Standard Template for a Candidate Demonstration Project

Note: the questions with asterisk should be filled.

1.* Title of the project:

Ecosystem for financing development of an open source multiplex point of care (POC) diagnostic device for the differential diagnosis of fever or sepsis. Henceforward, this will be referred to as the Open Source Fever Diagnostic Project*

2.* Submitted by:

Médecins Sans Frontières/ Doctors without Borders (MSF)

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3.* Target disease or health condition:

(Focus on type II and III diseases and special R&D needs of developing countries in type I diseases where there is an identified health technology gap.)

Fever syndrome including sepsis.

4.* The suggested health technology that project seeks to develop:

(e.g. medicine; diagnostic test; medical device; vaccine etc.)

A diagnostic test, and in particular, an open multiplex and point of care (POC) diagnostic test for the differential diagnosis of fever or sepsis.

A key feature of the test will be the flexibility to use epidemiological data of major pathogens responsible for fever/sepsis in various settings and populations to tailor diagnostic algorithms (i.e., a menu of specific pathogens that is relevant for a particular region, country or setting - inpatient/outpatient/ICU/neonatal).

* We note that this proposal builds upon but also has some differences with earlier proposals to use prizes to stimulate the development of point of care diagnostics, including in particular the ideas from the April 2008 MSF expert meeting on IGWG and R&D for tuberculosis, the 2009 proposal by Bangladesh, Barbados, Bolivia, and Suriname for a Prize Fund for Development of Low-Cost Rapid Diagnostic Test for Tuberculosis to the WHO Expert Working Group on R&D financing and coordination, the work beginning in 2009 on a proposed TB Diagnostics XPrize, the 2011 Bio Ventures for Global Health (BVGH) proposal for the Global Health Innovation Quotient Prize: A Milestone-Based Prize to Stimulate R&D for Point-of-Care Fever Diagnostics, submitted to the WHO Consultative Expert Working Group (CEWG) on R&D. A comparison of the different proposals is available upon request.
In this context, open means that the technologies are fully disclosed and that follow-on innovation, or use of the innovation by third parties, is possible; new knowledge, data or technology is available on a non-discriminatory basis, either royalty free or on fair and reasonable terms. The intellectual property rights and the architecture of the diagnostic technology must be open enough that it can be modified to make it inter-operable with third-party supplied components (i.e. third-party assay cartridges, batteries, etc).

5.* Project summary:

Low-cost, open source, multiplex point of care (POC) diagnostic test for the differential diagnosis of fever/sepsis

The project is a multi-government collaboration to fund a low-cost multiplex point of care (POC) diagnostic test for the differential diagnosis of fever/sepsis. The motivation is to improve the diagnosis of patients suffering from fever in low-resource settings, thus enhancing treatment options, and also, reducing inappropriate use of antibiotic drugs. While motivated by the need for tests in resource-poor settings, the innovation will be also useful in non-resource poor settings and high-income countries, increasing the global social value of the innovation.

The project begins with the identification of an innovation need, and then proposes a method of financing investments to achieve the needed diagnostic services. The voluntary plurilateral funding by governments will be used in a combination of push and pull funding mechanisms, implemented with full de-linkage of R&D costs from product prices. The cost of the project is between US$70 million to $200 million, depending upon the level of funding support secured. The value of a successful innovation vastly exceeds the high end of the project funding, and the bulk of the funding would be in the form of obligations to only reward successful innovations, substantially lowering the risks and improving the expected cost benefit of the project to the project’s funders/donors.

The Target Product Profile (TPP) being developed for this test is targeted for use at the minimum in district health settings for patients (neonates, children and adults) presenting with fever syndromes. Because the causative pathogens of fever will differ by clinical setting and geographical region, one key feature of this diagnostic test is the flexibility to integrate epidemiological data of fever pathogens in various settings into the test. The final selection of the pathogens that need to be included in the test should be informed by the particular geographical and clinical setting for which the fever diagnostic test will be used.

In order to meet the needs in resource-limited settings, the specifications are in accordance with previously established WHO ‘assured’ criteria for the test to be ‘affordable, sensitive, specific, user-friendly, rapid, robust, equipment-free and deliverable to end-users.’

Governance and Administration

The governance of the project would include an Executive Board, consisting of the project’s funders/donors, high burden countries and representatives from affected communities. Rules to
disclose and manage potential conflicts of interest would be created. The work of the Executive Board would be informed by a technical advisory committee within the WHO that would analyse and provide data on causes of fever in different geographic regions; draw on expertise within WHO on quality assurance of medical devices and on standards for interoperability of devices in order to inform and align the work of the Executive Board. The Executive Board would set high-level policies and enter into a contract with one or more entities to manage a portfolio of grants and innovation prizes. We anticipate that the Special Program for Research and Training in Tropical Diseases (TDR), UNITAID or the World Bank would be among the entities that could manage the grants and/or prizes portfolio.

**Medical Need**

Fever is the most common presentation of infections. Fever without focal signs and symptoms is one of the most common reasons for admission to hospitals in low-income countries. [1,2] While accurate malaria diagnosis is now possible with the availability of a rapid diagnostic test (RDT)[3], there still remains a lack of diagnostic microbiology services for bloodstream infections and other common causes of fever despite efforts in improving laboratory capacity [4, 5, 6]. Because of this, health care workers use an empirical approach to the treatment of fever syndromes, which leads to either inappropriate use of antibacterial drugs and/or missing a critical window for diagnosis of certain diseases, leading to both unfavourable clinical outcomes as well as risking the promotion of antimicrobial resistance[2].

**Flexible donor funding of push or pull**

The project’s funders will have the opportunity to provide general support for the project, which the Executive Board would allocate to either grants or innovation prizes, or to choose to fund either grants or innovation prizes.

**Open licensing of intellectual property rights, data and know-how**

The intellectual property rights from the grants and innovation prizes would be conditioned upon the open licensing of intellectual property, data and technology transfer, possibly within a field of use, to ensure open and competitive access to research outcomes.

**Grants and contracts**

Funding for research grants and contracts will be sought from funders/donors. Grants (or contracts) will be particularly useful to focus research on areas where prizes are considered too costly to manage or where project managers have greater confidence in their ability to identify and manage research projects to achieve research objectives.

**Innovation Prize Funds**

The program would include four different types of innovation prize funds.
(1) **Biannual best progress prizes.** One set of prizes would be awarded every two years to reward the best progress toward the development of the ‘end point’, which is an open-source, low cost multiplex point of care (POC) diagnostic test for the differential diagnosis of fever/sepsis.

(2) **Milestone prizes.** The Executive Board and the selected administrator of prizes could also provide funding for various milestone prizes, rewarding the successful achievement of specific research objectives considered to be useful in achieving the end point. For example, a milestone might be the identification of a biomarker that distinguishes between bacterial and viral causes of fever.

(3) **End Product Prizes.** The end product prize would be available to one or more entities that achieve the desired end point, as defined by the Executive Board. If the funding of the end product prizes is sufficiently large, the competition will have a lower threshold to qualify, and be sufficient to induce the development of multiple competing designs that divide the prize money. If the funding of the end product prize is less than $20 million, it will have a higher and more difficult set of qualifying criteria that would be won by the first contestant or set of contestants to qualify during a round of the periodic evaluation of designs seeking to win the end product prize. The end product prizes will be the most expensive element in the project, but also the least risky to the project’s funders/donors, because the money will only be spent if a design achieves the desired end point. We recommend end product prize funding of $20 to $100 million, with the larger amount resulting in a higher probability of success and a more rapid development schedule.

(4) **Open source dividend.** Between five and ten percent of the end product prize money will be given out to parties not affiliated with the contestant submitting the winning design. In order to qualify for the open source dividend, a potential recipient of the prize money must have provided royalty-free and non-discriminatory access to knowledge, data, materials or technologies that were considered to have been important in the successful development of the product that wins an end product prize. Recipients of earlier grants or prizes will be eligible for the open source dividend rewards. The process for awarding the open source dividend will be the appointment of a temporary jury of experts who will receive nominations for the open source dividend prizes and allocate the prize money based upon the evidence from the nominations.

**Note on grants versus prizes**

There is no bright line that separates a target innovation into candidates for grants versus prizes. The flexibility to use either grants and contracts or competitive prize contests is an important aspect of this project.

When does one choose a grant or a prize to finance innovation? This is a difficult question to answer definitively. If one thinks of patent monopolies as a type of a particular type of prize, then it is clear that there is nothing that a patent or a different type of prize could reward that could not also be financed by a grant, including any and all stages of product development. However, the converse is not true. There are tasks that are poor candidates for patents or prizes, including work for which, while useful and perhaps even necessary, are unlikely to rewarded for inventive or stellar performances, or for, where the suppliers are uncomfortable, unable or unwilling to bear the risk of not being paid, or where asymmetric information makes it difficult
to assess the risks of success or failure or to evaluate the quality of the effort or output, or any number of practical reasons why creating and managing a competitive contest using cash prizes is an inefficient approach.

The grant system itself can and frequently does lend itself to a certain amount of competition, both in terms of who receives grants from a grant-making agency, and even between grant-making agencies seeking to address common objectives. Indeed, the project could choose to divide its own grant-making portfolio among different grant-making agencies, creating some creative tension, competition and diversity in management of the grants. But prize contests can introduce a degree a competition and a shift in risk bearing that can be beneficial to the party financing the innovation. Among the potential benefits of prizes include the ability to reward unconventional approaches to problems when championed by those who think differently and are willing to bear the risks of failure. The persons who become ‘solvers’ in prize competitions may be a wider cast of characters than the ‘usual suspects’ that are likely to obtain grants. The shifting of risk in prize contests also presents attractive opportunities for a funder/donor to only pay for what works, and not worry about justifying outlays on dead-ends that sometimes turn up despite the most optimistic and promising beginnings.

**Note risk bearing, as it relates to grants versus prizes**

One of the major differences between grants and prizes, and between different prizes is the distribution of risk bearing between the researcher/developer and the project’s funders/donors. Since failure is not a rare occurrence in product/diagnostic development, the question of who bears the risk is important, as are the consequences. At the risk of some oversimplification, this can be described as follows:

- **When grants are used**, governments (and other funders/donors) bear all of the risks of failure. When this happens, researchers and product developers are likely to be somewhat lax on due diligence and screening of the projects they pursue.

- **When milestone, best progress or other interim prizes are used**, the risks are divided between the project’s funders/donors and the researcher/product developers. With shared risks, researchers and product developers will be more rigorous and careful in their assessment about what might achieve the milestone, but remain less concerned over whether or not the milestone itself will lead to useful products.

- **When end product prizes are used**, the project’s funders/donors bears little risk, other than the time and costs of administering the prize contest. In such cases, researchers and product managers will exercise a good deal of caution before investing their own money in R&D efforts.

**The Ecosystem Approach**

This project is designed to create multiple mechanisms to finance development an open source multiplex point of care (POC) diagnostic tests for the differential diagnosis of fever/sepsis. Each of the mechanisms, grants and research contracts, milestone prizes, best progress prizes,
end product prizes and the open source dividend, have strong points, but also gaps and weaknesses. The project embraces an ecosystem approach, using multiple mechanisms to advance and acquire development of new technology for fever diagnosis. In this sense, the sum is greater than the individual parts.

6.* Public health needs that the proposed project aims to address:
(Explain the public health need in terms of burden of disease; prevalence; incidence; fatality rate; geographical spread; current interventions and their limitations; and what proposed new technology would change in terms of disease prevention, control, diagnosis, treatment etc. If detailed information is not possible at present then please provide some basic level information)

Fever is the most common presentation of infections. Fever without focal signs and symptoms is one of the most common reasons for admission to hospitals in low income countries.[1,2] While accurate malaria diagnosis is now possible with the availability of rapid diagnostic tests (RDT)[3], there still remains a lack of diagnostic microbiology services for bloodstream infections and other common causes of fever despite efforts in improving laboratory capacity [4,5,6]. Because of this, health care workers use an empirical approach to the treatment of fever syndromes which leads to either inappropriate use of antibacterial drugs and/or missing a critical window for diagnosis of certain diseases leading to both unfavourable clinical outcomes as well as risking promotion of antimicrobial resistance[2].

The experience of malaria RDT has highlighted the lack of diagnostic tools to give an alternative diagnosis for patients who test negative for malaria. Studies have shown that there were worse outcomes for patients who received a negative malaria RDT which suggests that other diseases were missed and undiagnosed [7,8]. Because of the lack of alternative diagnosis, the practice was the prescription of antimalarial drugs despite a negative RDT or the over prescription of antibiotics [9,10].

This problem exists for both adults and children. Young children present in health facilities with a combination of symptoms of systemic inflammatory response syndrome (SIRS), such as high fever with tachycardia and tachypnoea and the clinical suspicion of infection leading to the diagnosis of sepsis. As the range of organisms responsible for this clinical presentation are multiple and cannot be differentiated on a clinical basis, children are usually treated with a broad-spectrum antibiotic and an anti-malarial if RDT for malaria positive. The clinician will not know if any clinical improvement is a direct response to antimalarials, antibiotics, or merely a function of rehydration and time, or a combination of the above. The results are an overuse of precious broad-spectrum antibiotics with the risk of development of resistance, poor practice of medicine including the potential missed diagnosis of treatable diseases. Regarding the use of presumptive antibiotic treatment, the duration of treatment is also problematic. Exposing children to long courses of antibiotics subjects them to potentially unnecessary long stays on wards, as well as the development of antimicrobial resistance.

Aside from diagnosing the pathogen responsible for fever, it would also be useful to have a biomarker of infection to help rule out an infection.
7.* Explain which new and innovative approaches and mechanisms to supporting financing and coordination of R&D this project would demonstrate?

(This is a very important part to be filled. The idea of these demonstrations projects is “to address identified gaps that disproportionately affect developing countries, particularly the poor, and for which immediate action can be taken” (WHA66.22). 66th WHA considered these demonstration projects as part of the efforts to “take forward action in relation to monitoring, coordination and financing for health research and development”. The assembly decided to identify such projects that: “(a) address identified research and development gaps related to discovery, development and/or delivery, including promising product pipelines, for diseases that disproportionately affect developing countries, particularly the poor, and for which immediate action can be taken; (b) utilize collaborative approaches, including open-knowledge approaches, for research and development coordination; (c) promote the de-linkage of the cost of research and development from product price; and (d) propose and foster financing mechanisms including innovative, sustainable and pooled funding; (2) The demonstration projects should provide evidence for long-term sustainable solutions.”)

A plurilateral funding and management approach demonstrates the ability of governments to collaborate on the financing of projects that may be too expensive for any one government. The particular financing approach proposed is to permit the project’s Executive Board to decide for themselves to fund various elements of the funding system, such as by just funding grants, which are a more traditional approach, or funding one or more of the innovation prize funds that would be part of the project. The use of best progress, milestone, end product and open source dividend prizes would be innovative for a WHO project, and particularly well suited to de-linkage strategies. The intellectual property rights policies fully embrace de-linkage of R&D costs and product prizes, and maximize the freedom to use research outcomes in follow-on research and product development.

The financing mechanism for stimulating a low cost open source point of care diagnostic test for fever could be modified and scaled for a number of other unmet needs as regards to low cost point of care diagnostic tests that can be used in resource poor settings.

Among the four types of innovation prizes, an open-source dividend, which is a shared reward from the end product prize, would be the most novel and potentially revolutionary, with regards to increasing new incentives to share research inputs and outcomes.

**Advantages of the Open Source Fever Diagnostic Project**

As compared to earlier proposals to use prizes to stimulate the development of point of care diagnostics, including the ones referenced above, the Open Source Fever Diagnostic Project would address more differential diagnoses of fever, for more age groups, and it focuses on the development of a more interoperable and extendable technology. Furthermore, intellectual property management are more favourable to the project’s funders/donors, and optimal for follow-on innovation.
The proposal embraces a wide set of prize types. The use of four prize mechanisms has several advantages, including by rewarding interim achievements that are not anticipated by prize managers (the biannual best of prizes), and by stimulating the sharing of knowledge and other research inputs (the open source dividend).

The Open Source Fever Diagnostic Project includes a push component (grants), which provides an additional instrument to advance the open-source platform.

The fact that the Executive Board may choose to resource and expand any of the project components (grants and any of the four prize types) will make the project more attractive to its funders who have more confidence or preference for a particular mechanism. For illustration, consider two special cases. The project’s funders/donors who have more confidence in the value of grants than prizes can put their money into grants. Those who only want to pay after a successful outcome, as it relates to a milestone or development of the end product, can escrow funds for a particular milestone prize, or for the end prize.

The flexible approach to funding extends to overall size of the project fund, the allocation of the funds between mechanisms, and quite importantly, to the freedom to increase funding overtime, if perceptions change as regards to the necessary size of prizes or grants to reach a successful outcome, or to achieve the outcome faster.

8.* Evidence of market failure/research landscape:
(Explain why there has been no investment in this technology or why investment has not resulted in access to the health care product.)

As regards market failures, there is a fundamental contradiction between the social value of inexpensive diagnostic tests and the profits from developing and selling such tests. Under traditional business models, as prices for tests approach zero, deployment and use goes up, while profits go down. At present, there are weak - if any - economic incentives to develop diagnostic products that can be manufactured and sold by multiple firms at low prices. There are also few, if any, economic incentives to share research outputs on a royalty-free and non-discriminatory basis, or to achieve certain interim research results that fall short of the development of a product, but which may enable products to be developed. The new business model proposed in this project would correct these market failures, by providing robust rewards for successful product development, and several prize types (best of, milestone and open source dividend) that reward interim progress and open sharing of knowledge, data, materials, technology and know-how.

As regards the research landscape, infections can be caused by a wide variety of pathogens; the diagnosis of some infections is complicated since there is a considerable overlap in symptoms and clinical presentation. Accurate microbial identification is one of the key steps of infectious disease management. Blood culture has been the gold standard test for diagnosing febrile illness and sepsis, but these systems require microbiology laboratory services. There are a lot of barriers to improve laboratory capacity in the developing world and even with capacity building efforts, diagnostic services will be restricted to centralized reference labs. Even where there are rapid, inexpensive, easy-to-use tests such as the malaria RDT, such tests are limited in informing
differential diagnosis if the test is negative. Recent advances in molecular diagnostic methods have opened the possibility of improving the diagnosis of pathogens causing bloodstream infections within hours. Non-POC multiplex systems based on molecular techniques have been developed in resource-rich settings to improve diagnostic testing of various infections limited by conventional blood culture system[11]. While there is some interest by some manufacturers to produce a multiplex POC fever platform using newer molecular techniques, there are patent thickets that inhibit the application of new technologies in making this feasible. For those who have successfully navigated the patent barriers, the diagnostic platforms do not allow for the development of other assays to be used in the platform. For example, while the GeneXpert RDT for tuberculosis has several specific cartridges to be used in its platform, other manufacturers who are able to produce cartridges for other pathogens for use in the GeneXpert platform will not be able to.

9. The scientific and technical feasibility:
(Describe the scientific and technical basis for the proposed technology in terms of the state of the art e.g. candidate molecules; biomarkers; pipeline; previous efforts, if any, to develop same or similar technology etc. Include some risk analysis)

Scientific advances in relevant fields, as described below, suggest the outcome is technically feasible, if approached with a new and transformational business model.

Most of the current point of care (POC) diagnostic tests used in resource-limited settings are simple to use and provide rapid results. The most common test is immuno-chromatographic tests (dipstick, lateral flow test) which provide a quick yes/no result in minutes in the form of a visible band. There are limitations of immuno-chromatographic tests. Advances in micro-devices can enable diagnostic tests to be miniaturized for POC use. Micro-fluidic systems can be designed to automate complex diagnostic steps and procedures that are normally performed in a centralized laboratory into a micro-fluidic chip.

For diagnosis of infectious diseases, the potential applications of these technologies are immunoassays and nucleic acid amplification testing or molecular detection.

Immunoassays make use of binding interactions between antigens and antibodies to detect protein markers from either pathogen or host immune responses. Analytes for immunoassays can be from viruses (i.e. anti-HIV antibodies and p24 antigen for HIV) to bacteria (i.e. anti-treponemal antibodies for syphilis) and parasites (i.e., histidine rich protein 2 for malaria).

Molecular detection or nucleic acid amplification can provide results more rapidly compared to traditional blood culture systems. Molecular detection identifies DNA and can be very specific for a particular microbe. There are specific conserved target regions for bacteria and fungi that are used for molecular detection methods (i.e., 16S and 23S ribosomal RNA as well as 18S and 5-6S fungal ribosomal RNA). Other advantages of molecular identification of the microbe include its higher sensitivity in identifying microbes where antibiotics have already been started and where conventional blood culture may not allow it to grow. It may also be useful in the detection of microbes that are fastidious or uncultivable in blood culture medium. The most common nucleic acid amplification technique is PCR. Other non-PCR based, isothermal nucleic
amplification includes transcription mediated amplification (TMA), nucleic acid sequence-based amplification (NASBA), strand displacement assay, loop-mediated isothermal amplification (LAMP), and single primer isothermal amplification (SPIA).

Multiplex assays allows for simultaneous measurement of multiple analytes in a single run. Examples of multiplex assay technique include nucleic acid based (DNA microarray, multiplex PCR, Luminex technology) and protein based multiplex techniques (protein microarray, antibody microarray, Luminex technology).

An example of a near point of care test using these technologies is GeneXpert, which uses microfluidics technology for their PCR based nucleic amplification and detection of TB and resistance to rifampicin. Other technologies that have been shown to provide rapid results include mass spectrometry. In recent years, there has been research work in developing small field-portable units.

An open system platform allows for other manufacturers to use the technology (i.e. develop the same platform and/or the plug in cartridges) and will have the potential to lower costs by promoting competition and eventually increasing access.

One important barrier in developing an open platform is the management of various intellectual property (IP) assets related to developing a multiplex POC platform. Manufacturers have either found a way around the existing patents by having their own proprietary assays or nucleic acid amplification technique or have waited for IPs to expire. Other issues that have been raised in opening up IP to other manufacturers include the control of quality-assurance of the devices.

There are several risks to this project. One is that the solution, while assumed to be feasible, will not be known within the project's life. The risk of not solving the end points is greater when the end product prizes are smaller, and lower when the end product prizes are higher.

Another risk is the potential for products to be manufactured that do not meet quality standards and prove unreliable in the field. This can be mitigated through requiring that both the device and assay/cartridge components are submitted to a Stringent Regulatory Authority (SRA) body for validation. The benchmark for the identification of quality diagnostics for HIV/AIDS, malaria and hepatitis B and C is the WHO List of Prequalified Diagnostic Products (WHO Prequalification) which evaluates diagnostic and monitoring test manufacturers according to WHO-recommended standards of quality and compliance with Good Manufacturing Practices. In addition the International Medical Device Regulators Forum (IMDRF), founded in 2011 has set standards for quality diagnostics. The IMDRF is composed of a voluntary group of medical device regulators from countries around the world with the aim of accelerating harmonisation and convergence. At present the mandate for WHO Prequalification does not cover fever diagnostics, but if this could be expanded to fever, the Executive Board could stipulate that devices and component parts such as assay cartridges must receive WHO prequalification or be authorised for use by an alternative regulatory authority that is a member of the IMDRF.

We also note that the funding associated with end product prizes reduces the financial risks to the project’s funders/donors, because the money is not actually spent if the end point is not reached.
There is a risk that a third party will patent a possible useful technology and not agree to the open licensing incentives. Somewhat mitigating this risk are the incentives to place more prior art in the public domain, such as the biannual best progress prizes and the open source dividend prizes. Another possibility is to have a defensive patenting strategy.

10. **Reasons for proposing:**

(Provide details if any priority setting and/or selection criteria that has underpinned the consideration to take up this area of technology for development.)

An early and accurate diagnosis of the causative agent of fever and sepsis is important for the individual patient and for public health. It allows prompt and proper treatment of patients, limits the spread of disease in the population and minimizes the waste of resources in ineffective treatments. Sepsis, in particular, is an example of a life-threatening infection for which it is very important that appropriate antibiotics be given within a critical time window and initiation of proper antimicrobial therapy significantly increases the probability of survival. In the absence of diagnostic tests, infections are managed empirically. This approach has been associated with the overuse of broad spectrum antibiotics with subsequent development of antimicrobial multidrug resistance and emergence of hospital acquired infections.

While infectious diseases continues to be a large burden in developing countries, other than HIV, malaria and TB – which have received a dedicated focus from the international community - there has not been a more organised and prioritized approach in addressing other infections. Developing a diagnostic test that targets identification of common causes of fever/sepsis instead of developing an individual test by pathogen is a more efficient strategy. There are advances in the field and technological landscape that are already being used to make a point of care multiplex diagnostic test development a promising endeavour, such that intervening in the system now is likely to yield fruitful results. An open multiplex POC fever diagnostic test is an area amenable to testing out new models for push- and pull-financing, IP management and coordination that could yield broader lessons for new approaches to R&D.

11. **Who could potentially develop the technology/carry out the research?**

(Provide known details: individual researcher? Group of researchers? Research/coordination organization including PDPs? Group of research organizations working together? Combination of these? What would be the process of selection of developers?)

The development of the diagnostic test will involve a diverse set of skills and insights, ranging from biology, chemistry, engineering, manufacturing, software development, business, finance, and design, among other areas of expertise. It is anticipated that researchers and product developers will include individuals and groups, and profit and non-profit entities, working on different aspects of the project. The system of grants, plus four different types of prize mechanisms, will provide opportunities for diverse actors around the world to contribute.
12. **Who could potentially manufacture the final product?**

*Multinational company? Local production? Joint venture? How the decision will be made about the producer?*

The project features open licensing of intellectual property and transfer of know-how. Ideally the device and testing components will be manufactured by multiple firms. Joint ventures, collaborations with a PDP, or local production are all possibilities as regards suppliers.

13. **What could be the role of WHO, if any, in this demonstration project to bring this venture to fruition?**

It is proposed that a technical advisory committee would be set up within the WHO that would define the Target Product Profile (TPP) for the fever diagnostic; analyse and provide data on causes of fever in different geographic regions; draw on expertise within WHO on quality assurance of medical devices and on standards for interoperability of devices in order to inform and align the work of the Executive Board. This technical advisory committee would also provide technical expertise and advice on the end points for the milestone and end product prizes.

If work on standards for medical device interoperability moves forward within the WHO, the technical advisory committee would be expected to ensure these are communicated to the Executive Board in order to ensure alignment.

At present the mandate for WHO Prequalification does not cover fever diagnostics, but if this could be expanded, the Executive Board could stipulate that devices and component parts such as assay cartridges must receive WHO prequalification or be authorised for use by an alternative regulatory authority that is a member of the IMDRF.

14. **Please outline a timeframe and projected milestones for the project covering the first 5 years. This should also highlight the immediate actions that need to be taken?**

   **Year 1 - 2:**
   - Project governance and administration including Executive Board and WHO technical advisory Committee is set up
   - Enter into contracts with the managers of grants and prizes
   - Conflict of interest policy adopted
   - Auditors selected
   - Escrow accounts created for prize funds
   - Target product profile (TPP) finalized
   - Intellectual property licensing terms for grants and prizes
   - Development of rules for end product prize, best progress and open source dividend prizes

   **Year 3:**
   - First grants disbursed
   - One or more milestone prize awarded
• First biannual ‘best progress’ prize award

Year 5:
• Additional more milestone prizes awarded
• Second biannual ‘best progress’ prize award

Beyond year 5 through year 10
• Continued biannual best progress prizes
• Grants awarded
• Additional milestone prizes
• End stage prize awarded

15. What is the intellectual property (IP) landscape relative to this project? Is there any IP, e.g. patents that need to be licensed in to be able to develop and market the product in developing countries? How would IP and related intellectual assets, including knowhow, proposed to be managed in this project?

The intellectual property landscape for fever diagnostics is challenging, and successful projects would have to demonstrate a feasible open source pathway to the market. We believe this is feasible in part because: 1) many of the foundation patents have expired or are at the end of their patent terms; 2) some technologies are not widely patented in resource-poor countries; 3) the reward systems will induce voluntary licensing; and 4) some countries will be able to grant compulsory licences on patented technologies.

Anyone receiving funding from the project, whether from grants or from any of the four types of innovation prizes, will be required to openly licence the research outputs, including knowledge, data, materials, technology and know-how.

16.* What would be the strategy to ensure access to the product once it is developed?

(Access is an important dimension of these demonstration projects, it is important for the projects to begin with the end in mind, explain how this project would deliver the technologies to the needy patients i.e. price and affordability; modes of supply; storage; prescription; dispensing; and compliance; WHO will develop guiding principles for ensuring access to any products coming out of the demonstration projects)

The most important strategy is to insist on a technology that is inexpensive and can be manufactured by multiple suppliers. The de-linkage and open source business model is well suited to this strategy.

The end product prize(s) will only be available to products that are actually deployed and reach market penetration and usability requirements. Device and incremental testing costs are both subject to maximum prices to be determined in consultation with WHO and other relevant public health officials.
Standards for Sustainable Affordability and Access

The standards for affordability and access would focus on pricing ceilings and a market penetration test.

An initial target for the price of the test would be $1 to $7, and this will be revised after consultation with a wider range of stakeholders and experts.

Price ceilings would be established for both the device itself and the incremental cost of testing, either as a mandatory requirement, or as an optional requirement, that could be substituted for an alternative market penetration test.

A market penetration test would be a requirement that the diagnostic device was actually manufactured, distributed and used by a large enough population to provide evidence that the device would in fact be affordable and acceptable for target populations.

One particularly interesting version of the market penetration test would be where the diagnostic device would be manufactured and sold by one or more third parties without subsidies from the prize applicant, in order to establish the feasibility and sustainability of a competitive supply. Upon reaching sufficient scale of distribution, the standard for affordability and access could be satisfied.

The size of the market penetration test could be smaller for cases where a maximum observed price was met. In cases where a maximum price is not used, the market test would have to be large enough to prove that the actual market price would likely be affordable to the target populations.

More complex would be the case where the prize applicant asserts that device can be manufactured for an affordable price, and even distributes an initial supply of devices, but where there is no assurance that the diagnostic device supply would be sustainable at an affordable price, once the prize money was paid. In such a case, a contestant would be required to provide sufficient assurances, covered by financial guarantees, that the products will be manufactured in sufficient quantities and of acceptable quality, at affordable prices.

17. How could the project be financed paying particular attention to the need to demonstrate new and innovative forms of financing? Also provide an estimated cost of the project.

This issue is also discussed in the answer to question 7. The use of innovation prizes as a mechanism to stimulate investments and effort in R&D is innovative, particularly when the prize awards are associated with open licensing of intellectual property and end products, and when funded by more than one government.

Given the challenges, the project should at least be funded at $70 million, and up to $200 million or more would be appropriate given the potential benefits, with the higher funding level associated with a higher probability of success, and faster development times. Funding
committed to the end product prize will not actually be spent unless a new low-cost diagnostic test is available, affordable and in use, and the new cost-saving technology will be far more valuable than the cost of the prize.

Cost Benefit of the Project

According to a 2007 Rand Corporation Research Brief [12], “a quick, easy-to-use test for bacterial pneumonia could save at least 405,000 lives each year” referring to a test with “good” performance and requiring “minimal infrastructure.” In the Rand analysis, 250,000 of the 405,000 million lives saved “would be the result of reductions in over treatment.” Rand found that in Africa the primary benefit of the test would be to reduce the disease burden, while in Latin America and Asia, the primary benefit would be from reducing over treatment, noting that in Asia in particular “overuse of antibiotics is a significant problem.”

Some consider global public health or development interventions are cost effective at $30,000, and highly cost effective at less than $3,000. Using these parameters, development of a “good” test that was widely available, including in places with minimal infrastructure would have benefits of $1.2 to $12.15 billion per year, just as regards bacterial pneumonia.

We do not have the data to estimate the deaths prevented or other benefits from the use of the diagnostic test for other diseases.

18. How could the project be governed and coordinated paying particular attention to the need to demonstrate better way of coordination?

The governance of the project would include an Executive Board, consisting of the project’s donors, high burden countries and representatives from affected communities. Rules to disclose and manage potential conflicts of interest would be created. The work of the Executive Board would be informed by a technical advisory committee within the WHO that would analyse and provide data on causes of fever in different geographic regions; draw on expertise within WHO on quality assurance of medical devices and on standards for interoperability of devices in order to inform and align the work of the Executive Board. The Executive Board would set high-level policies and enter into a contract with one or more entities to manage a portfolio of grants and innovation prizes. We anticipate that the Special Program for Research and Training in Tropical Diseases (TDR), UNITAID or the World Bank would be among the entities that could manage the grants and/or prizes portfolio.

19. Have any donor agencies/governments already indicated interest in supporting the project?

On October 23rd 2013, representatives of health authorities in the Americas selected, by consensus, this proposal as one of the proposals to represent the region before the Committee of World Experts that meets in December in the World Health Organization (WHO). MSF has also shared this proposal with countries in other WHO regions.
References: