

The Open Source Fever Diagnostic Project

Proposal for a CEWG Demonstration Project

WHAT IS THE ‘OPEN SOURCE FEVER PROJECT’?

The aim of ‘open source fever project’ is to create a new ecosystem for financing the development of an open source, multiplex, point of care (POC) diagnostic test for the differential diagnosis of fever or sepsis. This project incorporates novel approaches to financing in order to accelerate innovation and provide more equitable access to better diagnostic tools. It has been developed based on the principles and recommendations put forward in the 2012 WHO Consultative Expert Working Group (CEWG) report and the 2008 WHO Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property (WHA 61.21).

The proposal uses ‘push’ funding to finance R&D activities upfront, ‘pull’ funding to incentivise R&D activities through the promise of financial rewards on the achievement of specific objectives and does so in a way that fully separates or “de-links” the cost of the R&D from the price of the resulting diagnostic device so that access and affordability are ensured. All funded technologies will be fully disclosed and available for use and license to third parties.

WHY DO WE NEED THE ‘OPEN SOURCE FEVER PROJECT’ FOR FEVER & SEPSIS

Fever is the most common presentation of infections and it is the most common reason for hospital admission in low-income countries. 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, as initiation of 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.

The need for a diagnostic test that is able to differentiate between the different origins of fever is integral to the progress of promoting global health, and avoiding the complications of non-specific and haphazard medical management. Furthermore, these tests must account for the fact that febrile illnesses in low-resource settings may be caused by a multitude of geographically restricted infections and neglected tropical diseases, such as salmonellosis, dengue fever, tick-borne infections, visceral leishmaniasis, and human African trypanosomiasis.

ABOUT THE WORLD HEALTH ORGANIZATION’S CALL FOR R&D PROPOSALS

The World Health Organization (WHO), as part of its broader efforts to address health R&D gaps for the poor, is conducting a process whereby member states will support “health R&D demonstration projects” aimed at developing health technologies (medicines, diagnostics, medical devices, vaccines, etc.) for diseases that disproportionately affect developing countries and for which identified R&D gaps remain unaddressed due to market failures.

MSF’s ‘open source fever project’ proposal is one of 24 proposals selected by WHO regional offices to be considered by a group of experts at the WHO’s Global Technical Consultative meeting in December 2013. The experts will develop a shortlist of projects to be considered at the WHO Executive Board and World Health Assembly in January and May 2014, respectively.

BACKGROUND: WEAKNESSES IN THE CURRENT R&D SYSTEM HINDER INNOVATION FOR DIAGNOSTIC TOOLS FOR FEVER AND SEPSIS

INADEQUATE FINANCIAL INCENTIVES FOR INNOVATION: The market for a fever diagnostic is far less lucrative than for other technologies and is therefore marked by underinvestment. 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.

BARRIERS TO R&D FOR LOW COST DIAGNOSTICS: While there is interest by some manufacturers to produce a multiplex POC fever platform using new molecular techniques, there are patent thickets that inhibit the application of new technologies which would improve its feasibility. For developers that have successfully navigated the patent barriers, the diagnostic platforms do not allow for the development and inclusion of other assays. For example, while the GeneXpert rapid diagnostic test 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 are permitted to do so.

ACCESS AND AFFORDABILITY NOT GUARANTEED: Even when products come to market, they may not be affordable for L&MICs where disease burden is highest. There are 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.

AN ECOSYSTEM APPROACH TO R&D FINANCING

This project is designed to create multiple mechanisms to finance development of 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.

STEP 1: ENCOURAGE RESEARCH AND DEVELOPMENT OF KEY OBJECTIVES TOWARD ACHIEVING FEVER DIAGNOSTIC THROUGH GRANTS AND MILESTONE PRIZES: Milestone prizes will be given to reward the successful achievement of specific research objectives considered useful in the overall process of achieving the end goal of the diagnostic device (e.g. the development of a biomarker that distinguished between viral and bacterial causes of fever). Grants or contracts will also be used to fund research where project managers feel more confident in their ability to identify and manage research projects to achieve research objectives or where prizes are considered too costly to manage. A Target Product Profile (TPP) being developed for this test is targeted for use in district health settings for patients (neonates, children, and adults) presenting with fever. 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.’

STEP 2: ACCELERATE PROGRESS THROUGH ADDITIONAL GRANTS AND PRIZES: Biannual best progress prizes awarded every two years will reward the best progress toward the development of the diagnostic device. End product prizes will be available to one or more entities that achieve the desired end goal of the diagnostic device. If funding of the end product prize is sufficiently large (up to \$100 million), the threshold to qualify will be lower, and the result will be the development of multiple competing designs that divide the prize money. If funding of the end product prize is less than \$20 million, qualifying criteria will be more difficult, and the prize will be awarded to the first contestant or set of contestants to qualify during a round of the periodic evaluation of designs in the competition. This is the most expensive element of the project but also the least risky to donors because the money will only be spent if a design achieves the desired end goal.

STEP 3: ENSURE OPEN ACCESS AND LICENSING OF INTELLECTUAL PROPERTY RIGHTS, DATA AND KNOW-HOW FOR FOLLOW-ON INNOVATION: Grants and innovation prizes will be awarded in exchange for the open licensing of intellectual property, data and technology transfer that will create an open and competitive environment for access to research outcomes. This will allow other innovators to build on the progress already accomplished by the project’s winners and competitors. Additionally, open source dividends of between 5-10% of the end product prize money will be given to parties not directly affiliated to the contestant with the winning design. In order to qualify for the open source dividend, a potential recipient must have provided royalty-free and non-discriminatory access to knowledge, data, materials or technologies that were integral to the successful development of the project that won the end product prize. This prize will be awarded by a temporary jury of experts who will receive nominations for the prize and allocate the prize money based upon the evidence from the nominations.

STEP 4: SECURE PRODUCTION OF THE DEVICE AND ENCOURAGE COMPETITION FROM MULTIPLE MANUFACTURERS THROUGH OPEN LICENSING OF INTELLECTUAL PROPERTY AND TRANSFER OF KNOW-HOW: Once the device and testing components are developed there will be no IPR barriers to their production by multiple firms. Joint ventures, collaborations with a PDP or local production are all possibilities as regards suppliers.

For the prize winner, standards for affordability and access would focus on price ceilings and a market penetration test. Price ceilings would be established for both the device itself and the incremental cost of testing. 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.

In addition, the promotion of competition in the manufacture of the device will act to ensure prices stay low in the long term and that incremental improvements are made.

FINANCING & ADMINISTRATION: The cost of the project is expected to be between US \$70-\$200 million, depending on the level of donor support. Governance of the project would include a Donor Committee, responsible for setting high-level policies and facilitating contracts with one or more entities to manage a portfolio of grants and innovation prizes (for example, the Special Program for Research and Training in Tropical Diseases (TDR), UNITAID, or the World Bank). Financing for the projects and research is flexible; donors will have the opportunity to provide general support for the project, which the Donor Committee would allocate to either grants or innovation prizes, or to choose to fund either grants or innovation prizes. Thus donors who have more confidence in the value of grants than prizes can put their money into grants. Donors 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 fact that donors 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 donors who have more confidence or preference for a particular mechanism.

CONCLUSION: The new ecosystem approach proposed in this project 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. It offers multiple benefits compared to the current market incentives for development of diagnostic tools for use in developing countries:

By facilitating research and encouraging innovation by the above-stated mechanisms and approach, the project hopes to create a fever diagnostic test that accomplishes the following tasks:

- enables health workers in low resource settings to more accurately diagnose the underlying cause of fever in their patients and provide appropriate treatment leading to improved morbidity and mortality, rather than relying on empiric treatments and generalized treatment algorithms;
- reduces or avoids the inappropriate use of antibiotics and thus helps reduce the prevalence antibiotic-resistant organisms;
- It corrects market failures, by providing robust rewards for successful product development of a tool that provides a differential diagnosis of fever and sepsis;
- It rewards unconventional approaches to problems and unanticipated interim achievements in the development of a more interoperable and extendable technology;
- It ensures open sharing of knowledge, data, materials, technology and know-how for future innovation. The open-source dividend is a particularly novel and potentially revolutionary approach to incentivizing open-access research.

Sources:

1. Reddy E., Shaw A.V., Crump J. Community-acquired bloodstream infections in Africa: a systematic review and meta-analysis. *The Lancet Infectious Diseases* 2010; 10:417–32.
2. Crump J., Gove S., Parry C.M. Management of adolescents and adults with febrile illness in resource limited areas. *BMJ (Clinical Research Ed.)* 2011; 343:d4847.
3. Vial L., Diatta G., Tall A., et al. Incidence of tick-borne relapsing fever in West Africa: longitudinal study. *Lancet* 2006; 34: 295-303.
4. Marlet M.V., Sang D.K., Ritmeijer K., Muga R.O., et al. Emergence or re-emergence of visceral leishmaniasis in areas of Somalia, northeastern Kenya, and southeastern Ethiopia in 2000-2001. *Trans R Soc Trop Med Hyg* 2003; 97: 515-8.