gates's due diligence. PDPs would not have an extra report to produce. This option has its attractions, but it would not have universal acceptance. Some stakeholders opine that decision making is too concentrated in the current system and believe that the system would benefit from widening decision making and introducing challenges to the status quo.

[20] For example, advising drug discovery teams in academia which industrial partner would be a good match for development and commercialization work.

[21] Rather like UNITAID's market-shaping approach in the pediatric and second-line ARV sectors, where it has become the dominant funder, has done things that the Global fund cannot do, and has demonstrated impact.

7. CONCLUSIONS

The case for establishing one or more of the pooled funding mechanisms examined in this paper would be stronger if the defects the proponents of these new mechanisms claim they will address were better documented. Unfortunately, the evidence is not as compelling as one might wish. For example, the funding shortfalls facing new global health product developers are not well documented. Anecdotally, we heard that a number of PDPs are facing financial crunches, and some of the most neglected tropical diseases have not received a great deal of funding over the past decade. Recent data suggest that funding for neglected diseases has moved away from PDPs and is flowing to basic research, but the numbers are not solid.[22] Hopefully, a study commissioned by the BMGF on funding needs for product development will reveal some firmer figures on this financial deficit.

The same is true for the current portfolio management practices of PDPs and of the donors that contribute to the efforts of the PDPs. Some PDP officials argue that their portfolio management arrangements are rigorous and represent good value for money. Outside critics, especially those in industry and some donors, complain that portfolio management is weak and results in wasted resources. Detailed analysis on this point is mostly lacking.

Nevertheless, there is a widespread feeling among those interviewed for this project that the current state of product development (drugs, vaccines, diagnostic tests) for the major diseases of low- and middle-income countries is far from ideal. More money is needed. It should be more predictable for product development organizations and teams doing a good job, as compared to the hand to mouth situation that some of them currently face. The money should also allow such organizations greater flexibility in making spending decisions, without earmarking that ties their hands. Incentives to draw in more expertise from biopharma organizations to collaborate with nonprofit PDPs would also be a positive force. If the bilateral transactions between PDPs and individual donors could also somehow be consolidated into a single channel, or at least into fewer channels, this would also be a boon for the PDPs.

Of course, these funding arrangements would need to be consistent with efficient portfolio management, so that poorly performing product development organizations and teams would be cut off and more funds directed to the projects with the highest chances of success. The overall finding from interviews was that such portfolio management could be improved.

From the perspective of donors, especially smaller institutions or newcomers to product development and those lacking internal technical expertise, having a well-managed common fund might also make it easier and more efficient for them to contribute their resources to the search for better drugs, vaccines, and diagnostics. But not all donors were keen to join such a common fund with a wide-angle view of portfolio opportunities and risks.

Based on these moderately well-informed “impressions” of the current state of global health product development efforts and of the areas where improvements are desirable and possible, our interviews and our independent analysis suggest that all three pooled funding mechanisms we examined—PDP-FF, IRFF, and FRIND—have positive features worth considering. At the same time, all three proposed mechanisms have significant weaknesses or areas of risk, which make the proposals less attractive.

---

[22] M. Moran, et al., “Neglected Disease Research and Development: Is the Global Financial Crisis Changing R&D?,” Report, PolicyCures, 2010. Available online at http://www.policycures.org/downloads/g-finder_2010.pdf.

Certainly, in the current environment of flattening donor aid, many of the largest funders of health R&D expressed their doubts about backing PDP-FF, IRFF, and FRIND at this time.

We aim to summarize very briefly below what we see as the key technical strengths and weaknesses of the three proposed pooling mechanisms.

PDP-FF. The PDP-FF has exciting potential to expand and frontload funding for product development through the use of private capital market resources backed with public sector guarantees and repaid through revenue streams on sales of finished products. It would also give PDPs greater assurance of stable long-term funding. There are major questions to be answered, however, concerning the riskiness of the underlying product portfolio and the willingness of governments to guarantee bond issues. Negotiating royalties and structuring a system of premiums on sales in low-income markets could also be problematic. The governance of PDP-FF also looks challenging, and could be more complex than its proponents have alleged.

IRFF. IRFF has a certain alluring simplicity in its design, in that it would augment funds for existing PDPs and encourage them to form more partnerships with private biopharma organizations. It also offers the potential to be a repository for fresh funds from donor organizations wishing to back health product development for the first time, without much knowledge of this area. On the other hand, some of these goals may already have been achieved, or have advanced considerably, over the past six years since IRFF was conceived; for example, PDPs have lately become more active and skilled in partnering with industry. And in the current climate of stagnant foreign aid, it does not appear that there is a lot of fresh donor cash looking for a home in health product development.

FRIND. FRIND, as a "mega-fund" for neglected-disease product development, has not garnered a great deal of support from PDPs or from donors, to date. The PDPs fear that FRIND would impose portfolio management from above and restrict their ability to operate, without necessarily having greater scientific knowledge that would enhance portfolio spending decisions. The larger existing donors are not keen to hand over all of their spending decisions to such an unproven fund. Even if FRIND was well organized and staffed, what criteria would it use to allocate resources across a series of diseases and products where the return on investment is not defined in commercial terms, but rather in terms of lives saved or some other public health metric? On the other hand, we believe that a smaller and more focused version of FRIND that would pool funds from existing and new sources to create a critical mass of money for costly Phase III trials might find more favor with stakeholders and might be feasible in financial and organizational terms.

If any of the pooled funding mechanisms stands a chance of being launched in the next few years, we believe that this would be such a FRIND-like fund for Phase III efficacy trials, or possibly a small IRFF that could collect modest resources from new public sector and private philanthropic funders and match those with a limited portfolio of successful and emerging PDPs. PDP-FF is potentially the most innovative of the proposed ideas but may be hardest to get off the ground in the current environment, and it faces the additional design challenges mentioned above.

It is also important to keep in mind that even if none of the three pooled funding proposals takes off in the next few years, there is also scope for improvements in the current product development space in other ways, and these should be pursued. For example, existing funding streams for PDPs could become more stable and predictable if donors agreed to make five-, seven-, or even ten-year commitments. They could show greater flexibility toward individual PDPs by providing core funds and removing earmarks. Donors could lighten transaction costs for PDPs by accepting common reporting arrangements. Better coordination within certain disease and product spaces is already happening (for

example, through the critical path initiative for TB drugs, the AIDS vaccine enterprise, and a similar group jointly looking at investment options for microbicide development), and can be pushed further.

Furthermore, if one of the three pooled funding ideas does begin to gain traction in the coming years, its proponents and financial backers should also be mindful of the latest changes occurring in the health R&D arena, which could dictate new features to their proposals. For example, a number of private biopharma firms and nonprofit ventures are emerging in countries such as India, China, Brazil, and South Africa. Future pooled funding schemes should be designed to support promising initiatives in their countries, too, whether as part of collaborations with PDPs or "northern" firms, or on their own. There are also some new signs that markets assumed previously to be unprofitable (e.g., drugs for Chagas' disease in Latin America and parts of the United States) may be commercially more attractive, making it possible for PDPs to enter into new kinds of R&D partnerships with biopharma companies.

If a pooled funding proposal is to prosper in the future, an important step in gaining traction with these pooled funding ideas would be to obtain better evidence on financial resource gaps and needs and on R&D portfolio management performance to date.

A second step would be to address the question, "Where are the potential pockets of new money for health R&D, and how does one construct a pooled fund that meets the needs of those donors?" Our interviews suggest that the focus should be on new donors without due diligence capacity who are willing to work with others.

At the same time, existing donors who might be open to the idea of making a supplemental contribution to a pooled fund, without necessarily abandoning their current bilateral investments in R&D, should also be approached. In this regard, BMGF is vitally important, since it has helped to spawn many of the PDPs, and other donors look to BMGF for its views on an issue such as pooled funding.

Appendix A: Bibliography

1. Pisano, G. *Science Business: The Promise, the Reality, and the Future of Biotech*. Cambridge, MA: Harvard Business School Press, 2006.
2. Munos, B. "Lessons from 60 years of Pharmaceutical Innovation." *Nature Reviews Drug Discovery* 8 (2009): 959–68.
3. Kaitin, KI. "Deconstructing the Drug Development Process: The New Face of Innovation." *Clinical Pharmacology & Therapeutics* 87 (2010): 356–61.
4. Paul, SM, et al. "How to Improve R&D Productivity: The Pharmaceutical Industry's Grand Challenge." *Nature Review Drug Discovery* 9 (2010): 203–14.
5. Cockburn, I., and Henderson, R. “Scale and scope in Drug Development: Unpacking the Advantages of Size in Pharmaceutical Research.” *Journal of Health Economics* 20 (2001): 1033–57.
6. Grace, C., and Kyle, M. “Comparative Advantages of Push and Pull Incentives: Lessons for Neglected Disease Technology Development.” *Global Forum Update on Research for Health* 6 (2009): 147.
7. Holmstrom, B. “Agency Costs to Innovation.” *Journal of Economic Behavior and Organization* 12 (1989): 305–27.
8. Zenger, T.R. “Explaining Organizational Diseconomies of Scale in R&D: Agency Problems and the Allocation of Engineering Talent, Ideas and Effort by Firm Size.” *Management Science* 40 (1994): 708–29.
9. Chandler, A. *Scale and Scope*. Cambridge, MA: MIT Press, 1990.
10. Freeman, C. *The Economics of Industrial Innovation*. Cambridge, MA: MIT Press, 1982.
11. Panzar, J. “Technological Determinants of Firm and Industry Structure.” In *Handbook of Industrial Organization*, Vol. 2, edited by R. Schmalensee and R. Willig. North Holland, Amsterdam: John Wiley and Sons, 1982.
12. Grace, C., and Druce, N. “External Review of Product Development Partnership Grant Framework.” Report, funded by the Netherlands Ministry of Foreign Affairs, 2009.
13. Widdus, R., White, K. “Combating Diseases Associated with Poverty.” Report, Global Forum for Health Research, 2008.
14. “PDPs in 2009: State of the Art.” Boston Consulting Group analysis presented at PDP Forum, July 2009.
15. Ravishankar, N., Gubbins, P., Cooley, R,. Leach-Kemon, K., Michaud, C., Jamison, D., Murray, C. “Financing of Global Health: Tracking Development Assistance for Health from 1990 to 2007.” *The Lancet* 373 (2009): 2113–24.
16. Hughes, B. “Evolving R&D for Emerging Markets.” *Nature Reviews Drug Discovery* 9 (2010): 417–20.

17. "New Investment Strategy: Innovative Developing Country Research Awards." Report, Global Forum for Health Research, March 31, 2010. Available online at http://www.managementtoday.co.uk/news/985297/GlaxoSmithKline-its-medicine/?DCMP=ILC-SEARCH.
18. Frew, S.E., Liu, V.Y., and Singer, P.A. "A Business Plan to Help the 'Global South' in Its Fight against Neglected Diseases." *Health Affairs* 28, 6 (2009): 1760–73.
19. "Neglected Disease Research & Development: New Times, New Trends." Report, The George Institute, 2009. Also available online at http://www.thegeorgeinstitute.org/shadomx/apps/fms/fmsdownload.cfm?file_uuid=9072CD41-01A5-1E41-113B- z0752D7FE2DCE&siteName=iih.
20. "The New Landscape of Neglected Disease Drug Development." Report, Pharmaceutical R&D Policy Project, 2005. Also available online at http://www.policycures.org/downloads/The_new_landscape_of_neglected_disease_drug_development.pdf.
21. DiMasi, J.A., Hansen, R.W., Grabowski, H.G. "The Price of Innovation: New Estimates of Drug Development Costs." *Journal of Health Economics* 22, 2 (2003):151–85.
22. Moran, M., Guzman, J., Henderson, K., Abela-Oversteegen, L., Wu, L., Omune, B., Gouglas, D., Chapman, N., Zmudzki, F. "Neglected Disease Research and Development: Is the Global Financial Crisis Changing R&D?" Report, PolicyCures, 2010. Available online at http://www.policycures.org/downloads/g-finder_2010.pdf .
23. Towse, A., "Donor Investment Choices: Modeling the Value for Money of Investing in PD PPPs as Compared to Other Health Care and Non-Health Care Interventions." Report, Office of Health Economics, 2006.
24. Skolnik, et al. "Evaluation of the International AIDS Vaccine Initiative: 2003–2007." Report, IAVI, 2009. Available online at http://www.iavi.org/about-IAVI/careers/Documents/Final%20Report%20-%20Evaluation%20of%20IAVI%202003-2007_version%20Mar%2016%2009.pdf.
25. "International Partnership for Microbicides Evaluation." Report, Foundation Strategy Group in association with HLSP, 2008.
26. Lucas et al. "Independent Review of Medicines for Malaria Venture." Report, DFID Health Resource Centre, 2005. Available online at http://siteresources.worldbank.org/EXTGLOREGPARPROG/Resources/mmv.pdf.
27. CEPA LLP, in association with Applied Strategies. "Second GAVI Evaluation." Report, GAVI Alliance, 2010. Available online at http://www.gavialliance.org/resources/GAVI_Second_Evaluation_Report_Final_13Sep2010.pdf
28. Herrling, P. "Making Drugs Accessible to Poor Populations: A Funding Model." *Global Forum for Health Research* 5 (2008): 152.

29. IAVI. “Financing the Accelerated Development of Vaccines for AIDS, TB, and Malaria: Design of the PDP Financing Facility and an Analysis of Its Feasibility.” Report to Aeras, IAVI, and MVI, 2009. Available online at http://healthresearchpolicy.org/content/product-development-partnership-financing-facility-pdpff
30. “Why Won’t AIDS Donors Confirm Their Best New Hope for Avoiding Future Treatment Costs.” Report, Mead Over, Centre for Global Development, 2010.

Appendix B: Range of institutions interviewed

Institutions
Aeras Global TB Vaccine Foundation
Anacor
AusAid
AVAC
Bayer
BMGF
BVGH
Credit Suisse
Dalberg Global Development Advisors
Department of Foreign Affairs, Ireland
DFID
DNDi
EMVI
FIND
GSK
IAVI
Imperial College London
International Partnership for Microbicides
Lion's Head Global Partners
The McLaughlin-Rotman Centre for Global Health
Merck
MMV
Morgan Stanley
MVI
National Chemical Laboratory
National Science and Technology Development Agency
Netherlands Ministry of Foreign Affairs
Novartis
PATH
Philbridge
Policy Cures
Results for Development (former World Bank staff) Sanofi Pasteur
Sequella
TB Alliance
TDR
TropMedPharma
University of Dundee
US NIH, Fogarty International Center
Wellcome Trust
WHO

Appendix C: Modelling R&D for neglected diseases

C.1 Introduction

This short paper sets out the findings of some illustrative modelling aimed at shedding light on some of the potential advantages and disadvantages of pooling donor support for neglected-diseases R&D. Although it tries to use reasonable assumptions, actual data are lacking and this is not an attempt to model the real world.[23] However, it can help illustrate how sensitive results are to particular assumptions. Thus, while it may not be able to say quite how efficient or inefficient portfolio management is, we can begin to look at what the implications are if we assume certain levels of inefficiency and how different types of inefficiency compare.

The focus is on three major types of inefficiency:

- Portfolio-related inefficiency
- Inefficiency related to imbalances in resource allocations between portfolios
- Inefficiency within portfolios

The analysis starts from the perspective that all portfolio management decisions (including selection of projects and their subsequent progression through trial stages) are correct and that each portfolio is on average likely to have a range of equally beneficial projects. It also assumes that the aim is to maximize the levels of benefits achieved. It then introduces a series of assumptions, including

- the establishment of a resource ceiling (which forces choices between competing projects);
- allowing for a mismatch between donor support and the value for money of the different projects (i.e., that some portfolios are likely to be relatively over-funded);
- that portfolios make wrong decisions (i.e., drop likely successes and maintain likely failures).

The implications of using different sizes of pools are set against these broad assumptions, and their impact on overall benefits is assessed.

Key hypotheses tested include the following:

- Investment in a pooled fund is likely to increase a donor's chance of being associated with a success (and thus reducing its chances of being associated only with failures).
- The adoption of a larger pool is likely to have a significant impact on overall benefits, especially where there is a mismatch between donor support and best buys.
- The quality of portfolio management is more important than the effect of pooling.
- Pooling is more effective when chances of failure are highest.

[23] Although some work has been done in these areas, data on cost of trials (e.g., DiMasi 2003) have been questioned, and what little work has been done to determine cost effectiveness (Towse 2006) relies on heroic assumptions.

C.2 Key assumptions

The model assumes certainty in terms of knowing exactly

- how much each type of trial costs (to reiterate, these are purely illustrative and merely aim to reflect the changing attrition rates at different stages);
- the benefits of a successful product;
- what the chances of success and failure are for the different types of products at different stages of clinical trials.

Key assumptions in the model are outlined in red.

Table C.1. Cost of trials

	Cost per type of trial
Phase I	30
Phase II	50
Phase III	80
Phase IV	120
Total (if complete)	280

Table C.2. Type of project (differ by level of impact)

Type of project	Benefit level	Value of benefits* ($M)	% of projects
1	Marginal	1,000	40
2	Reasonable	1,400	25
3	Average	2,500	18
4	High value	5,000	12
5	Exceptional	10,000	5

* Benefits are measured in terms of what the product is worth to users. It does not reflect the price of any product or give any notion of commercial value.

Table C.3. Chances of trial success

Chances of passing individual hurdle by type of project						
	1	2	3	4	5	Weighted average
Phase I	0.40	0.35	0.30	0.25	0.20	0.34
Phase II	0.50	0.45	0.40	0.35	0.30	0.44
Phase III	0.60	0.55	0.50	0.45	0.40	0.54
Phase IV	0.70	0.65	0.60	0.55	0.50	0.64

Implication of these assumptions

Average chance of successful conclusion of trials is 5.7%, ranging from 8.4% for less risky/lower benefit projects to 1.2% for more risky/more beneficial projects. Total benefits exceed costs by 26% (by over 150% for risky projects, around 5% for safer ones).

Table C.4. Implications of assumptions

Benefit level	Chance of success	Expected costs	Expected benefits	Expected benefit/cost ratio (%)
Marginal	0.084	80.4	84.0	104.5
Reasonable	0.056	70.5	78.8	111.8
Average	0.036	61.8	90.0	145.6
High value	0.022	54.2	108.3	199.7
Exceptional	0.012	47.7	120.0	251.7
Weighted average	0.057	69.8	88.5	126.8

Choice of projects

Introduce budget constraint of $3 billion (as all 100 projects would cost an estimated $6.98 billion). Five different types of portfolio are considered according to level of risk (i.e., assumes single pool of 37 to 49 projects).

Table C.5. Portfolio type by risk

Portfolio	Number of projects chosen by type					Total	Expected* cost ($M)
	1	2	3	4	5		
A. Low risk	37	0	0	0	0	37	2,975
B. High risk		14	18	12	5	49	2,988
C. Low to medium risk	3	23	18			44	2,975
D. Medium to high risk	4	9	18	12	5	48	2,958
E. Mixed	18	9	8	5	2	42	2,943

*Due to lumpiness of investments, these are not equal and do not add up to the available budget of $3 billion.

Analysis

Assuming each portfolio has an equal chance of having the best buys and portfolio management is efficient

The following is based on the mixed portfolio (E in table C.5). (It assumes a single pool of 42 projects, two pools of 21 each, and four pools of 10 or 11 projects.)

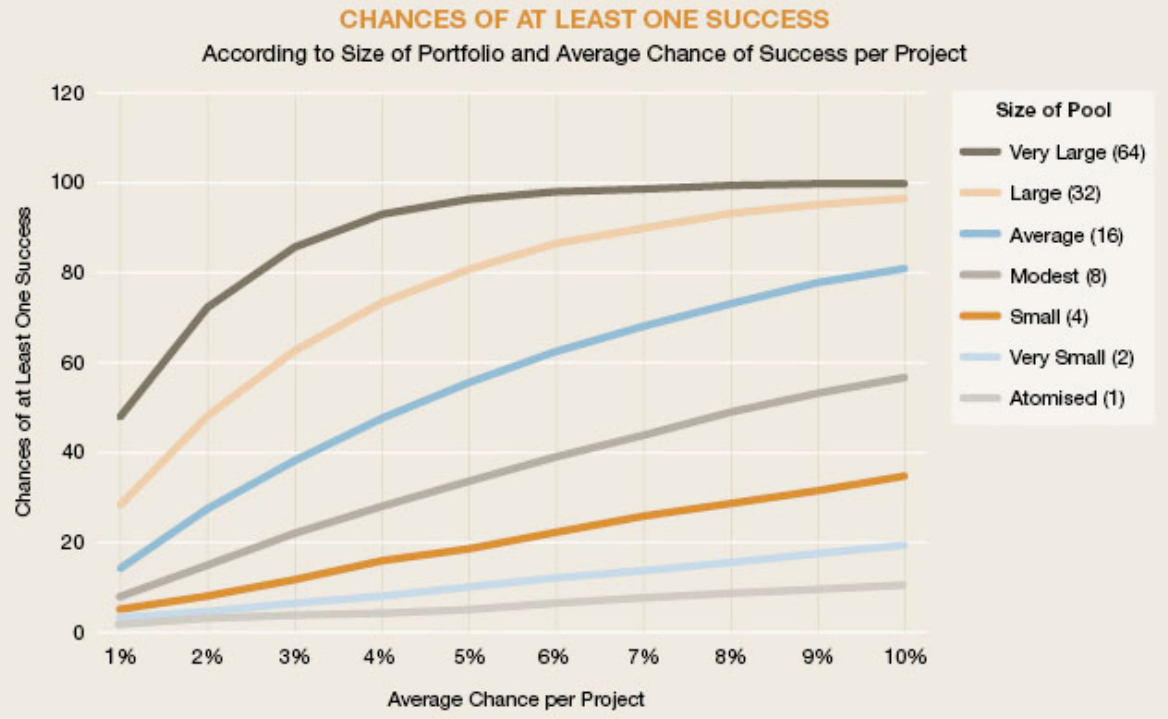
It looks at the following questions:

- To what extent does pooling (and a donor being in a pool) increase the chances of it being associated with a success?
- To what extent does pooling potentially lead to more efficient solutions (i.e., generate greater benefits)?

Impact of pooling on donor success

Our analysis shows that where average project success rate is ~5%, a pool comprising 32 projects has an 80% chance of at least one success. Where the pool is small (four projects), the chance is less than 20%.

Figure C.1. Chances of at Least One Success



The benefits of pooling in terms of ensuring at least one success decline rapidly as the average chance of success increases, but remains substantial (over 15%) for a pool of 32 projects at a 5% success rate.

Figure C.2. Pooling Benefits

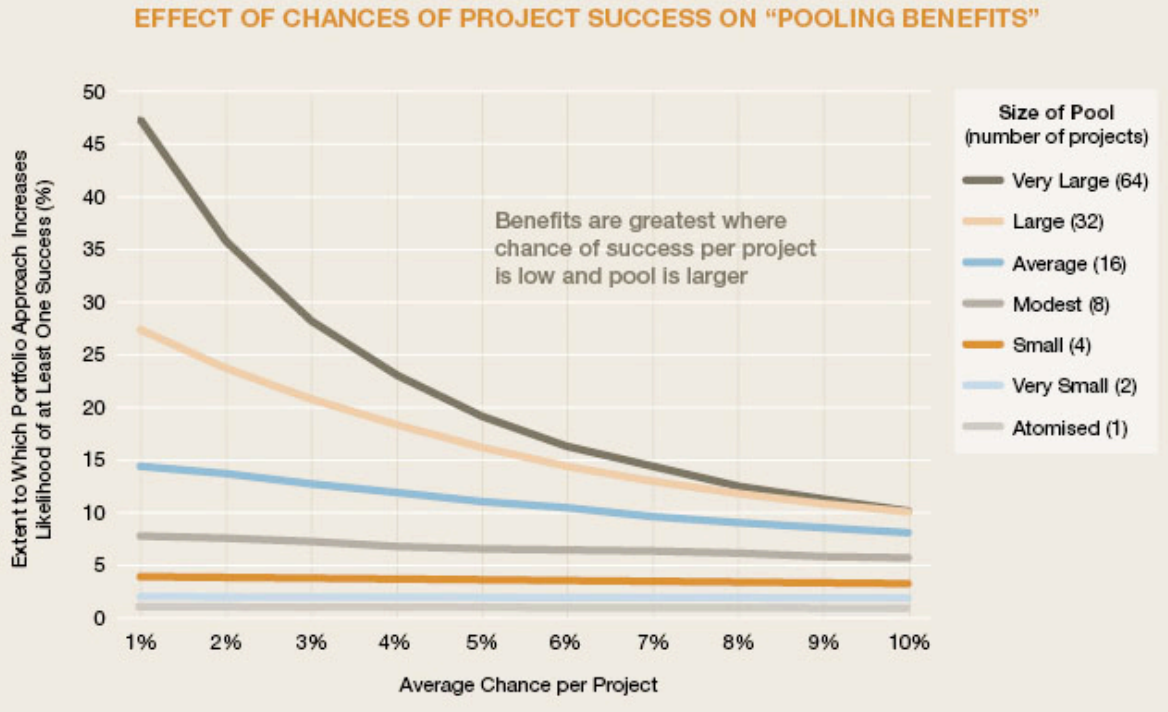
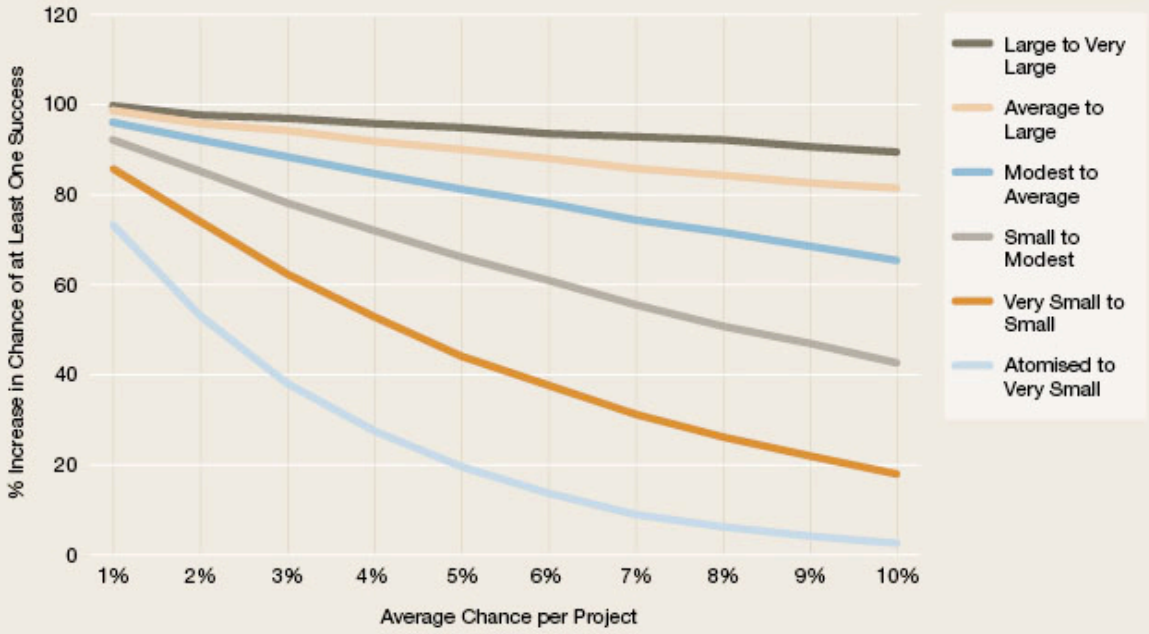


Figure C.3. Increase in Chance of Success



Benefits from increasing the size of pool increase rapidly at low levels but fall off rapidly thereafter (i.e., moving from a two to four-project pool increases likelihood of success by over 90%, for an average 5% project success rate, though this increase is from a very low base). Increasing from a 32- to 64-project pool only increases chances of a success by 20%.

C.3 Impact of pooling on overall benefits

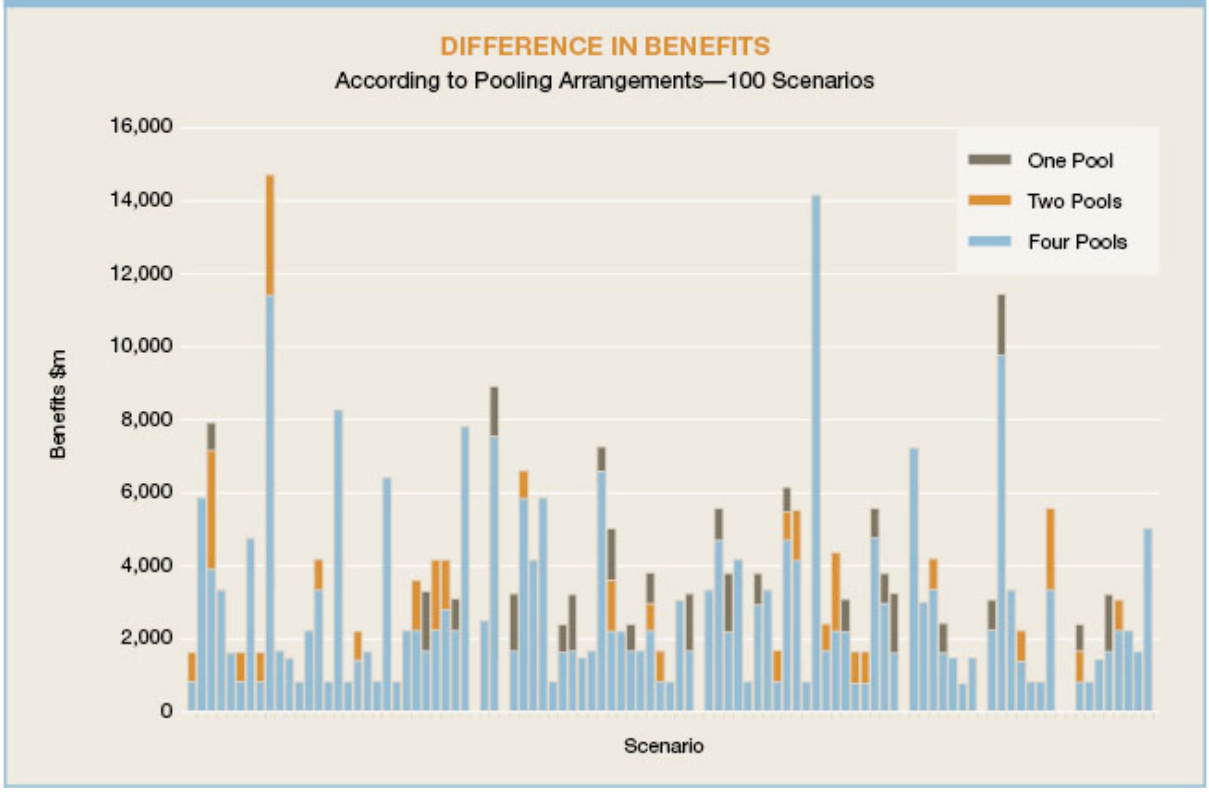
Why is pooling more efficient?

In the model, the large pool can afford to take the top four projects through to completion. Where there are four pools, the pool can only afford to take the top option. Often this makes no difference, but when one pool, by chance, has two or more of the more attractive proposals (which would all have been taken up in the single pool), it has to drop one of them. Hence the smaller pool has the potential to miss opportunities due to the lack of resources.

To what extent is pooling more efficient?

What difference does this make? The chart below shows the extent to which the above failure to take forward attractive proposals happens.

Figure C.4. Difference in Benefits



Based on 100 scenarios, the table below shows that the single pool results in more benefits than a two-pool arrangement in just over a quarter of cases (26) and more benefits than a four-pool arrangement in just under half of cases (46). On average, benefits are around 9% and 18% less than those enjoyed by the single pool.

Table C.6. Benefits of different pool arrangements

	Average benefits ($M)	% by which benefits are below those enjoyed by the single pool	Number of times benefits are lower than fully pooled (out of 100 scenarios)
Four pools	2,598	18.4	46
Two pools	2,906	8.8	26
One pool	3,185		

Assuming there is a difference in best buys

Figure C.5. Reduction in Benefits

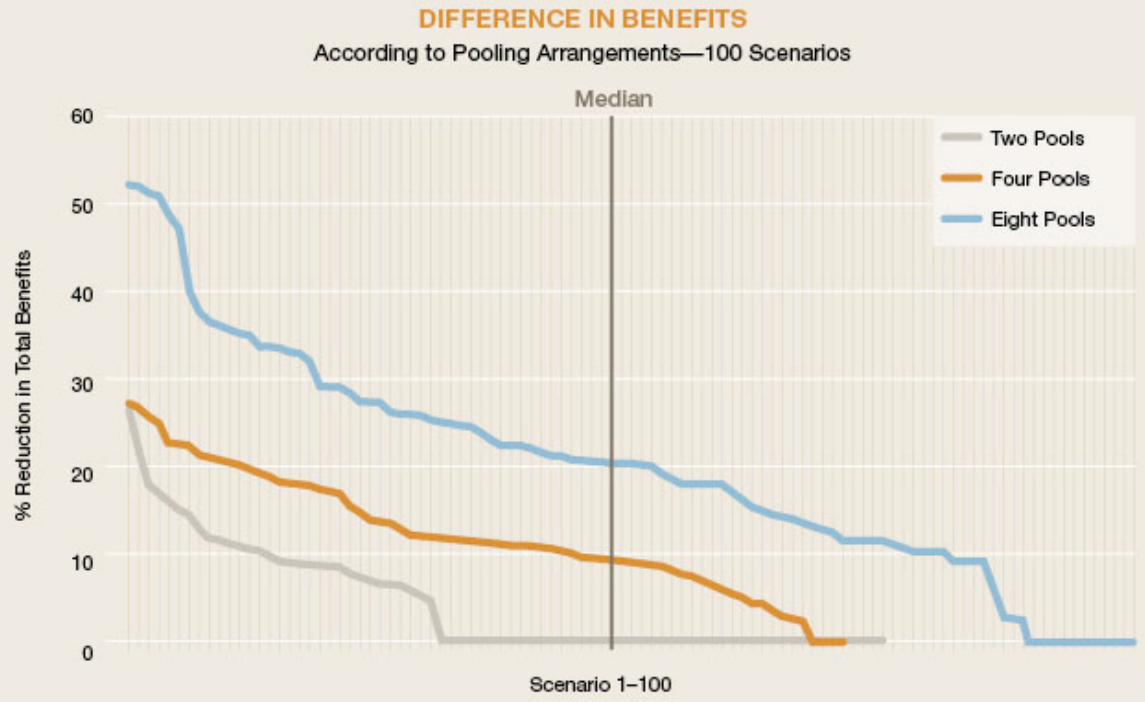
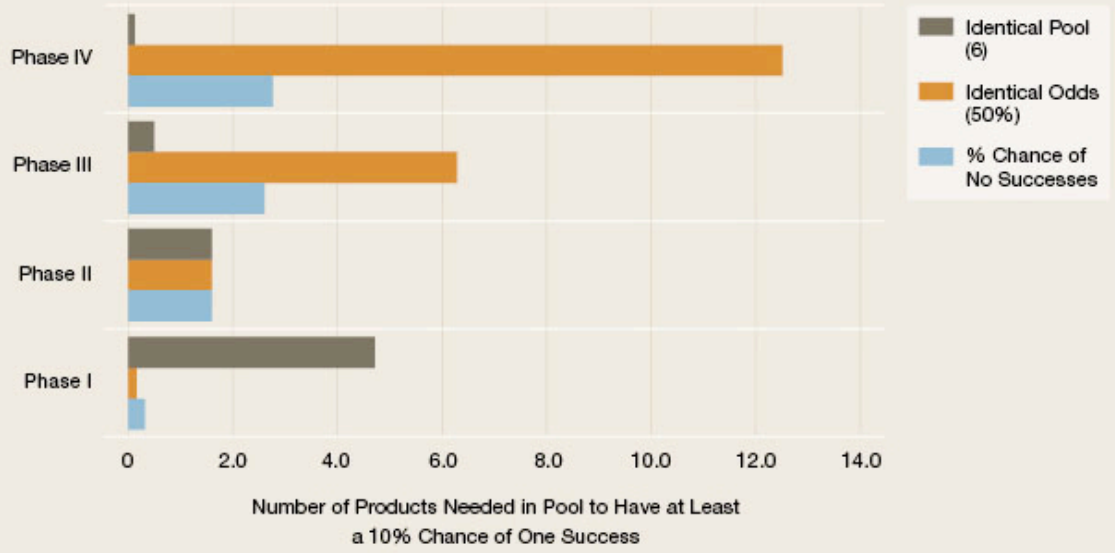


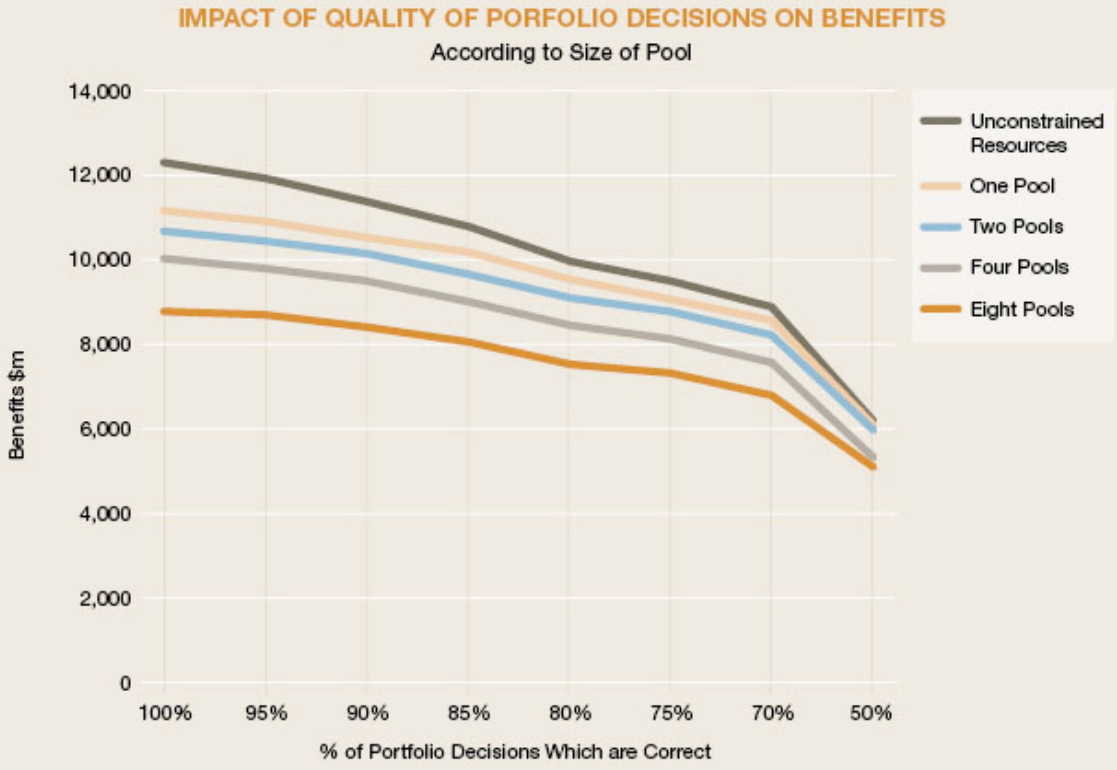
Figure C.6. Impact of Size of Pool and Chances of Success



Assuming portfolio management is not efficient

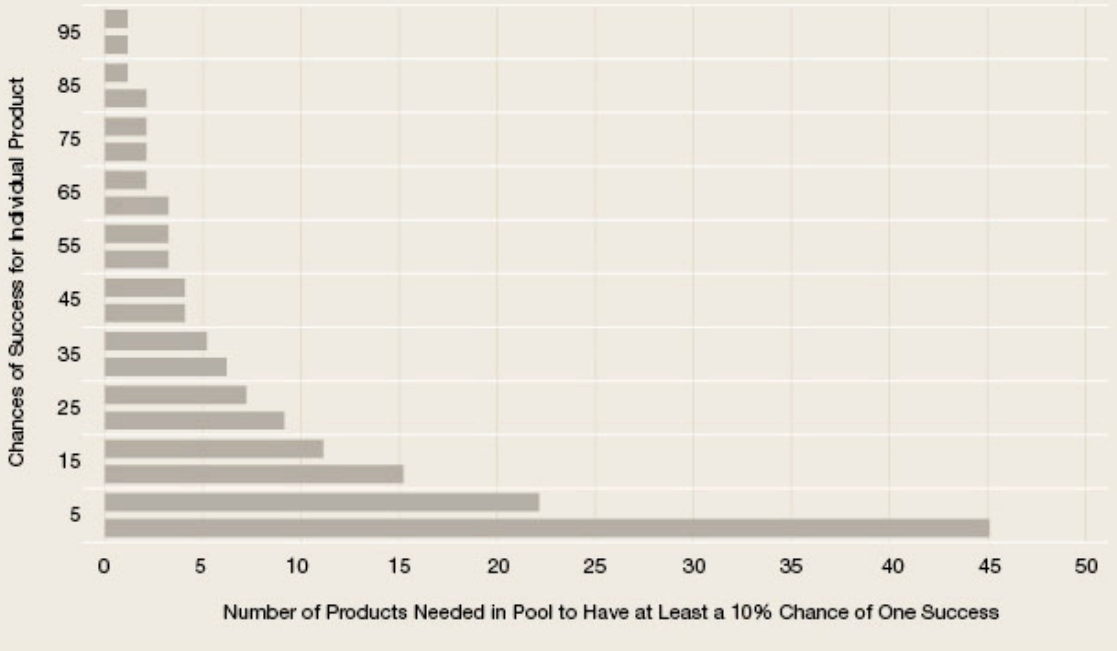
The above analysis always assumes that the right decision is made.

Figure C.7. Impact of Quality of Decisions



Where can a pool have most impact?

Figure C.8. Relationship Between Chances of Success and Size of Product Pool



Conclusion

Based on the model used and assumptions made, the potential benefits of a central pool could be substantial. (This holds even if the pools have equal resource allocations and a portfolio of similar projects with similar impact.) The potential benefits would presumably rise significantly if there were a mismatch (i.e., some portfolios have different impact projects and those with higher than average impact have less resources).

Possible next steps

- Redoing this with more realistic real data
- Introducing uncertainty?
- Seeing how the results differ when looking at different approaches to risk? That is, does adopting portfolio A, B, C, or D make much difference?
- Assess impact of mismatch between project impact and resource allocation (i.e., one pool always has the most cost effective projects)
- Impact of upstream versus downstream: Does pooling make more sense at earlier or later stages (i.e., low risk/high value vs. high risk/low value)?

Appendix D: Overview of current PDP landscape—delivery and finance

D.1 Neglected-disease research and development architecture—delivery

The need

There is a need for health technologies to specifically address developing-country health problems, and the commercial sector has traditionally been reluctant to meet that need due to the costs and risks of such R&D traditionally being too high relative to the market potential. This situation has been a result of a constellation of factors:

- Lower capacity to pay for medicines in developing countries
- The divergence of disease patterns between rich and poor countries, with communicable diseases more common in poor countries
- Resources and expertise for new health technology development have resided primarily in Organization for Economic Cooperation and Development (OECD) countries, where the cost base is higher and revenue potential must be high enough to offset these costs
- Private health technology R&D investments are strongly skewed towards developing products for the noncommunicable, wealthy market disease patterns
- OECD governments have also been the predominant funders of public health research, and funding patterns are similarly skewed to promote research that serves their own citizens and economies

As a consequence of these factors, only 10% of the total health technology R&D each year has been specific to less developed country (LDC) diseases, and most of this was spent by the public sector, with little benefit arising from private sector investment, expertise, and innovation. The result: only 16 of 1,393 medicines developed between 1975 and 2000 were for LDC-specific diseases.

The response

PDPs arose about a decade ago as one way to address this need. Sixteen PDPs were founded between 1999 and 2003.[24] Investment to PDPs has scaled up dramatically from approximately $4 million, supporting two PDPs in 1998, to approximately $500 million, supporting more than a dozen PDPs (G-Finder 2008). The number of governments providing PDP funding has also increased from 9 in 2005 to 12 currently; however, BMGF remains the principal funder, accounting for around 50% of total funding for the field.

It should be acknowledged that PDPs are only part of the neglected-disease R&D delivery architecture. As detailed in the subsequent section (Financing), neglected-disease R&D investment channelled through PDPs is only about 25% of the total investment. European Commission funding goes to many universities for basic research, including that related to neglected diseases. Similarly, R&D funded from the US NIH is not usually channelled through PDPs, but conducted internally (intramural) or channelled

[24] Widdus, R., White, K., "Combating Diseases Associated with Poverty" (report, Global Forum for Health Research, 2008).

externally (extramural) to public R&D institutions through grants, and to a lesser extent, by private companies in the form of R&D subcontracts and small business innovation research (SBIR) and technology transfer grants for smaller firms. US NIH funding dwarfs all other neglected-disease investments, including funding originating from the Gates Foundation. PDPs may not always be direct recipients of EC and NIH funding (though sometimes they are); however, PDPs depend on this investment to fuel their pipelines. As an example, four of the five TB vaccine candidates in Aeras's portfolio originated from EC funding.

Apart from PDP R&D activity and government-funded activity channelled primarily through universities and public R&D institutions, there is also independent activity within pharma and within the firms present in innovative developing countries (IDCs).[25] Please see below, under Emerging Opportunities, for further details.

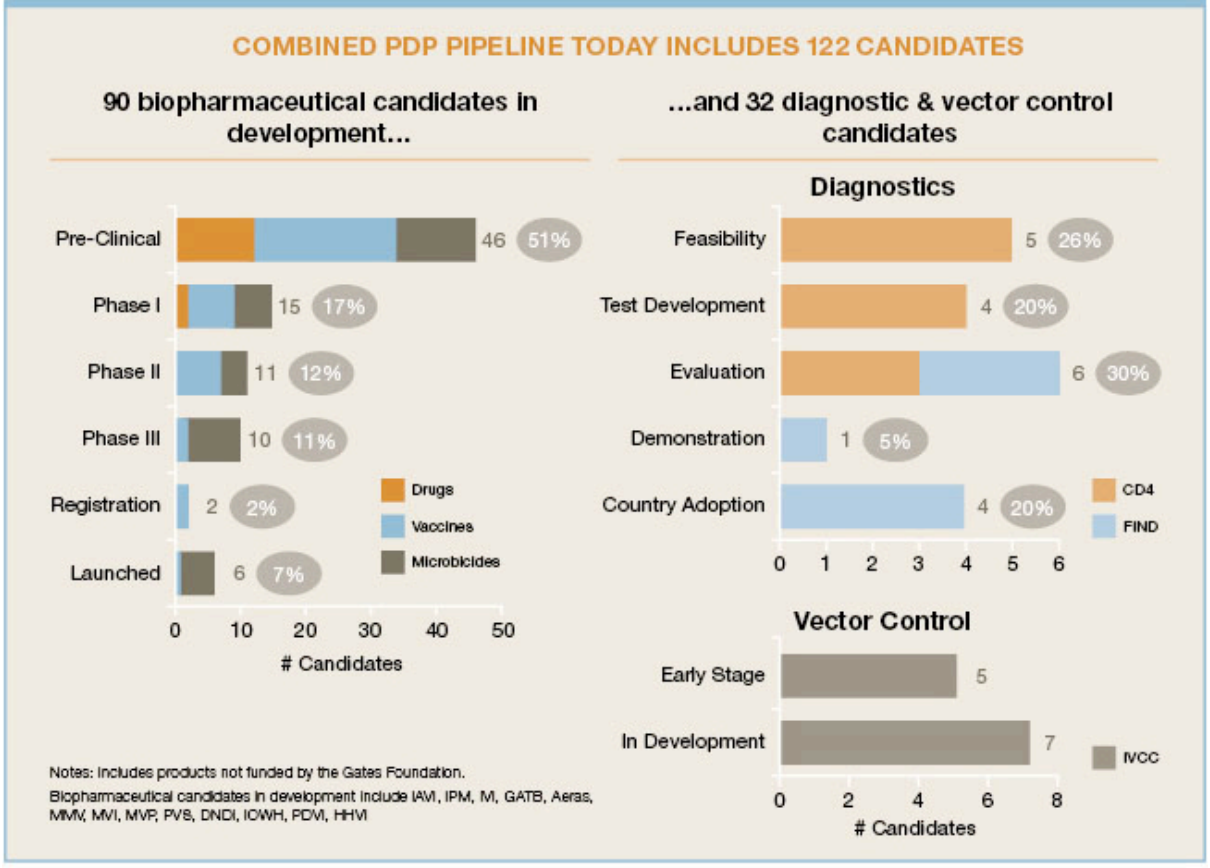
Successes

PDPs are achieving tangible results, notably, rich pipelines of technologies in development (see figure below) and ten product launches since their start, and there is evidence that they are contributing to "ripple effects" that are more difficult to quantify but equally as important.[26] One of these ripple effects is capacity strengthening of clinical trial infrastructure for neglected-disease research in developing countries. This is one example of a PDP's impact on the global access architecture, which may facilitate product development and delivery even beyond the PDP's own disease or product sphere. Another example is the evidence PDPs produce to make developing-country markets less opaque. When this information is made public, it may encourage industry activity even independently of the PDP. Examples include burden of disease studies, demand studies including projection of future financing, and studies that characterize the needs of the product user at different levels of the health system.

[25] For example, India, Brazil, South Africa, and China.

[26] Products through regulatory approval: Coartem D (MMV), Paromomycin (India) (iOWH), JE Vaccine India (PATH), inactivated oral cholera vaccine (IVI), liquid culture drug susceptibility testing (FIND), Rapid MTB ID (FIND), LPA line probe assay (FIND), Minicolumns (mAECT) (FIND), AS+AQ (DNDi), AS+MQ (DNDi).

Figure D.1. PDP Pipeline



Source: PDPs

There are currently 122 candidates in the development pipelines of the PDPs collectively. This includes 90 biopharmaceutical candidates (up from five projects in 1990) and 32 diagnostic / vector control candidates.

Challenges

Funding: As products move into the more expensive phases of the R&D pipeline, R&D funding needs will grow, and funders need to see a strong likelihood that finance for uptake will be available. While the latter has looked more promising in recent years (e.g., with large increases in development assistance for health, from $5.6 billion in 1990 to $21.8 billion in 2007[27]) BMGF reports that there is a funding gap to finance the development of the current portfolio of PDP technologies.[28] Sustained and increased funding is critical if earlier investments are to result in the launch and use of new products.

Health impact: PDPs have demonstrated that they can deliver products to market, but can they deliver health impact? Achieving health impact requires innovative technologies with superior benefits over existing options for treatment, prevention, and diagnosis. A concern related to health impact is that most of the products developed so far by PDPs are incremental innovations, or "low-hanging fruit." We do not yet have sufficient evidence that PDPs can deliver breakthrough innovations with the potential to

[27] Ravishankar, N., et al., "Financing of Global Health: Tracking Development Assistance for Health from 1990 to 2007." *The Lancet* 373 (2009): 2113–24.

[28] Data on the timing and magnitude of funding needs are the focus of current work at BMGF but was not available during the timeframe of this assessment.

radically modify the way a disease will be addressed. IP agreements have been another challenging area for PDPs, as they attempt to negotiate availability of the technology at an affordable price within the countries and sectors where it can provide maximum public health impact.

Leveraging new opportunities: An emerging question, in relation to the overall innovation system for neglected-disease technology development, is the degree to which the current architecture recognizes and capitalizes on changes in the environment since PDPs starting emerging a decade ago.

Emerging opportunities in the neglected-isease research and development architecture

As mentioned, pharma is engaged in neglected-disease R&D activities as well. In recognition that 75% of growth in the pharmaceutical market globally will come from emerging markets over the next ten years, most pharma companies now include these markets as part of their mainstream business strategy.[29] This growth opportunity, combined with various opportunities to reconfigure pharma's cost structure, has changed the cost/benefit equation towards some technologies tailored for these markets. Recently, there has been a boost in the product discovery for NTDs through the creation of PPP discovery networks (e.g., African Network for Drugs and Diagnostics Innovation [ANDI]) or through pharma-industry-dedicated discovery programs for drugs, vaccines, and diagnostics (e.g., Novartis Vaccines Institute for Global Health/vaccines for enteric diseases; Novartis Institute for Tropical Diseases/drugs for malaria, TB, dengue; GSK dedicated research unit for malaria, HIV, and TB; GSK and other pharma companies supporting the establishment of a pool of IP to fight neglected tropical diseases; AstraZeneca and Pfizer increasing focus on TB R&D). Some of these efforts are established as nonprofit initiatives, while others have a clear commercial context.

Another change since PDPs first started is the emergence of firms in IDCs as active participants in the neglected-disease R&D space. Frew et al found that 25% of products from IDC biotech companies specifically target the health needs of developing countries.[30] Developing-country governments are also contributing significant funds to researching diseases that affect their populations; for example, Brazil and India are among the world's top five government funders of product R&D for the 30 neglected diseases studied by G-Finder.[31] As mentioned, aid assistance for health, and that devoted to health technology purchase, has increased substantially. This, combined with the substantial volumes purchased in the private sector of developing countries and in emerging markets, makes the markets for some NTD technologies more attractive.

While PDPs are tapping into these opportunities to a certain extent, there may be further scope to leverage these opportunities, as discussed further in appendix E.

---

[29] As confirmed in our interviews with stakeholders throughout the pharma value chain, from scientists working in discovery to pharma equity analysts in the major investment banks. For a good summary, see Hughes, B., "Evolving R&D for Emerging Markets," *Nature Reviews Drug Discovery* 9 (2010): 417–20. Also see "New Investment Strategy: Innovative Developing Country Research Awards" (report, Global Forum for Health Research, March 31, 2010), available online at http://www.managementtoday.co.uk/news/985297/GlaxoSmithKline-its-medicine/?DCMP=ILC-SEARCH.

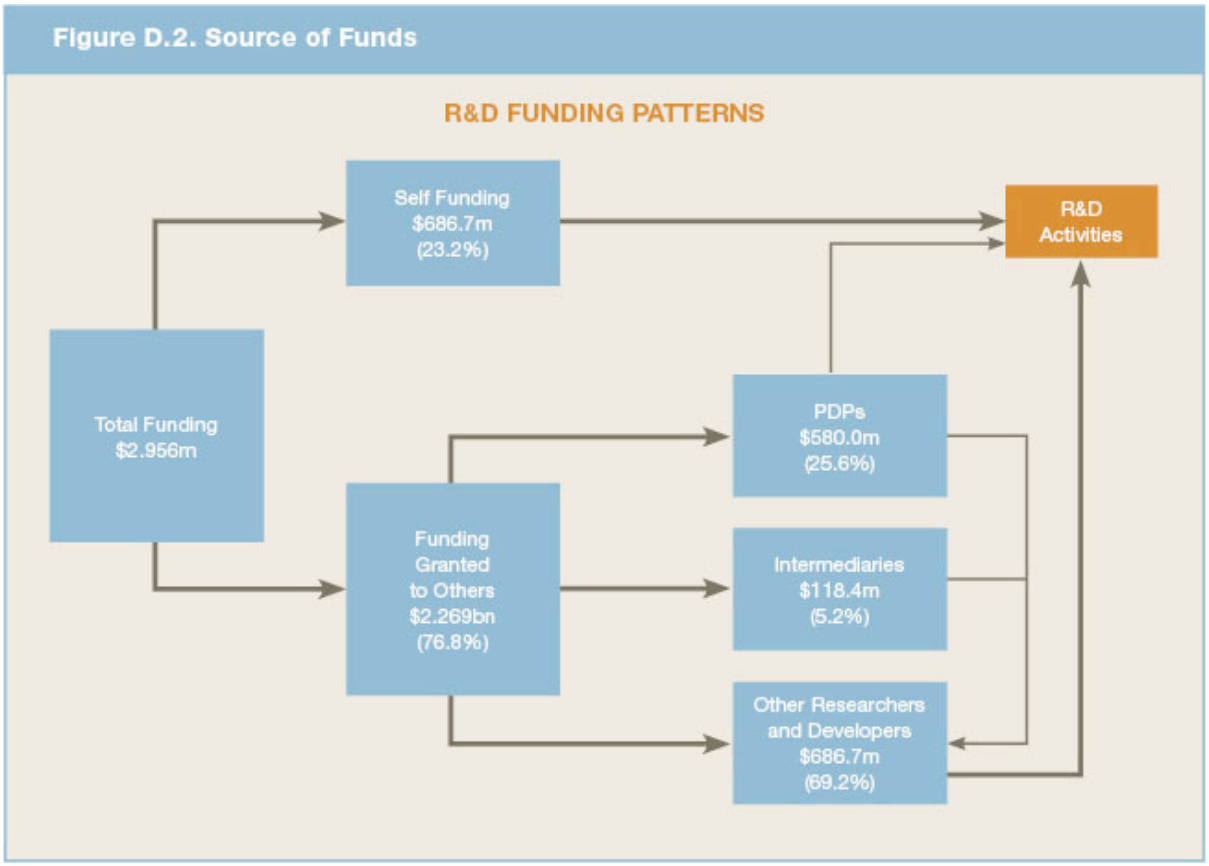
[30] Frew, S.E., Liu, V.Y., and Singer, P.A., "A Business Plan to Help the 'Global South' in Its Fight against Neglected Diseases," *Health Affairs* 28, 6 (2009): 1760–73.

[31] "Neglected Disease Research & Development: New Times, New Trends" (report, The George Institute, 2009), available online at http://www.thegeorgeinstitute.org/shadomx/apps/fms/fmsdownload.cfm?file_uuid=9072CD41-01A5-1E41-113B- z0752D7FE2DCE&siteName=iih.

D.2 Neglected-disease research and development architecture—financing

Spending trends

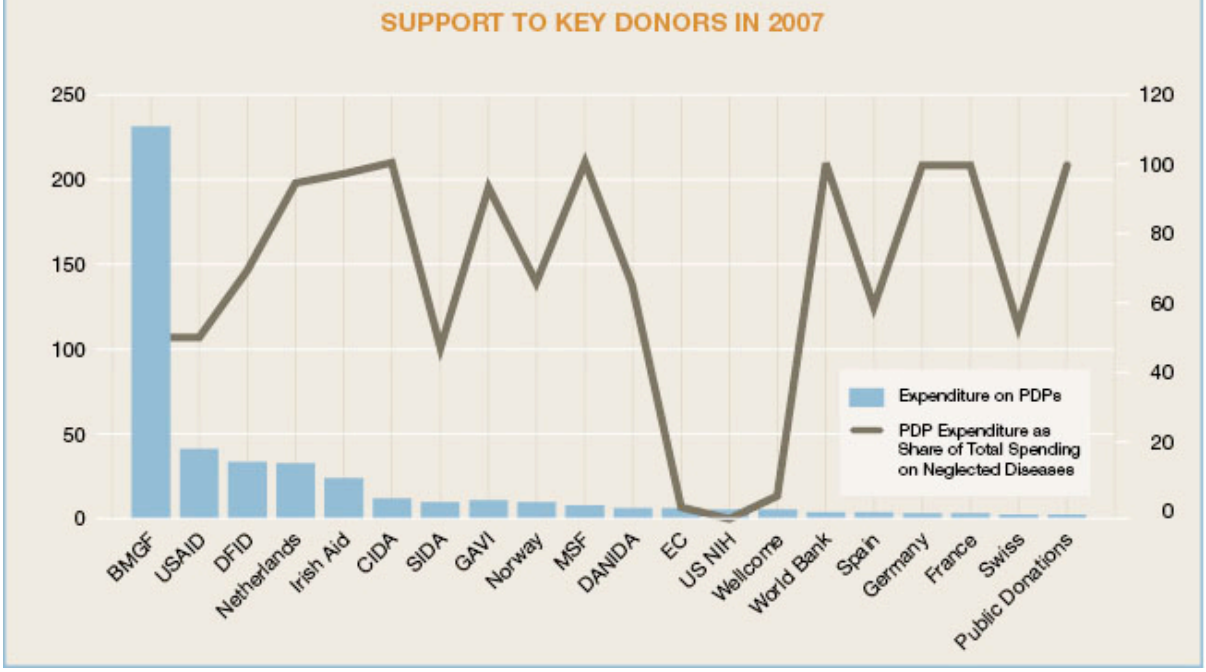
Figure D.2. Source of Funds



There has been huge growth in PDP expenditure in recent years, of the order of 60% per year. It currently amounts to over $500 million per year, but still only accounts for around a quarter of total flows in support of neglected-disease R&D (G-Finder 2008 figures).

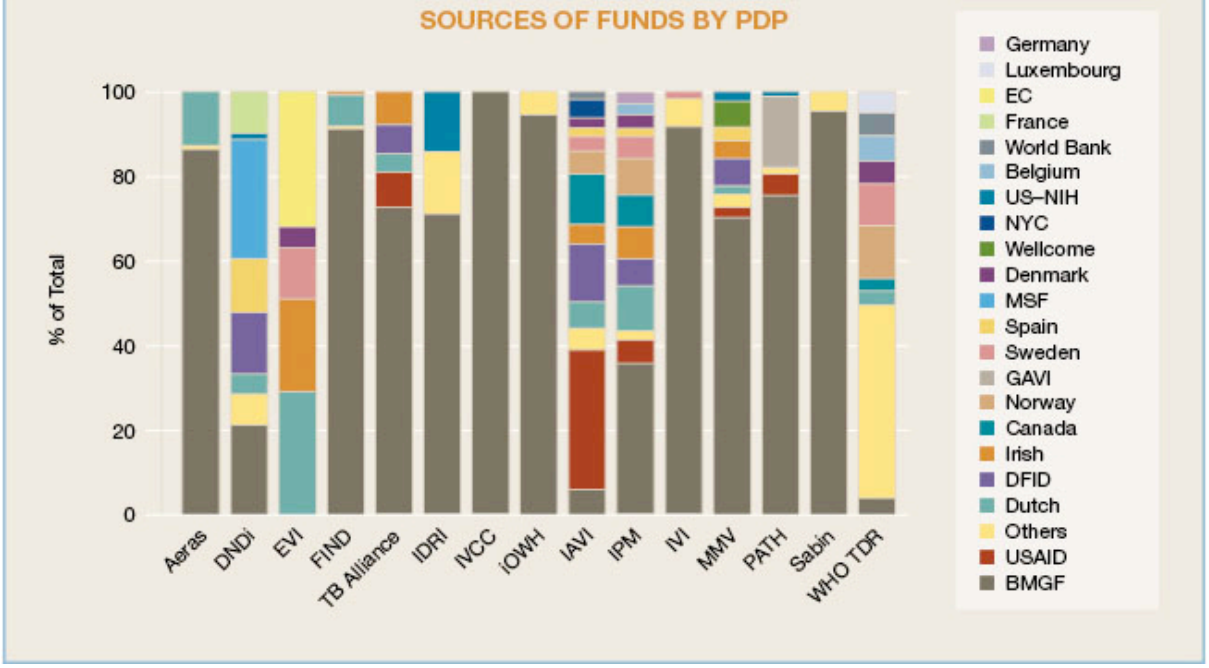
Effectively, BMGF has primed the pump by providing significant initial investments. However, the growth of PDP spending has not taken place within a clear overall long-term financing framework with a clear focus on sustainability and affordability. As one interviewee claimed, for an organization with a commercial orientation, BMGF has not adopted a businesslike approach—PDPs as a whole are heavily reliant on BMGF as a funding source. In this context, when critics talk about a fear of a new mechanism developing a monopoly in the allocation of resources, it is also worth remembering that BMGF already enjoys a near monopoly position in financing PDPs (see table below). Individual PDPs often have a monopoly in terms of providing a route to market for certain products.

Figure D.3. Support by Key Donors



Funding is heavily reliant on BMGF but is also extremely fragmented. The chart, using data taken from G-Finder, shows the key role played by the BMGF in overall funding (left axis and blocks). It also shows the fact that many donors choose to support neglected-disease R&D outside PDPs. Most of the bilateral donors support neglected-disease R&D through PDPs, like organizations such as BMGF and SIDA that provide as much through other channels as they do through PDPs, while the EC, Wellcome Trust, and NIH are modest PDP funders but channel the vast majority of their support through non-PDP routes.

Figure D.4. Funding Patterns



At the PDP level support is usually, but not always, heavily concentrated. In many cases, the share provided by BMGF is large. In a small number of cases, however (DNDi, IAVI, IPM, and WHO TDR), support is derived from a larger number of sources (source: Policy Cures).

Funds are delivered in a variety of ways, from unrestricted core funding to heavily earmarked support. Support from BMGF has become increasingly earmarked. Donors vary significantly in the degree of selectivity in PDP funding. Some (such as BMGF and the Dutch) are not particularly selective and fund a wide range of PDPs; others (including Médecins Sans Frontières [MSF] and the Wellcome Trust) are highly selective and only fund single PDPs. One hypothesis would be that those donors funding a range of PDPs are more likely to be amenable to funding through a pool as the funding profile of any pool would be more likely to mirror their current expenditure pattern. One might expect the single PDP supporters, by contrast, to be less willing to support a broad pool.

Figure D.5. Degree of Selectivity

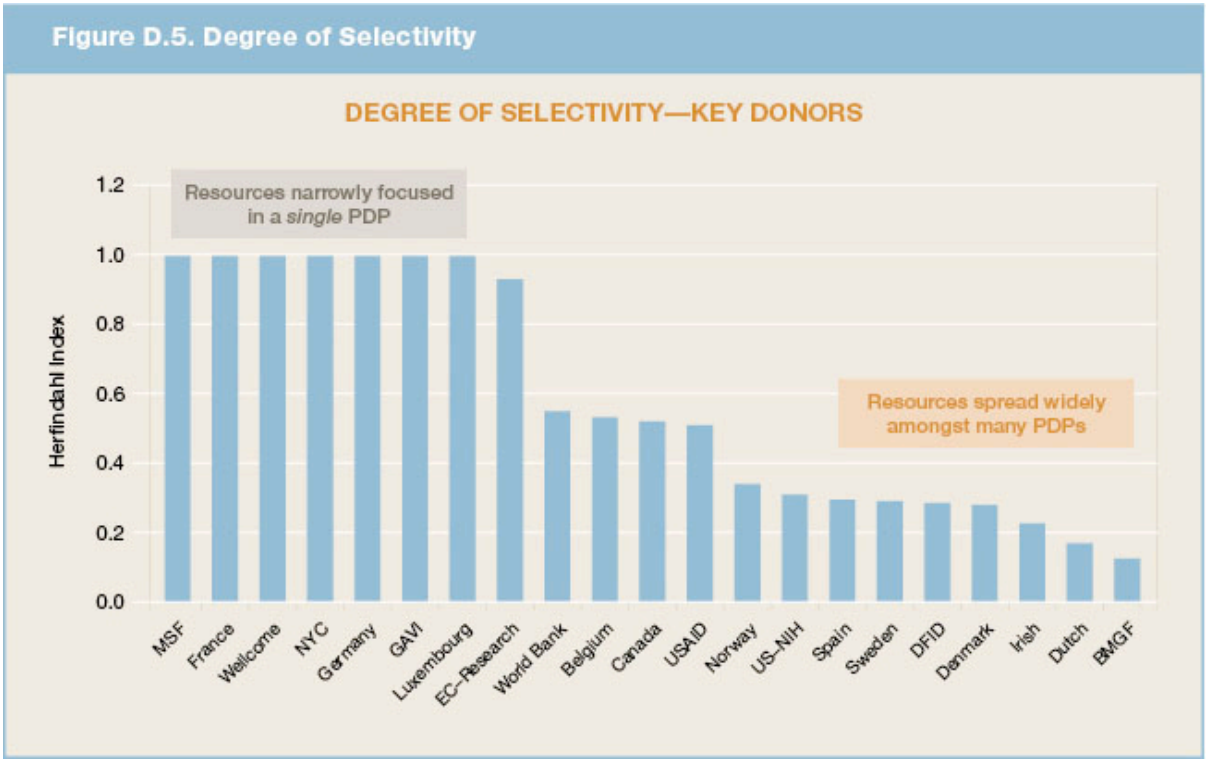
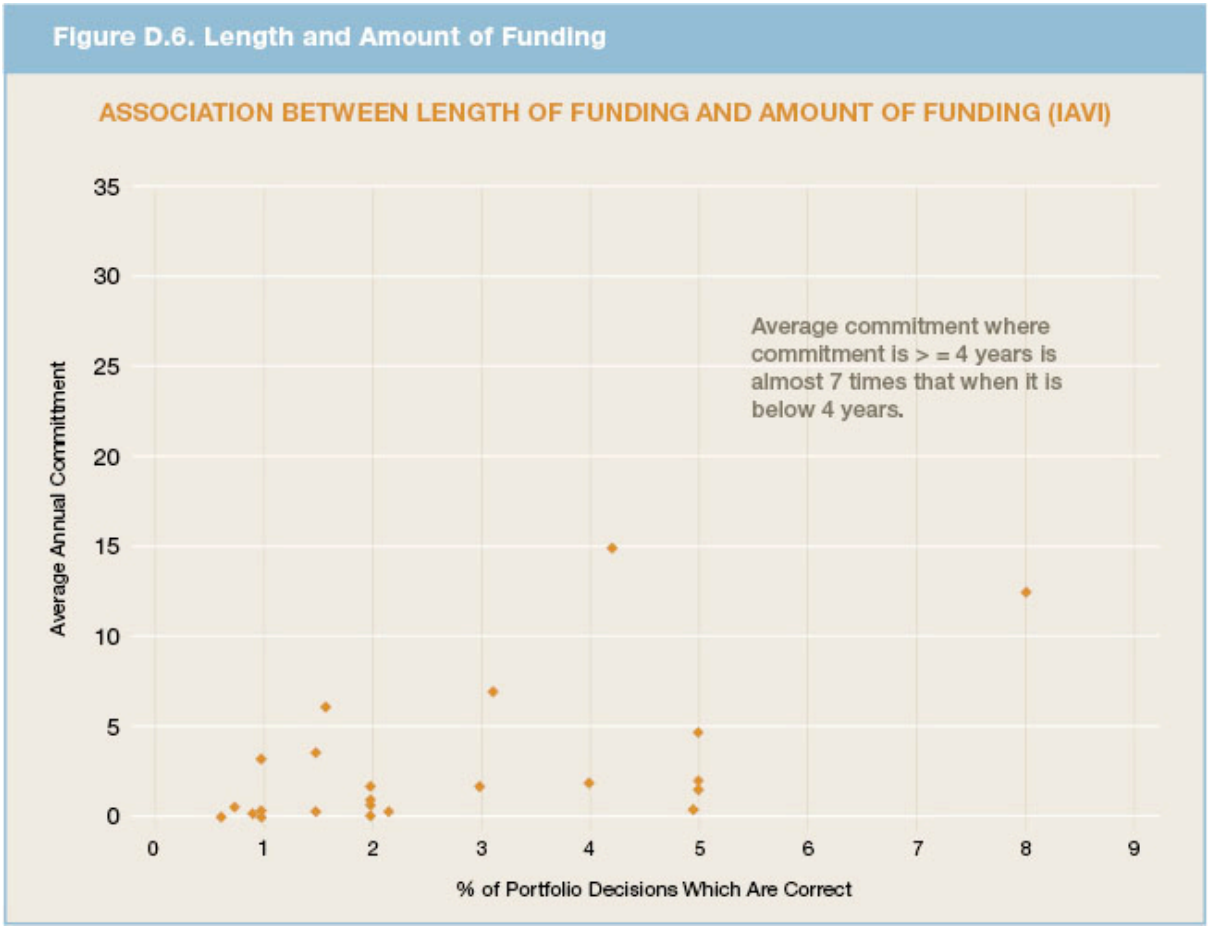


Figure D.6. Length and Amount of Funding



Funding is typically provided on a relatively short-term basis. As the chart below shows (using data on current IAVI funding as it receives funds from a number of sources), a large share of funders provide relatively small amounts of short-term support, with the bulk of support provided by a relatively small number of donors who provide relatively long-term support. Where funding patterns are diverse, which is only true for a small sample of PDPs, the larger donors tend to provide longer-term funding; the implication is that the majority of transaction costs are related to a large number of smaller funders who account for relatively little of the overall support.

Appendix E: Product research and development for neglected tropical diseases and the pharma industry

By Janis Lazdins

Product R&D for tropical diseases flourished during the first half of the 20th century, responding mostly to the needs of colonial interests in Africa and Asia to manage diseases such as malaria, sleeping sickness, filariasis, etc. (quinine, chloroquine, suramin, melasoprol, piperazine, diethylcarbamizine, etc.). During the 1970s and onwards, the R&D activities for NTDs saw a noticeable decline in interest by the pharmaceutical industry (pharma). Of the approximately 1,600 new chemical entities that were registered by western health authorities between 1975 and 2003. only 17 were specifically indicated for tropical diseases.

Some products were developed specifically for human use responding to disease interests/objectives (e.g., malaria: mefloquine, halofantrine, artemether, artemether-lumefantriune; Chagas' disease: nifurtimox, benznidazol; TB: rifampicin, isoniazid; leprosy: multidrug therapy; sleeping sickness: pentamidine, efloornithine). Others took advantage of the opportunity provided by products that had been developed for animal health purposes, adapting them to address human diseases (e.g., onchocerciasis: ivermectin; schistosomiasis: praziquantel, oxamniquine; liver fluke: triclabendazole; intestinal helminths: pyrantel, piperazine, albendazole, mebendazole, levamisole, etc.).

During the 1980s and 1990s, thanks to the product R&D activities of TDR working in partnership with academia and the pharma sector, the product pipeline for NTDs was kept alive. The framework for this interaction was simple: through a network of researchers funded by TDR's public funds, TDR would identify potential molecular candidates for TDR diseases. If these candidates belonged to pharma, TDR approached the owner company making a case for the need to further development. If the molecule came from the public sector, TDR identified a possible development partner or directly assumed the development activities. In the TDR-pharma partnership, TDR would facilitate and finance the necessary preclinical and clinical studies, while pharma assumed other development activities and, after registration, would commit to production and access at conditions prenegotiated with WHO. Through this framework, more than half of the 17 products mentioned above became important public health tools, some provided by pharma at cost, others as donations. Among these, it is important to highlight Ivermectin (Merck), which constitutes the basis of the current success of the onchocerciasis control programs and the development of the pediatric malaria indication for artemether-lumefantrine that later led to the development and registration of a pediatric formulation of the product (MMV/Novartis).

Despite the success of the model developed by TDR, it was clear that the product pipeline for NTDs was highly insufficient and pharma engagement marginal. Discussions addressing the neglect of diseases that affect a great proportion of the human population (10/90 gap) highlighted the need to create new frameworks to fill the product gaps. It was through these discussions that the concept of public–private partnerships (PDPs) for product R&D for NTDs was born within TDR. TDR played an important role during the incubation phase of some of the first PDPs (e.g., MMV, FIND, DNDi). Many pharma companies, being aware of the TDR experience, saw in the PDPs an opportunity to respond to the public sector demands as well as to create a reasonable framework to minimize risks by relieving the costs associated with some R&D activities, streamlining the development processes and having access to disease information and expertise, expertise that the industry had lost. The product R&D PDP model was built on the expectation that the pharma industry would focus on many of the technical aspects of the R&D process, while the PDPs working with disease experts and health programs would provide strategic direction (product portfolio decisions); provide linkage with patients, clinical experts, clinical

research centers, and health authorities; and coordinate key development activities. Furthermore, the PDPs would play an important role in facilitating the post-registration and access activities (e.g., linkage with user communities to rationally address production and deployment of products). Within this conceptual framework, through public and philanthropic funding, many PDPs were established, and many pharma companies have been engaged with PDPs now for more than ten years in drug, vaccine, and diagnostic R&D activities for NTDs. However, despite an apparent richness of PDPs dedicated to specific diseases or products, there have been only a few new products registered or brought to use, and most of these, while highly relevant, are not in the strict sense innovative. Furthermore, some of these products are struggling to be scaled up within disease control strategies.

An explanation could be that the initial focus of the PDP partnerships has been on demonstration of operational capability to manage the R&D process and less on health impact. Regulatory approval for products for NTDs is not a guarantee for immediate uptake or health impact. Furthermore, the target product profile developed within the PDP context, relying on the opinion of experts or advisers in some cases, has not been necessarily best aligned to the needs and possibilities of the users and their health systems. This can be illustrated through the experience from the development of the antimalarial Lapdap (chloroproguanil-dapsone) and its artemisinin-based fixed-dose combination "decart."

Lapdap was developed by GSK in partnership with TDR. The product, while highly effective and affordable, had limited introduction in endemic countries mainly because of uncertainties related to potential risks of hemolytic anemia in individuals with G6PD deficiency (given the resource limitations of developing-country health systems, this risk was unlikely to be manageable). Furthermore, after the publication of the malaria treatment guidelines emphasizing the use of artemisinin-based combinations, it became clear to the sponsors of Lapdap and their advisors that the product had to be re-engineered as an artemisinin fixed-dose combination. Consequently, the advisory board of the PDP MMV recommended that MMV develop Lapdap in combination with an artemisinin derivative (decart) in partnership with GSK. After extensive product development activities and clinical studies, it was only late in the development of decart that the implications of the risk of hemolytic anemia associated with G6PD deficiency were fully realized and development was terminated based on Phase III study results. Shortly after this decision, GSK also withdrew Lapdap from the market. Similar observations can be made for other drugs recently developed for NTDs in partnership with pharma under the PDP framework (e.g., oral miltefosine, paromomycin); these are highly effective drugs but with potential safety issues. The safety issues would not preclude their use under optimal health structures, but their use does represent special challenges when used under poor resource settings. Furthermore, after registration, the scientific community has highlighted that because of the suboptimal settings for their use, these products run the risk of being rapidly lost due to emergence of resistance, urging that these products should be used in combination with other available products.

These considerations, not addressed during the product development, and their present implementation have considerably slowed down the uptake of the products. In the area of antimalarials, under the background of extensive use of artemether-lumefantrine, several artemisinin-based drug combinations have been registered and more are currently in late development. However, it is not clear how the claimed competitive advantages of these new products will potentiate current malaria control activities. These examples highlight the fact that while the current PDP framework can efficiently address development activities (including lowering activity costs), the model still needs improvement on strategic decision making, risk management, and strengthening the interaction with health systems and their decision makers in order to achieve an early "buy in" for use after regulatory approval so that the pharma sponsors can plan accordingly to fulfil their commitments and the public sector benefit fully and timely from the innovation.

The urgency to improve the above mentioned aspects becomes more pressing if one notices that recently there has been a boost of the product discovery for NTDs through the creation of PPP discovery networks (e.g., ANDI) or through pharma industry dedicated discovery programs for drugs, vaccines, and diagnostics, as previously detailed. The primary mission of these initiatives is to provide a flow of molecules that can feed development pipelines at a rate to guarantee delivery of innovative products. Most of these initiatives state that for progression of the identified development candidates, a strong partnership with institutions from the public sector will be necessary. The initiatives promoted by the pharma industry or the public discovery networks implicitly will require a strong and effective strategic portfolio management and coordination that not only focuses on technical or scientific criteria but also on criteria defined by the nature and dimensions of the diseases to be addressed. To guarantee continuous engagement and expansion of stakeholders and shareholders, project management for NTDs will require highly skilled teams to address strategic decisions in order to focus on "innovation for success" enhancing rational use of resources, avoiding duplications, making rapid decisions based on pre-established go/no go criteria or new demands arriving from the field; synergizing R&D activities across diverse products and diseases will have to be considered as well. Diagnostics R&D must be contextualized with drug or vaccine development (not only to identify those in need for interventions but also to establish efficacy of the interventions).

Within the pharma sector, the R&D activities for several diseases or products for NTDs usually are managed under a single strategic product portfolio management process. On the other hand, PDPs are generally established as single disease/single product organizations. This can result in operational challenges for the pharma partners, when they need to match their "single" portfolio with that of different PDPs with different strategic and management processes. It is not unreasonable to question if, in the future, PDPs that are differently structured, managed, and funded will continue to attract pharma partners that will have to accommodate their own portfolio management practices with that of different PDPs. Furthermore, the pharma industry is also increasingly active in the areas of capacity building and institutional strengthening for NTD product clinical research, most likely in order to channel their research projects through these, and so are aligning the regulatory requirements with internal processes. This is relevant because the ultimate responsibility for presenting a case to regulatory authorities for a marketing authorization, even within the PDP framework, rests with the pharma sponsor. This further highlights the question of how will the PDPs align themselves (or provide added value) to these initiatives.

In conclusion, the presence of the pharma industry (particularly innovators) and public R&D networks addressing R&D for products for NTDs is in expansion, bringing forward R&D capabilities and proprietary information as never before. This is a unique opportunity to fulfill a gap that the public sector alone has not been able to address. If the PDPs (and their funders) are to play the role as mediators or brokers between the private and public sector, there might be a need to redesign the concept underlying PDPs. Great attention will have to be given to disease priority setting, portfolio and project management across diseases and products, and creating an environment that is amenable (and not restrictive) for all parties—public or private—to provide the best of their competencies and capabilities towards creating product pipelines affordable and accessible that can be measured in the context of indicators such as those highlighted in the millennium development goals.