Health Product Research and Development Fund

Operational Plan for
Voluntary Pooled Funding Mechanism

Includes two diseases case studies on priority health products for Leishmaniasis and Schistosomiasis

Version 3.1

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Operational plan for health product research and development fund
Background document 70th World Health Assembly Agenda item 13.5

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Operational plan for health product research and development fund
Background document 70th World Health Assembly Agenda item 13.5

Contents
Abbreviations ........................................................................................................ 5
Abstract .................................................................................................................. 6
1 Introduction ......................................................................................................... 6
  1.1 Scope ............................................................................................................. 6
  1.2 Background .................................................................................................. 7
2 Basic principles, affordability, operating model and governance .................. 8
  2.1 Mandate and basic principles ..................................................................... 8
  2.2 Voluntary pooled fund ............................................................................... 8
  2.3 Benefits of the fund .................................................................................... 9
  2.4 Affordability of products coming out of the mechanism ......................... 9
  2.5 Management, and governance of funds .................................................... 10
3 Intellectual Property ........................................................................................ 11
4 Financing options ............................................................................................. 11
5 Decision process ............................................................................................... 12
  5.1 Decision process for prioritizing areas for Health Research & Development .. 12
  5.2 Decision process for release of funds ......................................................... 13
  5.3 Roles and responsibilities in decision process ........................................... 14
    5.3.1 Global Observatory on Health Research and Development .............. 14
    5.3.2 Expert Committee on Health Research and Development .............. 14
    5.3.3 Scientific Working Group .................................................................... 14
    5.3.4 Secretariat within TDR ......................................................................... 15
  5.4 Coordination with WHO technical departments and Regional Offices ...... 15
  5.5 Coordination with other mechanisms ....................................................... 16
6 Administrative considerations ........................................................................... 16
  6.1 Operational costs ......................................................................................... 16
  6.2 Human Resources ....................................................................................... 17
7 Monitoring & Evaluation .................................................................................. 17
  7.1 Monitoring of fund’s milestones .................................................................. 17
  7.2 M&E of research projects submitted ............................................................ 18
8 Communication .................................................................................................. 19
  8.1 Reporting to different committees ............................................................... 19
  8.2 Reporting to donors .................................................................................... 19
Annexes ............................................................................................................... 20
Annex I Selection of SWG members .................................................................. 20
Annex II SWG members profile ......................................................................... 22
Annex III Role of the Scientific Working Group ................................................ 23
Operational plan for health product research and development fund
Background document 70th World Health Assembly Agenda item 13.5

Annex IV Calls for proposal, review and selection of projects ........................................... 24
Annex V Organization of SWG meetings ................................................................. 27
Annex VI Responsibilities of the R&D Secretariat....................................................... 28
Annex VII Suggested criteria for selecting projects ...................................................... 29
Section I: Assessment of project plan and financing .................................................. 29
Section II: Analysis of the Extent of Innovative Components .................................... 29
Annex VII Elements of a communication plan ......................................................... 31
Appendices .................................................................................................................. 32
Appendix 1 Case study Schistosomiasis ....................................................................... 33

Introduction ................................................................................................................. 34
1 Priority definition HR&D Observatory ................................................................. 35
2 Specific HR&D gaps and health products needed ................................................. 36
3 Prioritizing Interventions ...................................................................................... 38
4 Sourcing and validation of Preferred Product Profiles .......................................... 40
5 Health Research & Development Pipeline ......................................................... 40
6 Incentive mechanisms ........................................................................................... 41
7 Review of applications ......................................................................................... 42
8 Monitoring and evaluation of selected projects .................................................. 42
9 Conclusion ............................................................................................................. 43
10 Analysis for R&D Schistosomiasis ..................................................................... 43
11 Using PPP criteria fulfilment to filter and prioritize diagnostics projects ............ 49
12 Product Preferred Profile ..................................................................................... 49
Appendix 2 Case study Cutaneous Leishmaniasis ...................................................... 50

Introduction ................................................................................................................. 51
1 Priority definition Health Research & Development Observatory ....................... 53
2 Specific HR&D gaps and health products needed ................................................. 54
3 Prioritizing Interventions ...................................................................................... 56
4 Sourcing and validation of Preferred Product Profiles .......................................... 58
5 Health Research & Development Pipeline ......................................................... 59
6 Incentive mechanisms ........................................................................................... 60
7 Review of applications ......................................................................................... 61
8 Monitoring and evaluation of selected projects .................................................. 61
9 Conclusion ............................................................................................................. 61
10 Using PPP criteria fulfilment to filter and prioritize Therapeutic Products ......... 62
Operational plan for health product research and development fund
Background document 70th World Health Assembly Agenda item 13.5

Abbreviations

CEWG Consultative Expert Working Group on Research & Development: Financing and Coordination
CL Cutaneous Leishmaniasis
COI Conflicts of interest
DG Director General
ERC Ethics Review Committee
HR&D Health Research and Development
IP Intellectual Property
JCB Joint Coordinating Board of TDR
KPIs Key performance indicators
LMICs Low- and middle-income countries
M Million
MDA Mass Drug Administration
NCEs New chemical entities
NTD WHO’s department of Neglected Tropical Diseases
OC Operational Costs
PI Principal Investigator
R&D Research and Development
RTO Responsible Technical Officer
SOP Standard Operating Procedures
STAC Strategic and Technical Advisory Committee
SWG Scientific Working Group
TDR Special Programme for Research and Training in Tropical diseases
VL Visceral Leishmaniasis
WHA World Health Assembly
WHO World Health Organization
Abstract

The Operational Plan for Health Product Research and Development Fund was developed in response to the request of Member States to address the gaps in research and development for Type II and Type III diseases, and the specific research and development needs of developing countries in relation to Type I diseases. This operational plan sets out in detail the option that by 2030, the fund aims to be operational with an annual disbursement of US$ 100 million to cover the costs of up to 40 projects including five innovation projects, thus assisting in addressing some of the most critical funding gaps.

Two case studies, developed to illustrate the implementation of the financing mechanism, discuss evidence-based recommendations for priority health products for schistosomiasis and cutaneous leishmaniasis. These analysis were prepared by the Special Programme for Research and Training in Tropical Diseases in close collaboration with WHO’s department of Neglected Tropical Diseases. The short-term recommendation for schistosomiasis is to finalize the development of diagnostic tests for low prevalence areas and for interruption of transmission for a total of 300,000 US$ for one year. For cutaneous leishmaniasis, for the short term, a mobile phone application for improved surveillance and diagnosis of affected individuals in peripheral health areas is proposed. For the medium-term, the need for a topical/oral treatment was identified as a priority health product to address WHO’s strategy to reduce morbidity of cutaneous leishmaniasis, totalling 500,000 US$ for up to two years.

1 Introduction

This document is in response to the request of Member States through World Health Assembly (WHA) resolution WHA69.23 and is an additional background paper to World Health Assembly document WHA70/22.

1.1 Scope

This Operational Plan describes the set-up of a voluntary pooled fund of US$ 100 million in annual disbursements to address the gaps in research and development (R&D) for Type II and Type III diseases, and the specific R&D needs of developing countries in relation to Type I diseases. This document:

1) presents both pillars of the pooled fund, i.e. the Scientific Working Group (SWG) and the financial mechanism;
2) addresses coordination and collaboration with the WHO Observatory for Health R&D and the WHO Expert Committee on Health R&D;
3) proposes a governance structures as well as roles and responsibilities of different actors / stakeholders;
4) discusses links and synergies to other R&D initiatives; and
5) describes two case studies for illustration purposes on the functioning of the voluntary pooled fund.
1.2 Background

Diseases that primarily affect low- and middle-income countries (LMICs) are still a major cause of mortality, disability and poverty. The WHO defines such diseases as Type III ("overwhelmingly or exclusively incident in developing countries") and Type II ("incident in both rich and poor countries, but with a substantial proportion of the cases in poor countries"). These diseases are often referred to as neglected diseases or diseases of poverty. They consist mainly of infectious and parasitic diseases, but also include some nutritional deficiencies, maternal and neonatal conditions, respiratory infections, sensory organ diseases, cardiovascular diseases and digestive diseases. R&D for health products is still limited for several, if not most, Type III and II diseases. These diseases are often characterized by market failure, where the commercial potential for drugs, vaccines and diagnostics is too small to spur sufficient product development activity. Although they represent a high proportion of the disease burden in LMICs, a limited number of new treatments, only four out of 336 new chemical entities (NCEs) registered between 2000 and 2011 were developed and approved for these diseases. Furthermore, there is little coordination between funders on disease priorities for existing funding, meaning that individual efforts are sometimes fragmented.

In 2010, the WHA63.28, established the Consultative Expert Working Group on R&D: Financing and Coordination (CEWG), 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. In resolution WHA66.22 the Health Assembly requested WHO to explore and evaluate existing mechanisms for financial contributions to health research and development and, if there is no suitable mechanism, to develop a proposal for effective mechanisms, as well as a plan to monitor their effectiveness independently.¹ Building on this, in 2016, the WHA, asked WHO’s Director General (DG), through Resolution WHA69.23, to present an operational plan for a voluntary pooled fund. Specifically the Special Programme for Research and Training in Tropical diseases (TDR), was requested to develop a financial mechanism with voluntary contributions for product R&D for type III and II diseases, and the specific R&D needs of developing countries in relationship to Type I diseases to eventually lead to new health products (diagnostics, vaccines and treatments). This operational plan is based on the work conducted by the CEWG², as well as a study conducted by TDR on Health Product R&D.³

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² [http://apps.who.int/iris/bitstream/10665/254706/1/9789241503457-eng.pdf?ua=1](http://apps.who.int/iris/bitstream/10665/254706/1/9789241503457-eng.pdf?ua=1)
³ Health Product Research & Development Fund: A proposal for financing and operation [http://www.who.int/iris/handle/10665/204522](http://www.who.int/iris/handle/10665/204522)
2 Basic principles, affordability, operating model and governance

2.1 Mandate and basic principles

This document was prepared in response to the above mentioned request of Member States. The mandate for the development of this operational plan rests with WHO's Member States in order to describe the operation of a new funding mechanism for Member States and other stakeholders. This operational plan sets out in detail the option that by 2030, the fund aims to be operational with an annual disbursement of US$ 100 million to cover the costs of up to 40 projects including five innovation projects, thus assisting in addressing some of the most critical funding gaps.

This funding mechanism ensures that priorities identified by the Expert Committee for Health R&D will be addressed, effectively focussing on the most critical unmet needs in the R&D of health products.

The CEWG identified the following principles to ensure an efficient operation of a pooled voluntary fund:

- Ability to provide a sustainable and predictable source of funding;
- Equitable R&D to ensure affordability, effectiveness, efficiency, equity and to allow delinking the costs for the investment into R&D from the volume and price of the resulting health product;
- Flexibility in the allocation of donated resources to ensure that the resource allocation would be delinked from the specific research and development interests of the donor;
- Optimal acceptability and political will for efficient and timely implementation of the selected option;
- Use of existing mechanisms where appropriate;
- Accommodating a broad donor base;
- Ability to leverage additional funding to encourage further donors to provide funds for the voluntary pooled fund; and
- Ability to access new and untapped sources of funding (e.g. middle-income country donors, private donors).

2.2 Voluntary pooled fund

The pooled fund will address the priorities defined by the Global Observatory on Health R&D and the WHO Expert Committee on Health Research and Development) through focused R&D projects and build up a mixed research and development project portfolio over time. This “mixed model” scenario considers a diversified fund that finances multiple interventions across several diseases. The fund will start small and should demonstrate quick short-term successes before growing at scale. The mechanism will fund several development projects (e.g. funding phase III trials to bring a single intervention through to approval). If the fund becomes

4 http://www.who.int/phi/CEWG_Report_5_April_2012.pdf?ua=1
operational in 2017, the TDR estimates that three reformulation or repurposed drugs, one simple new chemical entity and one complex repurposed drug may be launched by 2030 as a result of this investment.\(^3\) A fund size of US$ 100 million, or more per year, is necessary to reduce the gaps in R&D and produce the results in product development that are needed to have an impact on the targeted diseases. Harmonization with existing funds and mechanisms will be a crucial element in operating this fund to avoid duplication in some areas and widening of/not addressing the R&D gap in other areas.

### 2.3 Benefits of the fund

A major advantage of this funding mechanism is that it will enable the inclusion of “new” funding that has not previously been available to finance global health R&D in Type III and II diseases. The new fund, operating under the transparent processes of WHO/TDR, offers a trusted route to accept contributions from all Member States including LMICs. This has already been demonstrated by the funding mechanism currently operational in support of the CEWG demonstration R&D projects.\(^5\) As the donors funding is pooled they will have a greater collective effort than they would at national or regional level. The pooled fund would assure stability by providing a “base” level of funding throughout the multi-year timescale typically needed for R&D projects. The designated (or earmarked) funds could complement this by encouraging project-specific contributions from funders interested in certain areas.

Other benefits of the pooled fund include:

- In conjunction with the Global Observatory on Health R&D and the Expert Committee on Health R&D, the fund will be an integrated mechanism, joining data analysis, priority setting and implementation;
- Collective effort to fund projects rather than spread resources among numerous initiatives therefore averting duplications;
- Shared risks of failure (which are high in R&D) and benefits;
- Spread of the burden of funding. By accommodating different sizes of contributions, the fund opens the door for smaller economies and LMICs to support global efforts in health R&D;
- A forum for donors to discuss health product development priorities, review opportunities, and coordinate and collaborate in R&D;
- A focus on existing donor investment and reducing redundant funding; and
- Cost-effectiveness, in particular if the fund utilizes existing structures and mechanisms and would not require the creation of a completely new organizational structure.

### 2.4 Affordability of products coming out of the mechanism

The pooled fund will operationalize a number of the principles and recommendations formulated by the Expert Committee on Health R&D, including the core principles as defined

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by the CEWG of affordability, effectiveness, efficiency, equity and the principle of delinking the costs for the investment into research and development from the volume and price of the resulting health products indicated in section 2.1. It will favour open collaboration and sharing of research and development results. Those who receive grants will have to adhere to the principles of transparency and knowledge sharing. Those who bring products to the market that were developed with funding from the pooled fund will have to commit to an affordable pricing policy and to manage any intellectual property (IP) in a way which prioritizes access (see also section 3). Conditions will be included in the grant proposals including for example an obligation to grantees to register new products in disease endemic countries and make the product available at affordable prices. More information on how this will be identified and used as part of the prioritization process can be found in Annex VII section II.

2.5 Management, and governance of funds

Currently, no existing mechanism is in place coordinating health research and development at the global level. Any independent mechanism to pool funding for research and development at global level would have to be able to:

- receive voluntary funding from a variety of sources, including WHO Member States;
- manage and disburse funds to private and/or public entities for the financing of research in various areas of diseases that disproportionately affect developing countries;
- put in place an appropriate access policy to ensure that any product developed using its funds is made available at an affordable price in countries in need;
- be accountable to Member States (regarding the handling of operational funds);
- fit within an existing governance structure or ensure establishing a transparent and non-political governance model;
- fuel the operating cycle by transparent, objective and non-political decision-making; and
- implement a simple, evidence-based process to quickly review projects and decide which to incentivize.

Any new mechanism would need to be grounded within the health sector and be able to draw on extensive experience with health product development to ensure a rigorous and high quality approach to portfolio management.

Based on the above the Member States requested the WHO to undertake a review of existing mechanisms in order to assess their suitability to perform the coordination function of health research and development. This comparative study, conducted in 2013 among a number of different organizations and mechanisms, identified TDR as one of the most appropriate organizations housing the voluntary pooled fund:

1. TDR is a global programme of scientific collaboration that helps coordinate, support and promote global research efforts to combat infectious diseases of the poor and disadvantaged. TDR also promotes the translation of innovation into ways of impacting health in disease endemic countries;

6 http://www.who.int/phi/documents/CEWG-WP/en/
2. TDR is co-sponsored by the United Nations Children's Fund, the United Nations Development Programme, the World Bank and WHO and operates within a broad framework of intergovernmental and interagency cooperation and participation;

3. TDR is the only global mechanism with Member States’ oversight and with a WHO led prioritization process. As such, the oversight through the WHA is open to all Member States.

This operational plan, therefore, proposes suggestions for using TDR’s structure and how the pooled voluntary fund could function within TDR. Establishing the financial mechanism within TDR reduces costs as existing structures and mechanisms will be used, thus not requiring the creation of a completely new organizational structure with considerable financial implications. The complete financial mechanism fits within the existing TDR governance structure. Communication will be facilitated as the Global Observatory on Health R&D will be housed in WHO as well. The SWG will be accountable to TDR’s Joint Coordinating Board (JCB) and report to the Member States through the WHA. As such, the governance model and decision-making process will be transparent and non-political. Member States, who wish to join the Health R&D process can apply to become a member of TDR’s JCB. If the pooled fund increases significantly (>US$ 100 million), a different set-up could be envisaged, e.g. setting up an independent structure.

Housing the fund within TDR, will ensure compliance monitoring through financial and progress reports submitted to both internal and external stakeholders. WHO would be responsible for all of the financial mechanism’s fundraising activities by drawing on Member State/donor pledges towards a pooled fund. TDR, as the secretariat, would be responsible for hosting and administering the funds according to their rules and regulations. The Secretariat would ensure appropriate management of conflicts of interest in subsequent decisions on the allocation of funds. A set of Standard Operating Procedures (SOP) will be adapted from TDR’s existing SOPs to guide the decision and execution process.

3 Intellectual Property

The management of IP will be guided by the CEWG core principles (see section 2.1) in particular to ensure affordability by applying delinkage. Where appropriate, the SWG may seek to secure IP for example, to secure quality of products marketed, as well as appropriate access, and pricing policies of potential licensees. All IP arrangements will aim at ensuring equitable and affordable access to treatments. The SWG will seek to learn lessons from other product development partnerships and the Medicines Patent Pool, to determine best practices, steadfast commitment to promote open sharing of research knowledge and data while ensuring an access-oriented approach to intellectual property management and licensing.

4 Financing options

WHO explored the different options for a sustainable funding of a pooled fund that would be able to disburse US$ 100 M annually. Among the different options, two have been identified as
most promising: 1) multi-source funding model with voluntary government payments and matching contributions from industry; and 2) a classical replenishment fund. More details can be found in the report “Options for Sustainable Funding of a Voluntary Pooled Fund to Support Health Research and Development”.

5 Decision process

5.1 Decision process for prioritizing areas for Health Research & Development

The Global Observatory on Health R&D aims to consolidate, monitor and analyse relevant information on health R&D needs of developing countries, with a view to contribute to the identification and the definition of gaps and opportunities for health R&D priorities. The data from the WHO Global Observatory on Health R&D and other sources will be analysed by the WHO Expert Committee on Health R&D to recommend priority areas for R&D of specific health products and technologies for specific health conditions of Type III, Type II and relevant Type I diseases. The Expert Committee on Health R&D will also draw on expertise from the existing WHO technical programmes and their scientific advisory panels. It may have to commission further studies to provide more in-depth analysis in a specific disease area. This will result in high level strategic advice on the global product characteristics required to fill an identified R&D gap.

Figure 1: Overview of outputs from and inputs to committees showing the separation of responsibilities between WHO and TDR.

* from among others: Policy Cures Grant Finder survey, WHO International Clinical Trials Registry Platform, PubMed, EUROSTAT, OECD, RICYT, UNESCO

7 http://apps.who.int/iris/bitstream/10665/254831/1/WHO-EMP-PHI-2016.08-eng.pdf?ua=1
5.2 Decision process for release of funds

The SWG operationalises the priorities established by the Expert Committee for Health R&D, determines specific detailed priorities and evaluates projects against a set of criteria that identifies “high potential” projects and determines the appropriate incentive mechanism based on a predefined framework. The SWG will use project selection criteria (see annex VII for a proposal of criteria) and employs financing (including soliciting, selecting, monitoring and evaluating of approved projects). They will take the ideal product characteristics and develop the best R&D response using the resources of the pooled fund. This could include a call for proposals, or commissioned work or milestone prizes utilizing the numerous push and pull incentives identified and evaluated in the CEWG report. Coordination with the WHO’s existing technical programmes both at headquarters level and in the Regional Offices is crucial to ensure that gaps identified by the technical programmes are incorporated into the decision making process. The SWG may also recommend deploying incentive mechanisms depending on the needs of the funded projects. The SWG will also link with the prequalification group in WHO, thus ensuring an end-to-end strategy from conception to prequalification of a health product.

The complete structure is exemplified in Figure 2.

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Figure 2: Schematic environment including Governance structure⁸

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http://apps.who.int/iris/bitstream/10665/204522/1/9789241510295_eng.pdf?ua=1
All funding will be issued with the goal of developing a needed health product that would be acceptable, available, accessible and affordable to LMIC populations. The fund will spread risk across a diversified portfolio, to leverage technically rigorous portfolio management practices and to engage in collaborative partnerships across the R&D value chain in order to spur R&D and product development in prioritized diseases. The model for funding is based on financing pre-medical to phase III clinical trials. The fund could, however, operate outside these phases. Manufacturing will not be funded nor will the costs of registration or prequalification.

To promote the potential for health impact, applications will be screened to ensure that data are compliant with regulatory requirements, and should indicate their scientific and technical feasibility. Regulatory agencies must be engaged as early as possible and studies from preclinical studies to clinical trials should be designed and conducted in full compliance with regulatory requirements.

5.3 Roles and responsibilities in decision process

A specific set of TORs is developed for each group/committee that forms part of the process.

5.3.1 Global Observatory on Health Research and Development
The role of the Global Observatory on Health R&D is to provide the fundamental data needed to prioritize research and development decisions. Such analyses will include data on the unaddressed public health needs for new products, ongoing research and development activities (products in the pipeline, clinical trials), investments, gaps, list of approved products, patents, as well as any established priorities for research and development for the diseases and conditions under its scope.9

5.3.2 Expert Committee on Health Research and Development
The Executive Committee will have the task of providing independent external technical advice to the DG, based on the analysis produced by Global Observatory on HR&D. The members are selected by WHO’s DG, ensuring a balanced geographical and gender distribution.10 Both the Expert Committee and the DG will draw on external experts or stakeholders, as needed and appropriate, to ensure that the process remains technical and impartial. The Expert committee will recommend priority areas for research and development of specific health products and technologies for specific health conditions; for example, the need for an innovative vaccine against pulmonary tuberculosis in adults which accounts for most of the tuberculosis cases worldwide, or an accurate and specific, easy-to-use diagnostic tool which can be used in rural health settings. Technical expertise from WHO’s technical departments and other entities will be drawn upon where needed.

5.3.3 Scientific Working Group
The SWG operationalises the health priorities by developing the detailed product characteristics, preparing calls for proposals, and by analysing product profile characteristics and the existing pipeline. The SWG also prepares a recommendation on the most appropriate

9 http://www.who.int/research-observatory/portal/en/
Operational plan for health product research and development fund
Background document 70th World Health Assembly Agenda item 13.5

incentive/disbursement mechanism. Assisted by the Secretariat, they monitor and review funded projects to measure progress and evaluate their impact potential. See Annex III for an overview of the role of the SWG. Figure 3 provides an overview of the portfolio tools to be applied by the SWG.

5.3.4 Secretariat within TDR
The day-to-day management of the R&D fund will be conducted by the Secretariat, provided by TDR. One of the key functions of the Secretariat will be the management of the project portfolio, ensuring communication at all levels through the organization of meetings and telephone conferences, and sharing of the information on progress and funds used, setting up a SharePoint (or similar structure) for all research projects. Annex VI provides an overview of specific tasks of the R&D Secretariat. Annex VIII provides an overview of communication considerations.

5.4 Coordination with WHO technical departments and Regional Offices
WHO has a number of existing disease-focused technical programmes that develop global R&D strategies and roadmaps, informed by independent scientific advisory panels and wide ranging consultation. The Expert Committee for Health R&D will also draw on this information to ensure that the committee maximizes benefit of the existing expertise from WHO technical programmes and their scientific advisory panels.

Figure 3: Portfolio management tools for the SWG

<table>
<thead>
<tr>
<th>ACTION</th>
<th>AVAILABLE TOOLS</th>
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<tbody>
<tr>
<td>Priority definition</td>
<td>WHO Prioritization Mechanism defines (bread or specific) R&amp;D priority</td>
</tr>
<tr>
<td>Convening of experts</td>
<td>Secretariat and SWG Chair convene experts to address defined R&amp;D priority area</td>
</tr>
<tr>
<td>Priority breakdown</td>
<td>If necessary, SWG details specific priorities (i.e., specific product R&amp;D need)</td>
</tr>
<tr>
<td>TPP finalization</td>
<td>SWG sources and validates TPPs that address granular priorities from compelling or newly commissioned</td>
</tr>
<tr>
<td>Pipeline review</td>
<td>SWG evaluates current pipeline against TPP to identify promising candidates</td>
</tr>
<tr>
<td>Determine mechanism</td>
<td>SWG determines appropriate incentive mechanisms targeted for a given scenario</td>
</tr>
<tr>
<td>Project assessment</td>
<td>SWG reviews applications; Secretariat begins disbursement</td>
</tr>
<tr>
<td>Project monitoring</td>
<td>As part of portfolio management, SWG reviews project progress on a regular basis</td>
</tr>
</tbody>
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ICTRP: International clinical trials registry platform; R&D: research and development; SWG: scientific working group; TPP: targets product profile.

http://apps.who.int/iris/bitstream/10665/77935/1/9789241503259_eng.pdf?ua=1
5.5 Coordination with other mechanisms

At the highest level, coordination between the different R&D mechanisms will be managed through the Expert Committee on Health R&D. The WHO Global Observatory on Health R&D already has the mandate to monitor and analyse all R&D activities for type III and type II diseases, as well as for selected type I diseases. The collaborative relationship between other mechanisms and the pooled fund would be crucial. Examples of new initiatives WHO has been associated with and their relationship to this new funding mechanism include:

- **GARDP**: an implementing entity and as such not a financing mechanism, and thus a potential receiver of funds from the pool as other PDPs.
- **CEPI**: an alliance to finance and coordinate the development of new vaccines to prevent and contain infectious disease epidemics. An overlap of diseases to be covered exists; when the SWG will prepare a call for a related R&D for a blueprint disease, they should coordinate upfront with CEPI. The CEPI activities are also monitored by the Global Observatory on Health R&D and the Expert Committee on Health R&D for the identification of priority areas.

For Antimicrobial resistance (AMR) activities no pooled fund has been setup. If Member States decide to set up such a mechanism close coordination will be necessary to avoid overlap and competition for resources.

6 Administrative considerations

6.1 Operational costs

The operational costs (OC) required to run the pooled fund are estimated up to US$ 7.6 million, including fund-hosting costs, meeting costs and human resources, if hosted by the TDR. The OC will increase progressively as the size of the fund increases over time. The first year of the fund the OC are estimated at US$~350,000 to cover the functioning of the SWG and initial staff. As the fund size increases to US$15 million, the OC will amount to US$1.6 million and to US$7.6 million after several years as the fund reaches the planned US$ 10 million. If a new mechanism would be established the overall OC would need to be reassessed. They might be higher as tasks absorbed by TDR’s infrastructure would need to be implemented/absorbed elsewhere. Examples include more staff would be needed to carry out the work, functioning of a governance board and oversight, as well as the need for additional administrative staff, financial management and office space.

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13 Coalition for Epidemic Preparedness Innovations  http://cepi.net/
15 http://www.who.int/antimicrobial-resistance/en/
16 The total amount of OC needed for a US$ 100 million pooled fund will be US$ 107.6 million
6.2 Human Resources

Initially two full-time staff (one project manager and one administrative assistant) will be needed to coordinate the day-to-day activities of the Secretariat and assist the SWG in performing the detailed prioritization. As the fund expands, three staff members will be needed to facilitate the work of the SWG and Expert Committee in performing detailed prioritization and project evaluation (estimated operating cost up to US$ 4.5 million annually). A gradual increase to 14 staff members can be expected to facilitate the SWG and the Expert Committee in managing fund disbursement, priority setting and portfolio management (the estimated human resources cost will add up to US$ 7.6 million for a fund of US$ 100 million).

<table>
<thead>
<tr>
<th>Fund size in US$</th>
<th>Operational costs in US$* (in % from total)</th>
<th>Staff needed</th>
<th>Non personnel costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 M</td>
<td>0.3 M (6%)</td>
<td>1 project manager 1 admin staff</td>
<td>Overhead costs SWG costs</td>
</tr>
<tr>
<td>15 M</td>
<td>1.6 M (11%)</td>
<td>1 project manager 1 advocacy/support 1 admin staff</td>
<td>Overhead costs Financial mgmt. of fund SWG costs</td>
</tr>
<tr>
<td>50 M</td>
<td>4.5 M (9%)</td>
<td>1 managing officer 1 project manager 5 project officers 1 advocacy/support 1 admin staff</td>
<td>Overhead costs Financial mgmt. of fund SWG costs</td>
</tr>
<tr>
<td>100 M</td>
<td>7.6 M (8%)</td>
<td>1 managing officer 1 project manager 7 project officers 3 advocacy/support 2 admin staff</td>
<td>Overhead costs Financial mgmt. of fund SWG costs</td>
</tr>
</tbody>
</table>

* operational costs include human resources, overhead and support function to SWG and Expert Committee, based on utilizing the existing governance mechanism within TDR.

Table 1: Operational costs and human resources needs

The OC calculation is based on an OC model that these should be less than 10% of the total funding required.

7 Monitoring & Evaluation

7.1 Monitoring of fund’s milestones

The success of the voluntary pooled fund will depend on its ability to attract sufficient amounts of funding, with an annual minimum size of US$ 100 million at year 10 of operation. The SWG
will need to define and adjust the milestones based on the funding received. Several groups of milestones exist:

- Targeted funding requirements (e.g. US$ 17 million is required at the launch if seven projects of mixed archetypes are to be funded);
- Number of diseases to be targeted (e.g. three different diseases addressed over a five year period);
- Number of projects funded (e.g. xx number of phase III trials, xx number of simple repurposed drugs or xx number of reformulation or repurposed drugs, xx number of simple NCE developed).

7.2 M&E of research projects submitted

Assisted by the Secretariat, the SWG will monitor and review the funded projects to measure progress and evaluate their impact potential. From a funding and planning prospective, critical key performance indicators (KPIs) and “go”/“no-go” decision points will be defined in advance and used to measure the achievement of milestones around key inflection points in the key stage-gate.

Once projects have been selected for funding and confirmed by interviews with stakeholders and target-based milestone reviews, the decision points will be used to evaluate and monitor the achievements. The SWG use these results to decide whether to continue or discontinue the funding at each critical point. In addition to the standard monitoring of project timelines and milestones, the four prioritization factors (impact, cost, risk and strategic fit) will be monitored to re-assess prioritization and determine whether or not to fund later stages of the project (as specified in the milestone agreement). Fund recipients will need to monitor and report on the project using pre-defined KPIs. Depending on the project, the KPIs will be further elaborated. Milestone goals for specific projects will need to be set and have clear achievement agreements to facilitate tracking progress. Reporting frequency will be set according to specific needs, e.g. reporting and evaluation may be necessary every few months for early preclinical projects, while late-stage clinical trials may need to be evaluated once a year.

Research implementation examples include: the tracking of inputs and their effective use; tracking if activities are implemented as planned; tracking how research activities are implemented; and the progress towards achieving objectives. In addition the extent of meeting datelines & targets as well as the level of deviation from planned budget & activities can be measured. TDR has published the document: “Monitoring and Evaluating an Implementation Research project”, WHO, 2014, which provides basic guidance. Annex VII section I includes the criteria for selection the projects; the funded projects will also be evaluated against these criteria.

At least once a year, a progress report or a final report, together with a financial report, should be submitted by the research’s principal investigator (PI) to the secretariat. These are reviewed and if needed, further clarification is requested from the PI. Following this, the report is submitted to the SWG. The SWG reviews the progress and proposes changes or recommendations if needed.

Progress review includes technical and financial aspects, e.g. the SWG may request the budget to be reduced if a part of the work-plan will not be implemented. Progress review is important to ensure quality and to provide evidence of the external review of the project by an independent established committee. Once the reports are endorsed by the SWG, they are reviewed internally for coherence and then submitted to the Strategic and Technical Advisory Committee (STAC) for review (if the fund is housed within TDR). The SWG’s recommendations are also reported to STAC.

8 Communication

8.1 Reporting to different committees

To ensure a regular and consistent mechanism with the stakeholders a quarterly debriefing to the different committees, technical departments and Regional Offices will be the principal corps of communication concerning funds activity. The report will include an overview of the research requests received, approved and rejected, the quantity of funds disbursed, as well as the individual progress of each project funded. A yearly financial report will also provide an overview of the operational costs incurred.

8.2 Reporting to donors

Annual reporting to donors will ensure a transparent overview for the donors as well as a clear understanding for what the funds have been used. Details of the information include an overview of the research requests received, approved and rejected, the quantity of funds disbursed. The details will be discussed during a stakeholder meeting. An additional benefit of a pooled fund is that the reporting burden will be reduced. There will only be one financial and one technical report on the activities of the pooled fund as a whole. These will be presented and reviewed by the highest governance structure. With TDR this will be at the annual meeting of the JCB.

An advocacy platform for donors could be envisaged, where donors can follow the progress made.
Annexes

Annex I   Selection of SWG members

The SWG is a TDR’s established independent committee with a scientific/technical mandate that will provide recommendations on technical and financial aspects of TDR projects and contracts. The SWG for Intervention and Implementation Research “Implementation and Operational Research” is set up for optimizing the translation of innovation to health impact in disease endemic countries; developing and evaluating methods, tools and strategies for effective treatment and control of disease.

Composition
- The SWG must have a minimum of six and a maximum of eight members (including the Chair).
- Chair must be a current member of STAC with the relevant scientific and technical expertise in one or more disciplines relevant to the work of the SWG.
- Members of SWGs, including the Chair, shall be appointed to serve for a period of one or two years and may be eligible for reappointment for one or more additional terms of one or two years each.
- Whenever possible, to maintain continuity of membership, the expiration of the terms of office of members of SWGs will be staggered.

Selection of SWG members
- Members are proposed by TDR staff and selected by Director TDR, in consultation with STAC.
- Members cannot be current recipients of TDR funding in order to maintain independence.
- Members will be asked to declare any possible conflict of interest by completing the WHO Declaration of Interests form and may be requested to excuse themselves from any discussion(s) related to the area(s) in question.

Categories of Membership
- Member: is appointed for a one or two year period and may be reappointed
- Chairperson: is usually appointed for the term of their SWG membership

Appointment and extension letters for STAC, SWGs and ad hoc review groups
- Once approved by Director TDR, appointment and extension letters should be prepared according to the instructions in the Expert Reviews section of the Administrative Handbook. Templates can also be found in this section.
End of Membership letter
A letter should be sent to members at the end of their term, thanking them for their contributions. These letters are signed by the Manager of the SWG or ad hoc group and Director TDR.

General principles
- In order to facilitate reporting by the TDR Secretariat to STAC, the SWGs will follow harmonized reporting processes.
- The SWGs make recommendations to the TDR Secretariat.
- The recommendations of the SWGs are reported by the TDR Secretariat to STAC and presented by the Chair of STAC to the next session of the JCB.
- TDR is responsible for establishing working procedures for the organization of SWG meetings, including the preparation of draft agendas and other documents to be submitted to the SWGs.
Annex II  SWG members profile

The selected SWG members should have experience in:

- infectious diseases;
- leading product development;
- assessing risks;
- making challenging portfolio decisions, from feasibility evaluation of chemistry; manufacturing and controls to clinical trials;
- evaluating regulatory compliance and providing regulatory guidance;
- working in health systems in low- and middle- income countries (LMICs);
- financing or developing businesses, including being able to assess projects’ potential to deliver health impacts and their probability of success, and assess teams’ capacities and experience;
- evaluating potential health impact and values from health economists’ point of views.

The core SWG, when needed can be supplemented by expert groups, such as legal and intellectual property experts, and disease and product specialists from the individual priority disease areas set by the R&D Expert Committee.

A diligent conflicts of interest (COI) policy would help ensure that guidance and decision-making would be objective and of high quality. This is particularly important because individuals with several competencies coming from companies in the private sector (e.g. product development or finance and business development) may also be potential funding applicants. For highly neglected diseases with a small number of active researchers, the COI risk may be higher, as SWG members might be direct collaborators in the funded research.
Annex III  Role of the Scientific Working Group

The role(s) of SWG members is defined by the invitation letter and may vary according to the specific needs. They are:

- To approve the prioritization process for future ERs;
- To review ER budget and work plan, to ensure quality of the project and value for money (economy, efficiency, cost effectiveness);
- To review progress of current and planned activities / ERs and, where appropriate, make recommendations for action and follow-up;
- To provide oversight for grants and contracts awarded by TDR:
  - To review, score and rank (“recommend”) the proposals received in response to calls, from the technical and financial perspective.
  - The committee can delegate the review and scoring tasks to an ad hoc group. In this case the Chair of the SWG reviews and signs off the outcome of the ad hoc group review process.
  - To review the progress made on projects and approve the renewal of contracts when the work is well engaged, or the release of funds at the end of the contract, when the contract has been respected.
  - To approve the progress and final reports of funded projects.
Annex IV  Calls for proposal, review and selection of projects

General principles

- In line with the principles of transparency and obtaining the best value for money, TDR invites applications through an open process that takes place online.
- The review and selection process must be fair and transparent and ensure the quality of the selected proposals. The selection process is done by the SWG, an independent external committee.
- Mandate for reviewers must be clear, for which specific activity and for a determined duration.
- Conflict of interest must be avoided.

Operational steps from proposal to reporting

- Drafting, reviewing and publishing the call for proposals or calls for letter of interest Reviewer selection and guidance (Terms of Reference, work instructions) for reviewing the proposals (can be after 3);
- Proposal submission, acknowledgment of reception and inclusion into a database (can be automated);
- Proposal assigned to reviewers taking into account potential conflict of interest;
- Proposal review and scoring in line with the criteria published in the call;
- Review of statistical coherence of scores across reviewers, correction of outliers;
- Proposal ranking;
- Recommendation of the selected application(s) by SWG Chair;
- Corresponding with applicants;
- Protocol development and approval (for research projects, Ethics Review Committee involved where applicable);
- Contracts / agreements issued for applications/proposals approved for funding;
- Review of progress report by project manager and SWG / ad-hoc group;
- Consolidation of recommendations / comments sent to the PI of the project;
- Progress and final reports reviewed by SWG / ad hoc group and signed off by the SWG Chair (or Project Manager if not linked to SWG);
Calls for proposals | letters of interest | letters of intent
Using the planner link, the team leader drafts a Call for Letters of Interest or applications/proposals. The Call is discussed and reviewed internally. The selection and scoring criteria are agreed with the SWG as relevant. All Calls should be standardized using the format provided by the Communications team.

The draft call is submitted to Director TDR for approval. Once approved, the Call is posted on the TDR Website, sent to the TDR Scientists e-mail list and included in the next TDR Enews, as well as disseminated through TDR Global.

Collecting Calls for Applications/Proposals
Using the standard link, applications should be submitted using an online submission process. The PI submits a proposal based on the requirements/specifications outlined in the call. The receipt of the application is acknowledged automatically.

Screening of proposals: The project manager/responsible technical officer (RTO) screens the proposals to eliminate those that are outside the scope of the call for proposals (using inclusion/exclusion criteria published in the call for proposals).

Inclusion/exclusion criteria are Yes/No type of criteria that may include: geographical location (e.g. sub-Saharan Africa, socio-economic status (e.g. low- middle-income country), gender (e.g. women), disease (e.g. malaria), specific type of research (e.g. implementation research), timeline (e.g. maximum 1 year), etc.

PIs of proposals that were screened out are informed accordingly by email, using standardized text.

The proposals that passed the screening step are prepared for scientific and technical review by external experts. The RTO verifies that the following, as applicable:

- national clearance is submitted if required (Ecuador, Chile, Sudan, Sri Lanka, India, Indonesia, Malaysia, China (and ROC Taiwan);
- proof of institutional and national ethical clearance, if research involves human subjects (see Ethic Review Committee (ERC) guidelines) ERC form should be included;
- budget breakdown and justification are attached;
- signature of PI and responsible administrative authority of institution are submitted;
- letters from collaborators are attached.

Review, scoring and ranking of proposals received

Number of reviewers:
Each proposal should be reviewed by 3 external reviewers. In cases with a high number of proposals and few reviewers, this can exceptionally be reduced to 2 reviewers per proposal.

In case of a non-responsive reviewer, another reviewer should be assigned in its place without delay.
Scoring criteria:

Scoring criteria help the reviewer establish the scientific value and the value for money of the proposal. Each call for proposals must include scoring and selection criteria, so that the applicants are able to do a self-assessment of their application. In joint calls for proposals, the scoring criteria must be agreed with the partner institution.

The scoring criteria should include three core criteria (scientific merit, relevance and feasibility) and as relevant other criteria specific to the call’s requirements (e.g. partnership, leverage, etc.). Each criterion should be scored from 1 to 10, where 1 is the lowest and 10 the highest score.

The criteria may be weighted if their importance is not equal. In this case, the weighting should be applied to each criterion’s score.

Proposal ranking:

The average of the three reviewers’ score should be used in ranking the proposals.

In order to reduce reviewer bias, an analysis should be done of each reviewer’s score range and average. For reviewers whose average scores fall outside +/- 20% of the group average, the scores should be normalized. For the reviewers with a very narrow range of scores, a case-by-case decision can be made by the Chair SWG as to whether the scores should be used or not.

The proposals where, after normalization of the scores, the difference between reviewers is higher than 2.5, should be reviewed by the Chair SWG or a designated arbiter. The Chair SWG will then make the decision on the final score, based on the arguments supporting each score.

The proposal ranking takes into consideration the proposal scores and any additional rule published in the call for proposal (geographical distribution, gender distribution, etc.). The final ranking of the proposals recommended for funding is signed off by the SWG Chair and sent to the Director TDR as a “Summary Recommendation Sheet”.

PIs of rejected letters are informed accordingly by email.

Implementation – letters of award, APWs18 and TSAs19

Each project received is given a project ID number in TIMS which enables it to be tracked.

A letter of award (see template) is generated spelling out the following (at minimum):

- TDR’s acceptance of the proposal as submitted or with changes;
- Rules that must be followed by the recipient and that are specific to TDR:
  - Acknowledgement of TDR’s support and funding in any publications using TDR’s standard text;
  - Acceptance of TDR’s open access publication policy;
  - Joining the TDR Global community.

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18 Agreement for performance of work (type of contract)
19 Technical services agreement (type of contract)
Annex V    Organization of SWG meetings

The SWGs will normally meet at least once a year. TDR may convene additional meetings, including through teleconferences and videoconferences, on an ad hoc basis. TDR may furthermore request members to carry out activities between meetings. Ad hoc review groups may or not need to meet (face-to-face or via teleconference) to conduct their work; in case they need to meet, the same process applies as for SWG meetings.

General principles

- A Rapporteur is appointed by the SWG members at the beginning of each meeting, from among the members. The Rapporteur is responsible for developing a timely and accurate report of the meeting, with assistance from the TDR Secretariat;
- Meeting documentation to follow the standard format and structure;
- Conflicts of interest (COIs) to be presented at the beginning of each meeting;
- A new COI/DOI form, or confirmation that the previous form remains unchanged, must be received prior to participation being confirmed and/or travel arrangements being made;
- Documentation to be finalized and shared with participants / members minimum 2 weeks prior to each meeting;
- The SWG SharePoint site (maintained by the secretariat) is to be used for sharing and storing meeting documentation.

Reporting

At the end of each meeting, the report will summarize as relevant:

- The SWG’s advice regarding work plan, portfolio of projects, priorities, etc.;
- Recommendations for project funding (selection and ranking of projects / proposals);
- Recommendations on continuation, modification or termination of ongoing projects;
- The recommendations of the SWGs are reported by the TDR Secretariat to STAC and presented by the Chair of STAC to the next session of the JCB;
- Meeting reports must follow the standard template and be finalized and shared with SWG members and TDR staff no more than 4 weeks after the meeting;
- Terminology to be consistent, e.g. recommendations versus advice versus support.
Annex VI  Responsibilities of the R&D Secretariat

The R&D Secretariat will:

1) deploy incentives;
2) solicit and process funding applications;
3) administer the R&D fund in accordance with WHO rules, regulations, procedures, policies and administration practices;
4) call for additional contributions allocated to specific projects;
5) ensure communication at all levels through the organization of meetings and telephone conferences;
6) keep record of:
   o all communications with the different Committees,
   o all correspondence and agreements with donors,
   o a specific folder for this purpose will be created on the department’s shared drive. All documentation and communication should be saved in this location to ensure access by all R&D secretariat members at all times.
7) track through monitoring tools:
   o the level of funds available,
   o approvals for release of funds, actual release the funds, and operational costs,
   o donations to the R&D fund,
   o project progress.
8) share the information on progress and funds used and set up a SharePoint (or similar structure) for all research projects.
Annex VII  Suggested criteria for selecting projects

The following list of criteria were compiled to select Health Research & Development projects to be funded through the Health R&D fund. They contain a practical approach to implementing the principles of delinkage and ensuring access when selecting projects to support.

Section I:  Assessment of project plan and financing

The below proposed assessment framework is to assess whether:
  o the project is fully developed?
  o project partners are identified?
  o appropriate funding is secured?
  o the project is ready for implementation?

A scoring mechanism based on “Yes/No/Partial” will aid the SWG in identifying the projects to be considered for funding.

1. **Project Plan**
   Major milestones identified
   1.2. Activities identified in a chronological order
   1.3. Organizations/institutions responsible for each activity identified, with clear roles for each of them
   1.4. Coordination mechanisms and governance in place
   1.5. Agreed timelines for completion of each activity
   1.6. Deliverables/outputs identified for each activity
   1.7. Cost of each activity identified
   1.8. Number of implementing partners

2. **Financing**
   Overall budget defined
   2.2. % Funds requested for first year of the project
   2.3. % Funds requested for second and third years of the project

3. **Engagement of other funders**
   3.1. Number of other funders
   3.2. Contribution of other funders
   3.3. % Funds pledged for first year of the project from other funders
   3.4. % Funds pledged for second and third years of the project from other funders

Section II:  Analysis of the Extent of Innovative Components

The following evaluation framework is based upon the assessment framework that was used to evaluate the innovative aspects of the proposals approved by Member States at the Global
Technical Consultative Meeting on 05 December 2013. It is also informed by the specific request by Member States for “the addition of an analysis of the extent of innovative components being implemented by the projects, including financing, the use of open access models, multisectoral research platforms, and delinkage, among other criteria” found in WHA67(15). Strong emphasis is placed throughout the assessment framework on the involvement of developing and endemic countries.

**Innovation Indicators**

<table>
<thead>
<tr>
<th>Innovative Components</th>
<th>Description of Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delinkage</td>
<td>The project clearly delinks the cost of research from the price of the product.</td>
</tr>
<tr>
<td>Open knowledge approaches</td>
<td>The project makes available for others to access and use research data and results.</td>
</tr>
<tr>
<td>Licensing for access</td>
<td>The project uses licensing terms that ensure access and affordability.</td>
</tr>
<tr>
<td>Coordination</td>
<td>1. The project links data and information coming from multiple sources and/or engages with a diversified array of partners, particularly in developing and endemic countries</td>
</tr>
<tr>
<td></td>
<td>2. The project involves institutions coming from multiple countries and regions.</td>
</tr>
<tr>
<td>Capacity building and technology transfer</td>
<td>The project builds capacity in developing and endemic countries. The project uses transfer of technologies as a means to decrease capacity in developing and endemic countries.</td>
</tr>
</tbody>
</table>
Annex VII  Elements of a communication plan

1. Reach out to select group of member states most supportive of the idea of an R&D financing mechanism (e.g., during EB and WHA discussions) to ensure their buy-in and make them “champions” of the fund;

2. Broad communication to Member States’ health ministers on the added value of a funding mechanism and health benefits;

3. Communication to Member States’ finance ministers on operational considerations/costs as well as the benefits (in terms of expected products);

4. “Socializing” the idea of an R&D financing mechanism in the PDP&NGO community to create broad support and potentially also “champions” there

5. After WHA, consider holding a “donor conference”.

Operational plan for health product research and development fund
Background document 70th World Health Assembly Agenda item 13.5

Appendices

Following consideration of this operational plan by the 140th Executive Board two case studies were developed to illustrate the implementation of the new financing mechanism, discussing evidence-based recommendations for priority health products for schistosomiasis and cutaneous leishmaniasis. These analysis were prepared by the Special Programme for Research and Training in Tropical diseases in close collaboration with WHO’s department of Neglected Tropical Diseases.
This case study on Schistosomiasis is developed to illustrate the Operational Plan for Voluntary Pooled Funding Mechanism of the Health Product Research and Development Fund that will be presented for consideration at the World Health Assembly in May 2017. The analysis was prepared by TDR in collaboration with WHO Disease Control Programs, specifically the Department of Neglected Tropical Diseases.

At this stage, as the voluntary pooled fund is not yet operational, the research projects are chosen to illustrate the functioning of the voluntary pooled fund. Once the fund is operational, a decision will be made on which projects will be funded.

In this example, following an analysis of public health needs, current WHO control strategy and gaps in products, the Scientific Working Group made a recommendation for the pooled fund to support diagnostics kits for a combined value up to 300,000 US$. 

Appendix 1 Case study Schistosomiasis

Introduction ................................................................. 34
1 Priority definition HR&D Observatory ................................. 35
2 Specific HR&D gaps and health products needed ................... 36
3 Prioritizing Interventions .................................................. 36
4 Sourcing and validation of Preferred Product Profiles .............. 40
5 Health Research & Development Pipeline ............................ 40
6 Incentive mechanisms ..................................................... 41
7 Review of applications ..................................................... 42
8 Monitoring and evaluation of selected projects ....................... 42
9 Conclusion ........................................................................ 43
10 Analysis for R&D Schistosomiasis ....................................... 43
11 Using PPP criteria fulfilment to filter and prioritize diagnostics projects ... 49
12 Product Preferred Profile ................................................ 49
Introduction

This study case is developed using the Operational Plan for the Voluntary Pooled Fund on Health Research & Development, to illustrate how the Fund will function. Once the fund is operational, actual project funding decisions will be made. This case study in no way suggests that certain research projects will be funded in the absence of available funds.

The economic and health effects of schistosomiasis are considerable and the disease disables more than it kills. In children, schistosomiasis can cause anaemia, stunting and a reduced ability to learn, although the effects are usually reversible with treatment. Chronic schistosomiasis may affect people’s ability to work and in some cases can result in death. The number of deaths due to schistosomiasis is difficult to estimate and WHO estimates that there are about 200,000 deaths globally each year due to schistosomiasis. 

The goal of the WHO Schistosomiasis program are to control morbidity due to schistosomiasis by 2020 in all endemic countries and eliminate schistosomiasis as a public-health problem by 2025 in all endemic countries.

The graph below (figure 4) illustrates how the priorities set by the Expert Committee on Health Research & Development (ECHR&D) could lead to identification and further refining of priority areas (vaccines, diagnostics, snail control) by the Scientific Working Group (SWG) in collaboration with expertise drawn upon from WHO’s Department of Neglected Tropical Diseases (NTD) and its network of advisors, based on WHO’s control and elimination strategy. This process is completed with the development and publication of the Preferred Product Profile (PPP), the potential projects to be financed and follow up through monitoring and evaluation of the financed projects.

20 http://www.who.int/mediacentre/factsheets/fs115/en/
21 http://www.who.int/schistosomiasis/resources/9789241503174/en/
22 At this stage, as the voluntary pooled fund has not yet been activated, the research projects are chosen for the purpose of illustrating how the voluntary pool fund will function once operational, at which time the actual funding decisions will be made.
1 Priority definition HR&D Observatory

The Executive Committee on HR&D uses the data presented in the HR&D Observatory to analyse which diseases are prioritized for investment through the Voluntary Pooled Fund.

Based on the burden of disease and the lack of investment in research for health products for Schistosomiasis as indicated in WHO’s Global Observatory on Health Research and Development23, Schistosomiasis was identified as one of the priority diseases for investment. For this case study the analysis was prepared by Special Programme for Tropical Disease Research (TDR) in collaboration with the Department of NTD. Annex I provides the analysis on Schistosomiasis including the epidemiology, WHO’s strategy, current interventions and research gaps on which this case study is based.

Investments to date are provided through the Global Observatory on Health R&D. In 2014, a total of US$ 214 million was spent on R&D for approximately 240 million affected people, amounting to less than one (1) US $ spent per affected person. Investment in preventing and controlling Schistosomiasis has been very low and financial resources are urgently needed to address the identified research gaps identified in section 2.

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23 [http://www.who.int/research-observatory/en/]
2 Specific HR&D gaps and health products needed

The Scientific Working Group of the HR&D fund convenes the WHO Disease Control Programme and their network of advisors to specify the specific R&D priority areas.

In collaboration with the disease experts in NTD, the SWG identified a number of research gaps hindering successful implementation of the global strategy to eliminate Schistosomiasis. These gaps include:

- Diagnostics - the existing diagnostic tools for schistosomiasis are outdated. The main need is for commercially available tests for low prevalence areas and for assessment of interruption of the transmission;
- Absence of a vaccine to prevent infection or re-infection;
- Absence of paediatric formula of praziquantel, the drug for treating infected infants and young children.

Essential to this effort is ensuring that funding for advancing research is available through the HR&D Fund once it is operational (see section 11.3 for an expanded overview).

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Concerns</th>
<th>Research Priorities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical treatment</td>
<td>Compliance (resistance within the population to repeated treatment)</td>
<td>Vaccine needed to prevent reinfection</td>
</tr>
<tr>
<td>Diagnosis at community level</td>
<td>Refined test for detecting prevalence unavailable</td>
<td>New diagnostic tests needed</td>
</tr>
<tr>
<td>Accurate monitoring and evaluation</td>
<td>The existing diagnostics tests are outdated as intensity and prevalence is reduced</td>
<td>Updated diagnostics needed</td>
</tr>
<tr>
<td>Snail control</td>
<td>Only one chemical compound is approved by WHOPES to kill the host and intermediate host</td>
<td>More specific compounds are needed</td>
</tr>
<tr>
<td>Vaccination</td>
<td>None available</td>
<td>Vaccine needed to prevent infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vaccine needed to lower morbidity</td>
</tr>
</tbody>
</table>

Table 2: Interventions, barriers and research gaps identified

The following, so far absent health products are crucial for successful elimination of Schistosomiasis, per the WHO strategy:
Diagnostics
Two types of high sensitive and specific diagnostic tests, usable in the field, are needed in addition to the existing tests:

1. Monitoring and evaluation prevalence of *S. haematobium*, *S. mekong* and *S. japonicum* in low transmission areas;

   The strategy is based on diagnosing stool and urine extracts to detect the eggs. After several rounds of treatment, the egg count is low. Therefore, a more sensitive test is required to detect prevalence in a given community. The test needs to be sensitive enough to detect one worm. This test can be urine based and would be easier to use and could be sent to a designated diagnostics laboratory to ensure proper reading of the results.

2. Verification of interruption of transmission for *S. haematobium*, *S. mekonge* and *S japonicum*

   A diagnostic tool for detecting absence of transmission to be used in survey assessments is needed to indicate that there is no longer infection in the individual and consequently in the communities. Currently, a test is available to measure *S. mansoni* in the urine, produced in South Africa by a private company (ICT) at US$1.80 per test. 24

Vaccines:
In the absence of a vaccine to prevent Schistosomiasis in the first place, two types of vaccine are needed to reduce the global burden of Schistosomiasis and work towards its elimination globally:

1. Anti-morbidity

   An anti-morbidity vaccine lowers the morbidity in the body of the infected person, resulting in decreased lesions and decreased egg output of worms. Phase II clinical trials are currently ongoing in Senegal.25 This clinical study is one of the six demonstration projects that were selected and funded as part of the process of setting up the Health Research and Development Observatory and Fund mechanism based on resolution WHA66.22. 26

2. Anti-re-infection/ prevention of reinfection

   A vaccine is needed that prevents re-infection for 3 – 5 years. The current medicine available treats infected people by killing the worm. If people are re-infected, they show fewer symptoms because the worm-load has decreased, and thus fewer clinical signs. Interruption /elimination of disease can be achieved by preventing reinfection. Currently studies are conducted in mice, as of yet, the trials have not been extended to humans.

24 discussion
26 “Development of a vaccine against schistosomiasis based on the recombinant Sm14, a member of the fatty acid -binding protein family: controlling transmission of a disease of poverty (proponent: Oswaldo Cruz Foundation, Brazil)"
The scientific article “Advancing a vaccine to prevent human schistosomiasis” published in *Vaccine* Volume 34, Issue 26, 3 June 2016, Pages 2988–2991 includes information on the ongoing different vaccine trials.\(^{27}\)

**Snail control**

Chemicals are needed that target specifically the host and intermediate host. Currently, one chemical compound (niclosamide) is approved to kill snails, including snails that carry Schistosomiasis. New compounds need to be evaluated in collaboration with WHOPES, for which they have developed an evaluation guide.\(^{28}\)

### 3 Prioritizing Interventions

The Scientific Working Group of the HR&D fund in collaboration with the WHO Disease Control Programme and their network of advisors specify the specific health products that need to be developed based on an assessment of the existing health products, identified research gaps, health products in the pipeline and their “close to market” status, and possible other sources of funding available for these research products.

The following 2x2 table 3 could be used to plot the different needs against feasibility and affordability to prioritize appropriate interventions. The third dimension is time, as shown in brackets, “+” indicates a result in a short timeline and “+++” indicating several years.

<table>
<thead>
<tr>
<th>Affordability</th>
<th>Feasibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>+</td>
</tr>
</tbody>
</table>

- Chemicals for snail control (+++)
- New medicine/transformation (+++)
- Vaccine for anti-morbidity (+++)
- Vaccine for anti-reinfection (+++)

<table>
<thead>
<tr>
<th>Affordability</th>
<th>Feasibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

- Diagnostic tools (+)

Table 3: Different needs plotted against affordability and feasibility.


Rationale for Intervention from the HR&D Fund

For this case study, the prioritized intervention to be addressed was chosen in collaboration with the department of NTD. Diagnostic tools for detecting both Schistosomiasis prevalence and verification of interruption of transmission would be the priority health product. So far little investments have been made in diagnostic tools, and the existing tools are outdated.

Current diagnostics for schistosomiasis are not sensitive enough to detect low levels of infection. Not only that they are labour-intensive and difficult to perform in the field. Given the decrease of the level of infection and the objective set for the elimination of schistosomiasis the current tests based on the observation of the parasite eggs need to be repeated several time in order to detect the infection. Improved diagnostics are imperative to collect data to direct schistosomiasis control and elimination efforts. The need for greater sensitivity is primarily to detect lower intensity infections that can still be transmitted after mass drug administration (MDA). The improved diagnostic tools will support late-stage control program decisions, such as when to stop MDA. They will also serve to ensure that infected individuals are treated immediately, thus halting transmission of the disease at the time of diagnosis and not months later. The enhanced ability to identify and target remaining reservoirs of infections more accurately that either persist or re-emerge could further expedite global elimination goals, and thereby wind down massive drug donation and control program costs.

From an investment point of view, updating diagnostic tools is a lower cost means of achieving a faster result. The tools are already in an advanced clinical phase, thus, making their risk for failure low, and they can be made available on the market within a relatively short time without significant additional investment.

**Prevalence test**

One product is awaiting Phase III clinical trials (currently, the principal research institute is recruiting volunteers). Hence, the feasibility of conducting Phase III clinical trials and thus finalizing the product is high and field evaluation of the product is relatively easy to conduct.

**Transmission interruption test**

Four different products are undergoing clinical trials. Once the HR&D fund is operational, a request for proposals will be sent to the research institutions involved. Upon receipt of the research proposals, the criteria for selecting the final candidate will be applied (annex VII of the operational plan) together with the PPP overview in section 11 of the case study.29

At present no funds are available in the pooled voluntary fund to invest in a new vaccine. The SWG can therefore not commit at this stage. There are however, monies being invested in the development of a vaccine against Schistosomiasis based on the recombinant Sm14, as noted earlier.

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29 Note: this process cannot be applied at this stage as no funding is available; requesting a proposal for investment would raise expectations that at present cannot be met.
4 Sourcing and validation of Preferred Product Profiles

The Scientific Working Group sources and validates the Preferred Product Profile addressing the minimum and ideal requirements for the chosen intervention.

Based on the Preferred product profile (PPP) template for diagnostic products included in the “Health Product Research & Development fund: a proposal for financing and operation”, as well as the PPP developed by PATH draft PPPs would be developed. Section 12 includes a reference for the PPPs for tests detecting prevalence as well as for detecting infectiousness/interruption of transmission. The PPPs will need final validation and publishing as part of the process.

5 Health Research & Development Pipeline

The SWG evaluates the health products currently in the pipeline against the Preferred Product Profile to identify promising candidates that could be considered for funding through the voluntary pooled fund.

Diagnostics test in the pipeline are included in the table 4 below. These tests are all in clinical stages. One test is focusing on prevalence testing (i.e. the presence of eggs/worms); the other four tests are looking at transmission (infectiousness).

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Type of test</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Upconverting phosphor lateral flow assay (UCP-LFA)</strong></td>
<td>Blood/urine/stool Prevalence/transmission</td>
</tr>
<tr>
<td>Leiden University; Ampath Laboratories; Swiss TPH; Wolfson Wellcome Biomedical Laboratories</td>
<td>Urine + Serum Prevalence/transmission</td>
</tr>
<tr>
<td><strong>SmCTF-RDT</strong></td>
<td>Serum Transmission (infection)</td>
</tr>
<tr>
<td>University of Nottingham; Swiss TPH; University of Basel; Omega Diagnostics</td>
<td>Serum Transmission (infection)</td>
</tr>
<tr>
<td><strong>ELISA-mAbCCA</strong></td>
<td>Serum Transmission (infection)</td>
</tr>
<tr>
<td>University of Georgia, FioCruz</td>
<td>Serum Transmission (infection)</td>
</tr>
<tr>
<td><strong>IMS-mAbCCA</strong></td>
<td>Serum Transmission (infection)</td>
</tr>
<tr>
<td>University of Georgia, FioCruz</td>
<td>Serum Transmission (infection)</td>
</tr>
<tr>
<td><strong>FluoIMS-mAbCCA</strong></td>
<td>Serum Transmission (infection)</td>
</tr>
<tr>
<td>University of Georgia, FioCruz</td>
<td>Serum Transmission (infection)</td>
</tr>
</tbody>
</table>

Table 4: Diagnostics test in the pipeline

Adapted from [http://www.bvgh.org/LinkClick.aspx?fileticket=50jsOoOQAQOV%3d&tabid=282](http://www.bvgh.org/LinkClick.aspx?fileticket=50jsOoOQAQOV%3d&tabid=282)

30 [http://sites.path.org/dx/ntd/resources-2/](http://sites.path.org/dx/ntd/resources-2/)
6 Incentive mechanisms

The SWG determines the appropriate incentive mechanisms for each given health product. Different options exist—push, pull or enablers—each suitable for different scenarios, depending on the level of market failure, the development phase of the health product and the R&D players involved.

Based on the different characteristics of diagnostic tests, the different incentive mechanisms were evaluated. Diagnostic tests for neglected diseases such as Schistosomiasis pertain to the category of products with “significant market failure” due to the absence of commercial markets and limited financing interest. As a result, most of these diagnostic tests, albeit in clinical phases, and getting close to market, remain stagnant due to the insufficient financial incentive to move them forward. The main R&D players are academic institutions, small developers and R&D partnerships.

Only one diagnostic test for prevalence detection is currently in the pipeline, and could therefore greatly benefit from a push mechanism, i.e. a direct grant to finalize the phase III clinical trial and the field evaluation.

For the infectivity diagnostic tests, four candidates are in the pipeline. A pull mechanism providing a prize could help expedite one or all of these products to reach finalize the CTs and reach the market. In the absence of any other investments, one diagnostic test in development could be selected for a direct grant (push mechanism). Figure 5 below provides an overview of the effectiveness of the different incentive mechanisms as proposed in the “Health Product Research and Development Fund: A Proposal for Financing and Operation”.
Review of applications

The SWG issues the call for proposals. The applications are reviewed and evaluated against a set of criteria taking in to consideration a number of the principles and recommendations formulated by the Expert Committee on Health R&D, including the core principles as defined by the CEWG* of affordability, effectiveness, efficiency, equity and the principle of delinking the costs for the investment into research and development from the volume and price of the resulting health products.

Once the call for proposals is issued, the applications of the different research institutes would be reviewed by the SWG. For this case study, two projects were selected for potential investment by TDR and NTD. A further analysis of the health products in the pipeline and the projects to be supported would be necessary once the actual fund is operational.

8 Monitoring and evaluation of selected projects

Bi-annual progress and final reports are submitted by the research institutes and reviewed by the SWG and signed off by the SWG Chair.
9 Conclusion

In collaboration with the Department of NTD, Schistosomiasis was chosen as one of the case studies to illustrate the Operational Plan for Voluntary Pooled Funding Mechanism of the Health Product Research and Development Fund. Based on the findings of the Global HR&D Observatory and the analysis conducted by TDR and NTD, two diagnostics tests were identified as priority health products. To address the WHO strategy of eliminating schistosomiasis by the year 2025, the main need is for commercially available tests for assessing both low prevalence areas and interruption of transmission. Once the voluntary fund is operational a call for proposals could be issued and a further analysis conducted of the specific health products in the pipeline. Based on the current available information, a push mechanism, i.e. a direct grant would be the preferred incentive mechanism to finalize development of the two identified diagnostic tests.

10 Analysis for R&D Schistosomiasis

10.1 The disease

Schistosomiasis is an acute and chronic parasitic disease caused by blood flukes (trematode worms) of the genus Schistosoma. People are infected during routine agricultural, domestic, occupational, and recreational activities, which expose them to infested water. Schistosomiasis control focuses on reducing disease through periodic, large-scale population treatment with praziquantel; a more comprehensive approach including potable water, adequate sanitation, and snail control would also reduce transmission.

Preventive treatment, which should be repeated over a number of years, will reduce and prevent morbidity. Schistosomiasis transmission has been reported from 78 countries. However, preventive chemotherapy for schistosomiasis, where people and communities are targeted for large-scale treatment, is only required in 52 endemic countries with moderate-to-high transmission.

Estimates show that at least 218 million people required preventive treatment in 2015. In 2015, over 66.5 million individuals (53.2 million school-aged children and 13.3 million adults) received preventive chemotherapy for schistosomiasis.31

31 http://apps.who.int/iris/bitstream/10665/251908/1/WER9149_50.pdf?ua=1
Epidemiology

People become infected when larval forms of the parasite – released by freshwater snails – penetrate the skin during contact with infested water. Transmission occurs when people suffering from schistosomiasis contaminate freshwater sources with their excreta containing parasite eggs, which hatch in water.

Schistosomiasis is prevalent in tropical and subtropical areas, especially in poor communities without access to safe drinking water and adequate sanitation. It is estimated that at least 90% of those requiring treatment for schistosomiasis live in Africa. There are 2 major forms of schistosomiasis – intestinal and urogenital – caused by 5 main species of blood fluke. Schistosomiasis in humans results from infection with parasitic blood flukes of the genus Schistosoma. Six species of schistosomes cause infection in humans.

Disease burden

200 million people in Africa are infected with schistosomiasis. Many of these cases are associated with severe morbidity. Long-term organ damage is often irreversible and chronic. Access to medication is often limited for the millions of people who live on less than US$ 2 per day. Additionally, awareness of the consequences of many NTDs is low – people fail to identify symptoms or do not realise treatment is available.

Risk groups

Schistosomiasis mostly affects poor and rural communities, particularly agricultural and fishing populations. Women doing domestic chores in infested water, such as washing clothes, are also at risk. Inadequate hygiene and contact with infected water make children especially vulnerable to infection.
Migration to urban areas and population movements are introducing the disease to new areas. Increasing population size and the corresponding needs for power and water often result in development schemes, and environmental modifications facilitate transmission. With the rise in eco-tourism and travel “off the beaten track”, increasing numbers of tourists are contracting schistosomiasis. At times, tourists present severe acute infection and unusual problems including paralysis. Urogenital schistosomiasis is also considered to be a risk factor for HIV infection, especially in women.

Risk areas

Schistosomiasis is endemic in five of WHO’s six regions. While the disease is now predominantly in Africa, it also occurs in the Americas, the Eastern Mediterranean region, the Southeast Asian region and the Western Pacific.35 Almost 93% of the people requiring preventive chemotherapy are in the African Region, and 6.1 are in the Eastern Mediterranean Region.36

Public Health and Economic impact of the disease

The economic and health effects of schistosomiasis are considerable and the disease disables more than it kills. In children, schistosomiasis can cause anaemia, stunting and a reduced ability to learn, although the effects are usually reversible with treatment. Chronic schistosomiasis may affect people’s ability to work and in some cases can result in death. The number of deaths due to schistosomiasis is difficult to estimate because of hidden pathologies such as liver and kidney failure and bladder cancer. WHO estimates that there are about 200 000 deaths globally each year due to schistosomiasis.37 The global burden of schistosomiasis is estimated at 4 026 000 DALYs (Disease Adjusted Life Years).38

WHO Strategy

The goal of the WHO Schistosomiasis program are to:

- control morbidity due to schistosomiasis by 2020 in all endemic countries through 100% geographical coverage, 75% national coverage and <5% prevalence of heavy-intensity infections achieved in all schistosomiasis-endemic countries
- eliminate schistosomiasis as a public-health problem by 2025 in all endemic countries through decreasing the prevalence of heavy-intensity infections is <1% in all endemic countries
- interrupt transmission of schistosomiasis in all endemic countries in the Region of the Americas, the Eastern Mediterranean Region, the European Region, the South-East Asia Region and the Western Pacific Region, and in selected countries of the African Region by 2025 the prevalence of heavy-intensity infections is <1% in all endemic countries.39

35 http://www.who.int/schistosomiasis/resources/9789241503174/en/
37 http://www.who.int/mediacentre/factsheets/fs115/en/
39 http://www.who.int/schistosomiasis/resources/9789241503174/en/
Critical assumptions to reach this are: (1) that solutions be found to make praziquantel widely available; and (2) that funding for implementation accompanies the scaling up of interventions, through sustained commitment of international donors and enhanced in-country support by the health and education sectors.\(^{40}\)

In 2012, Resolution WHA65.21 on the elimination of schistosomiasis was adopted requesting WHO to mobilize resources required to support integrated and multi-sectoral control programmes and for countries to initiate elimination campaigns.\(^{41}\)

10.2 Current interventions available

Diagnosis

Schistosomiasis is diagnosed through the detection of parasite eggs in stool or urine specimens. Antibodies and/or antigens detected in blood or urine samples are also indications of infection. (WHO) Examination of stool and/or urine for ova is the primary methods of diagnosis for suspected schistosome infections.\(^{42}\)

Prevention and control

The control of schistosomiasis is based on large-scale treatment of at-risk population groups, access to safe water, improved sanitation, hygiene education, and snail control. The WHO strategy for schistosomiasis control focuses on reducing disease through periodic, targeted treatment with praziquantel through the large-scale treatment (preventive chemotherapy) of affected populations. It involves regular treatment of all at-risk groups.

The frequency of treatment is determined by the prevalence of infection in school-age children. In high-transmission areas, treatment may have to be repeated every year for a number of years. Monitoring is essential to determine the impact of control interventions.

Praziquantel is the recommended treatment against all forms of schistosomiasis. It is effective, safe, and low-cost. Even though re-infection may occur after treatment, the risk of developing severe disease is diminished and even reversed when treatment is initiated and repeated in childhood.

10.3 Barriers to Success

The following factors have been identified as hampering successful implementation of WHO’s strategy to eliminate Schistosomiasis and need to be addressed as soon as possible. Essential to this effort is ensuring that funding for advancing research is available through the Health Research & Development Fund once it is operational.

\(^{40}\) http://apps.who.int/iris/bitstream/10665/251908/1/WER9149_50.pdf?ua=1
\(^{41}\) http://apps.who.int/gb/ebwha/pdf_files/WHA65-REC1/A65_REC1-en.pdf#page=25
\(^{42}\) https://www.cdc.gov/parasites/schistosomiasis/health_professionals/
Operational plan for health product research and development fund
Background document 70th World Health Assembly Agenda item 13.5

Delivery of chemotherapy
The major impediment to Schistosomiasis control has been the high cost of praziquantel, which means those who need it most cannot afford it. Moreover, many endemic countries do not have the public-health infrastructure or the necessary resources to implement adequate schistosomiasis control. 43

In 2007, Merck KGaA had committed to donating 200 million tablets of 600 mg praziquantel for distribution primarily to African school children. Though it originally planned to end the project in 2017, Merck KGaA will continue its efforts to fight schistosomiasis indefinitely with an amount of 250 million tablets per year; donation made through WHO.44

Paediatric formula of Praziquantel
The treatment of preschool-age children in public-health campaigns presents a common problem in paediatric medicines because there is no appropriate formulation of praziquantel for this age group and the drug is unpalatable. (f) There is a lack of safety trial data for the use of praziquantel in children less than 4 years of age or pregnant women. However, this drug has been distributed widely in mass drug administration programs, including now in pregnant women with positive results.(e) Similarly, WHO reports that there is growing evidence that infected children as young as 1 year old can be effectively treated with praziquantel without serious side effects. The drug, however, remains commonly available only in large, hard-to-swallow pills, which puts young children at risk for choking and other difficulties swallowing the drug. (e) Clinical trials are presently ongoing for a paediatric formula of praziquantel.

Diagnosis
Diagnostic tools for schistosomiasis are dated. While reagent strips provide a cost-effective and rapid means for diagnosing urogenital schistosomiasis, there is no equivalent test for intestinal schistosomiasis. There is a need to improve and validate the circulating cathodic antigen assay and other point-of-care tests for S. mansoni. As programmes succeed in controlling morbidity and lowering transmission, there is a need for more sensitive diagnostic techniques for people exposed to infection and transmission. It is possible to use serology to determine if schistosomiasis transmission has been interrupted or whether vectors snails are infected. Recombinant antigens are required to ensure that the serological tests can be standardized.45

Serologic testing may not be appropriate for determination of active infection in patients who have been repeatedly infected and treated in the past because specific antibodies can persist despite treatment. In these patients, serologic testing cannot distinguish resolved infection from active infection. An antigen test has been developed that can detect active infection based on the presence of schistosomal antigen, but this test is not yet commercially available and at this time is undergoing field evaluations for accurate diagnosis of low-intensity infections.46

46 https://www.cdc.gov/parasites/schistosomiasis/health_professionals/
Compliance
Individuals who have taken praziquantel for repeated schistosomiasis episodes, often no longer wish to be treated (again) with praziquantel, because they are no longer convinced of the benefits. Compliance of individuals to taking the drug remains critical in areas where transmission has been reduced and mass treatment is no longer required to prevent drug resistance.

Monitoring and evaluation
While the monitoring and evaluation activities of an ongoing control programme are mainly organized through sentinel sites for the assessment of the progressive decline in infection indicators, surveillance should be more widespread, systematic and sensitive, with the aim of detecting any new case of infection. Ideally, it should be integrated in routine health systems. Up to now, schistosomiasis is generally not a notifiable disease and infected individuals need to be duly reported to the national authorities and the appropriate action is taken.47

Vaccine
No vaccine is available for preventing infection or reinfection.

Snail control
Snail control through environmental management and chemical control becomes feasible when transmission foci can be clearly delineated and treated through improved diagnostic tools.48

Operational plan for health product research and development fund
Background document 70th World Health Assembly Agenda item 13.5

Geographic distribution of intestinal and urogenital schistosomiasis

<table>
<thead>
<tr>
<th>Organ system affected</th>
<th>Species</th>
<th>Geographic distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intestinal</td>
<td><em>S. mansoni</em></td>
<td>Africa, the Middle East, the Caribbean, Brazil, Venezuela, Suriname</td>
</tr>
<tr>
<td></td>
<td><em>S. japonicum</em></td>
<td>China, Indonesia, the Philippines</td>
</tr>
<tr>
<td></td>
<td><em>S. mekongi</em></td>
<td>Several districts of Cambodia and the Lao People’s Democratic Republic</td>
</tr>
<tr>
<td></td>
<td><em>S. guineensis</em> and related <em>S. intercalatum</em></td>
<td>Rain forest areas of central Africa</td>
</tr>
<tr>
<td>Urogenital</td>
<td><em>S. haematobium</em></td>
<td>Africa, the Middle East</td>
</tr>
</tbody>
</table>

11 Using PPP criteria fulfilment to filter and prioritize diagnostics projects

12 Product Preferred Profile

TPP lateral flow test exists for prevalence testing post elimination surveillance as developed by PATH [http://sites.path.org/dx/files/2015/02/2015.01.15_BMGF_SCH_postMDA_Ab.pdf](http://sites.path.org/dx/files/2015/02/2015.01.15_BMGF_SCH_postMDA_Ab.pdf)
This case study on Cutaneous Leishmaniasis is developed to illustrate the Operational Plan for Voluntary Pooled Funding Mechanism of the Health Product Research and Development Fund that will be presented for consideration at the World Health Assembly in May 2017. The analysis was prepared by the Special Programme for Research and Training in Tropical Diseases in collaboration with WHO Disease Control Programs, specifically the department of Neglected Tropical Diseases.

At this stage, as the voluntary pooled fund is not yet operational, the research projects are chosen to illustrate the functioning of the voluntary pooled fund. Once the fund is operational, a decision will be made on which projects will be funded.

In this example, following an analysis of public health needs, current WHO control strategy and gaps in products, the Scientific Working Group made a recommendation for the pooled fund to support development of a topical/oral treatment as well as a smartphone application to assist health workers to quickly define cutaneous leishmaniasis for a combined value up to 500,000 US$. 

Appendix 2  Case study Cutaneous Leishmaniasis

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>51</td>
</tr>
<tr>
<td>1 Priority definition HR&amp;D Observatory</td>
<td>53</td>
</tr>
<tr>
<td>2 Specific HR&amp;D gaps and health products needed</td>
<td>54</td>
</tr>
<tr>
<td>3 Prioritizing Interventions</td>
<td>56</td>
</tr>
<tr>
<td>4 Sourcing and validation of Preferred Product Profiles</td>
<td>56</td>
</tr>
<tr>
<td>5 Health Research &amp; Development Pipeline</td>
<td>58</td>
</tr>
<tr>
<td>6 Incentive mechanisms</td>
<td>60</td>
</tr>
<tr>
<td>7 Review of applications</td>
<td>61</td>
</tr>
<tr>
<td>8 Monitoring and evaluation of selected projects</td>
<td>61</td>
</tr>
<tr>
<td>9 Conclusion</td>
<td>61</td>
</tr>
<tr>
<td>10 Using PPP criteria fulfilment to filter and prioritize therapeutic products</td>
<td>62</td>
</tr>
</tbody>
</table>
Introduction
This study case is developed using the Operational Plan for the Voluntary Pooled Fund on Health Research & Development, to illustrate how the fund will function. Once the fund is operational, actual project funding decisions will be made. This case study in no way suggests that certain research projects will be funded in the absence of available funds.

Leishmaniasis is one of the world’s most neglected diseases, with an estimated 900,000–1.3 million new cases occurring annually, resulting in 20,000 to 30,000 deaths and 3,373,599 disability-adjusted life year DALYs lost. Lack of surveillance systems and frequency of the disease in remote areas and among marginalized populations makes it difficult to estimate the true incidence. Leishmaniasis is caused by parasites transmitted by the bite of sand-flies. The three main forms of leishmaniasis disease are (i) visceral leishmaniasis (VL), (ii) cutaneous leishmaniasis (CL) and (iii) mucocutaneous leishmaniasis. For this case study the focus will be on CL, which is characterized by disfiguring skin lesions that are sometimes self-healing within months or years, or become chronic. Although CL is generally not life-threatening, it causes disability and leaves permanent scars that can lead to social prejudice and related reduced quality of life and productivity consequences.

The goal of the WHO Leishmaniasis programme is to reduce morbidity and mortality from leishmaniasis. There is no global consensus on what is feasible in the long term. This makes it difficult to provide clear targets for control of CL. The immediate target is to reduce morbidity – specifically, prevention of highly stigmatizing large facial skin lesions.

Figure 7 describes how the priorities set by the Expert Committee on Health Research & Development (ECHR&D) could lead to identification and further refining of priority areas (topical/oral treatment, vaccines, diagnostics, mobile application for case detection) by the Scientific Working Group (SWG) in collaboration with expertise drawn upon from WHO’s Department of Neglected Tropical Diseases (NTD) and its network of advisors, based on WHO’s control strategy for Cutaneous Leishmaniasis. This process is completed with the development and publication of the Preferred Product Profile (PPP), the potential projects to be financed and follow up through monitoring and evaluation of the financed projects. This case study is developed by TDR and the department of NTD.

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49 http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0035671
50 At this stage, as the voluntary pooled fund has not yet been activated, the research projects are chosen for the purpose of illustrating how the voluntary pool fund will function once operational, at which time the actual funding decisions will be made.
Operational plan for health product research and development fund
Background document 70th World Health Assembly Agenda item 13.5

<table>
<thead>
<tr>
<th>Priority definition</th>
<th>Action</th>
<th>Case study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Convening of experts</td>
<td>2. Secretariat &amp; SWG Chair convened experts to specify R&amp;D priority area</td>
<td>Convenes Leishmaniasis experts to SWG</td>
</tr>
<tr>
<td>Priority break-down</td>
<td>3. SWG details specific priorities</td>
<td>Topical/oral treatment and smartphone application</td>
</tr>
<tr>
<td>PPP finalization</td>
<td>4. SWG sources and validates PPPs that address granular priorities (from compendium or newly commissioned)</td>
<td>PPP for new topical treatment is validated and published</td>
</tr>
<tr>
<td>Pipeline review</td>
<td>5. SWG evaluates current pipeline against PPP to identify promising candidates</td>
<td>Topical treatment in development fits PPP criteria</td>
</tr>
<tr>
<td>Determine incentive mechanism</td>
<td>6. SWG determines appropriate incentive mechanisms targeted for given scenario</td>
<td>Given projects are in clinical phase, direct project grants are recommended as most effective</td>
</tr>
<tr>
<td>Project assessment</td>
<td>7. SWG reviews applications; Secretariat begins disbursement</td>
<td>Fund grants $ 0.5M over 2 years to develop tx that match PPP</td>
</tr>
<tr>
<td>Project monitoring</td>
<td>8. As part of portfolio management, SWG reviews project progress on regular basis</td>
<td>Every 6 months, applicant submits project status update</td>
</tr>
</tbody>
</table>

Figure 7: Step-by-step overview of how priorities get translated into a project portfolio

Adapted from “Health Product Research and Development Fund: A proposal for financing and operation (2016)”
1 Priority definition Health Research & Development Observatory

The Executive Committee on HR&D uses the data presented in the HR&D Observatory to analyse which diseases are prioritized for investment through the Voluntary Pooled Fund.

Based on the burden of disease and the lack of investment in research for health products for CL as indicated in WHO's Global Observatory on Health Research and Development\textsuperscript{51}, the ECHR&D has identified CL as one of the priority diseases for investment. The preliminary analysis of Leishmaniasis prepared by the Global Health & Research Observatory in collaboration with the department of Neglected Tropical Diseases.\textsuperscript{52}

Investments to date are provided through the Global HR&D Observatory.\textsuperscript{53} In 2014, a total of US$ 456 M was spent on R&D. Unfortunately, the information available does not indicate how much was invested in CL. The website of BIO Ventures for Global Health indicates the health products in the pipeline, however these are mostly to treat and diagnose VL\textsuperscript{54} and few investments in CL are made. Investment in preventing and controlling leishmaniasis, specifically CL, has been very low and financial resources are urgently needed to address the identified research gaps indicated in section two.

World Health Assembly Resolution (WHA) 60.13 in 2007 on the Control of leishmaniasis recognized that Leishmaniasis is one of the most neglected diseases. The Member States encouraged research on leishmaniasis control in order to find alternative safe, effective and affordable medicines for oral, parenteral or topical administration involving shorter treatment cycles, less toxicity, and new drug combinations, and to define appropriate doses and duration of therapy schedules for these medicines.

In 2013, through WHA66.12, Member States called upon WHO's international partners to encourage initiatives for the research and development of new diagnostics, medicines, vaccines, and pesticides and biocides, improved tools and technologies and other innovative instruments for vector control and infection prevention and to support operational research to increase the efficiency and cost-effectiveness of interventions, taking into account the global strategy and plan of action on public health, innovation and intellectual property.

Unfortunately, in spite of these resolutions, research for CL remains almost non-existent.

\textsuperscript{51} http://www.who.int/research-observatory/en/
\textsuperscript{52} http://www.who.int/research-observatory/analyses/gohrd_analysis_leishmaniasis.pdf?ua=1
\textsuperscript{53} http://www.who.int/research-observatory/monitoring/inputs/neglected_diseases/en/
\textsuperscript{54} http://www.bvgh.org/Current-Programs/Neglected-Disease-Product-Pipelines/NTD-Pipelines.aspx
http://www.bvgh.org/Current-Programs/Neglected-Disease-Product-Pipelines/Global-Health-Primer/Diseases/cid/ViewDetails/ItemID/5.aspx
2 Specific HR&D gaps and health products needed

The Scientific Working Group of the HR&D fund convenes the WHO Disease Control Programme and their network of advisors to specify the specific R&D priority areas.

In collaboration with the disease experts in NTD, the SWG identified a number of research gaps hindering successful implementation of the global strategy to control Cutaneous Leishmaniasis. These gaps include:

- **Topical/oral treatment:** to date patients receive an intraleisonal injection of pentavalent antimonials to treat the infection.
- **Diagnostics tools:** a diagnostic test is needed that rapidly confirms CL, plus a mobile application assisting health workers in diagnosing CL and subsequently treating infected individuals in areas without laboratories and improving reporting on the number of screened and diagnosed people.
- **Vaccine:** absence of a vaccine preventing infection.

Essential to this effort is ensuring that funding for advancing research is available through the HR&D Fund once it is operational (more information is available in the analysis developed by NTD and the ECHR&D\(^{55}\)).

\(^{55}\) [http://www.who.int/research-observatory/analyses/gohrd_analysis_leishmaniasis.pdf?ua=1](http://www.who.int/research-observatory/analyses/gohrd_analysis_leishmaniasis.pdf?ua=1)
Table 5: Interventions, Barriers and Research Gaps Identified

The following, so far absent health products, are crucial to reduce morbidity of CL successfully, per the WHO strategy:

**Topical/oral treatment**
In comparison to VL, there are limited verified treatment options for CL. There is a need for a safe, topical or oral well tolerated, and affordable treatment which could cure the lesions quickly without leaving deep scars, and that can be deployed within primary healthcare systems for self-treatment without requiring follow up by health workers. Medicines used to treat leishmaniasis are very toxic, relatively expensive and therefore often unaffordable. The supply of medicines is not continuous and most of the medicines are produced by a single manufacturer only.

**Diagnostic tools**

1. **Diagnostic tests**
   Better diagnostic tests are needed that rapidly confirm CL. Current diagnostics are not sufficiently sensitive, are invasive, and not always available at the point of care. This makes it difficult to make an early diagnosis, and as a result, treatment for infected populations is delayed. For detecting CL, serological tests have limited value; clinical manifestation combined with parasitological tests are required to confirm the diagnosis.

2. Mobile app

CL diagnosis is often unavailable in the remote areas where most cases occur. Health workers (HWs) in areas, where no laboratories are available, would therefore benefit from a smartphone application assisting in detecting and treating common skin ailments, and neglected tropical diseases, including CL through a triage algorithm of symptoms. Most health workers use smartphones, therefore a smartphone application with such an algorithm would facilitate earlier detection of CL. This would enable early treatment of the infected individuals, halt the transmission of the disease sooner and less skin scarring and stigmatization. In addition the application would assist in reporting on screened, diagnosed and treated individuals, thus improving surveillance and prevalence mapping of skin diseases.

Vaccines:

As no vaccine exists to prevent CL in the first place, a health product priority would be a vaccine to prevent infection to reduce the global burden of cutaneous leishmaniasis. Vaccine development against leishmaniasis has been a goal for almost a century, pending better understanding of the pathogenesis of leishmaniasis and better animal models that reflect the human disease more accurately.

3 Prioritizing Interventions

The Scientific Working Group of the HR&D Fund in collaboration with the WHO Disease Control Programme and their network of advisors specify the specific health products that need to be developed based on an assessment of the existing health products, identified research gaps, health products in the pipeline and their “close to market” status, and possible other sources of funding available for these research products.
The following 2x2 table 6 can be used to plot the different needs against feasibility and affordability to prioritize appropriate interventions. The third dimension is time, as shown in brackets. “+” indicates a result in a short timeline and “+++” indicating several years.

<table>
<thead>
<tr>
<th>Affordability</th>
<th>Feasibility</th>
<th>Rationale for Intervention from the HR&amp;D Fund</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>+</td>
<td>For this case study, the further development of a topical/oral treatment and a smart phone application to assist HWs in case finding were the prioritized interventions chosen in collaboration with the NTD to be addressed.</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>There is a need for a simple and efficacious treatment for CL with an acceptable side-effect profile. So far little investment or progress have been made in developing a topical or oral treatment. With a topical/oral remedy on the market, patients would no longer need to rely on treatments that are toxic, not always available and often unaffordable. Another advantage to a topical or oral treatment is that health workers need not be present to administer it. Patients could be treated more expeditiously as well as effectively, thus reducing risk of serious scarring and the resultant societal stigmatization.</td>
</tr>
<tr>
<td>-</td>
<td>+</td>
<td>The smartphone application for case finding would lead to an improved diagnosis of CL at the peripheral health level where many health services, including laboratories, are not available. The application can be used as a diagnostic tool and a source of information on signs and symptoms of CL and other NTDs, as well as for surveillance and prevalence mapping. The application would also include information on the treatment or need for referral of the patient. This would allow for earlier detection of CL and immediate treatment of infected individuals, thereby, halt transmission of the disease at the time of diagnosis, and not months later, and thus also reduce scarring. Different pilot versions exist of a smartphone application and the list below with the two examples is not exhaustive:</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>Vaccine to prevent infection (+++).</td>
</tr>
</tbody>
</table>

Table 6: Different needs plotted against affordability and feasibility.
Operational plan for health product research and development fund
Background document 70th World Health Assembly Agenda item 13.5

- Skin4LApp in English and Portuguese, developed by the Netherlands Leprosy Relief, an International NGO
- Leishmaniasis in Spanish, developed by Grupo de Investigación en Informática y Telecomunicaciones de la Universidad Icesi in collaboration with the Centro Internacional de Entrenamiento e Investigaciones Médicas in Colombia

A French version would be necessary to assist HWs in Francophone Africa.

From an investment point of view, investing in the further development of a topical or oral treatment for CL is a lower costs means of achieving a faster result. Clinical trials are ongoing and the product could be on the market in a relative short time without significant additional investments. This would apply also to investing in the diagnostic smartphone application. Limited funds would be needed for improving the current versions, implementing a second round of testing as well as the development of a French version. For both products the risk for failure is low, and both the topical/oral treatment and the smartphone application could be made available on the market within a relative short time without significant additional investment.

4 Sourcing and validation of Preferred Product Profiles

![The Scientific Working Group sources and validates the Preferred Product Profile addressing the minimum and ideal requirements for the chosen intervention.](https://www.dndi.org/diseases-projects/leishmaniasis/tpp-cl/)

Based on the Preferred product profile (PPP) template for therapeutic products included in the “Health Product Research & Development fund: a proposal for financing and operation”, as well as the PPP developed by DNDi 57, a draft PPP was developed.

A new topical or oral treatment for CL would ideally be efficacious against all species, show at least 95% efficacy, be easy to use, short course (14-28 days), compatible for combination therapy, produce minimal scarring, be safe in pregnant and breastfeeding women, affordable, and adapted to tropical climates. 58

The PPPs will need final validation and publishing once the call for proposals is issued.

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58 [https://www.dndi.org](https://www.dndi.org)
5  Health Research & Development Pipeline

The SWG evaluates the health products currently in the pipeline against the Preferred Product Profile to identify promising candidates that could be considered for funding through the voluntary pooled fund.

Chemical treatments for CL include the following research studies. This table includes a limited number of ongoing trials and does not aim to exclude any ongoing study.\(^{59}\)\(^{60}\)

<table>
<thead>
<tr>
<th>Chemical treatment</th>
<th>Description</th>
<th>Clinical phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thermotherapy &amp; miltefosine combination proof-of-concept</td>
<td>Thermotherapy + a short course of miltefosine for the treatment of uncomplicated cutaneous leishmaniasis in the New World.</td>
<td>Phase II</td>
</tr>
<tr>
<td>NCT02687971  Colombia, Peru</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topical amphotericin B cream</td>
<td>Topical 3% amphotericin B cream for the treatment of cutaneous leishmaniasis in Colombia (anfoleish).</td>
<td>Phase I/II</td>
</tr>
<tr>
<td>NCT01845727  Colombia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imiquimod plus antimony immunochemotherapy</td>
<td>Imiquimod plus antimony immunochemotherapy for cutaneous leishmaniasis</td>
<td>Phase III</td>
</tr>
<tr>
<td>NCT00257530  Peru</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topical paromomycin with or without gentamicin for cutaneous leishmaniasis</td>
<td>Topical treatments containing 15% paromomycin, with and without 0.5% gentamicin</td>
<td>Phase III</td>
</tr>
<tr>
<td>NCT00606580  Tunisia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 7: Chemical treatments in the pipeline

\(^{59}\) https://www.dndi.org/2016/clinical-trials/clinical-trials-leish/
\(^{60}\) https://www.ncbi.nlm.nih.gov/pubmed/?term=cream+ben+salah+cutaneous+leishmaniasis
6 Incentive mechanisms

The SWG determines the appropriate incentive mechanisms for each given health product. Different options exist – push, pull or enablers – each suitable for different scenarios, depending on the level of market failure, the development phase of the health product and the R&D players involved.

Based on the different characteristics of topical/oral treatment, the different incentive mechanisms were evaluated. Topical/oral treatment for neglected diseases such as CL pertain to the category of products with “significant market failure” due to the absence of commercial markets and limited financing interest. As a result, the topical/oral treatments, albeit in clinical phases, and some getting close to market, remain stagnated due to the insufficient financial incentive to move them forward. The main R&D players are academic institutions, small developers and R&D partnerships.

Figure 8 below provides an overview of the effectiveness of the different incentive mechanisms as proposed in the “Health Product Research and Development Fund: A Proposal for Financing and Operation”.

Figure 8: Effectiveness of incentive mechanisms for diagnostic test for cutaneous leishmaniasis

Adapted from “Health Product Research and Development Fund: A proposal for financing and operation (2016)”

61 A lack of commercial markets does not imply a lack of clients as there is great need a safe treatment
7 Review of applications

The SWG issues the call for proposals. The applications are reviewed and evaluated against a set of criteria taking into consideration a number of the principles and recommendations formulated by the Expert Committee on Health R&D, including the core principles as defined by the CEWG* of affordability, effectiveness, efficiency, equity and the principle of delinking the costs for the investment into research and development from the volume and price of the resulting health products.

The SWG reviewed applications of the different research institutes and selected two projects for potential investment.

8 Monitoring and evaluation of selected projects

Bi-annual progress and final reports are submitted by the research institutes and reviewed by the SWG and signed off by the SWG Chair.

9 Conclusion

In collaboration with the Department of NTD, CL was chosen as one of the case studies to illustrate the Operational Plan for Voluntary Pooled Funding Mechanism of the Health Product Research & Development Fund. Based on the findings of the Global HR&D Observatory, the need for topical/oral treatment was identified as a priority health product to address the WHO strategy to reduce the morbidity from leishmaniasis and to prevent large facial skin lesions which are highly stigmatizing. Once the voluntary fund is operational, a call for proposals could be issued and a further analysis conducted of the specific health products in the pipeline. Based on the current available information, a push mechanism, i.e. direct grant would be the preferred incentive mechanism to finalize the development of a topical/oral treatment for CL. In addition the analysis showed the need for diagnostic tools in peripheral health areas. Once the fund is operational, a direct grant could be made available to further improve, translate and test a smartphone application to be used by HWs in areas where no laboratory is available to assist in quickly diagnosing CL and improving surveillance.
10 Using PPP criteria fulfilment to filter and prioritize Therapeutic Products

To be filled out once PPP and proposals have been received and reviewed.