Standard Template for a Candidate Demonstration Project

Note: the questions with asterisk should be filled.

1.* Title of the project:

Multiplexed Point-of-Care test for acute febrile illness (mPOCT)

2.* Submitted by:

Left blank to facilitate impartial evaluation.

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.)

Febrile illnesses (Dengue, Malaria, Typhoid/Paratyphoid, Chikungunya, Scrub Typhus, Leptospirosis) which mainly fall in Type II and III disease category.

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

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

Diagnostic device. The goal of this project is to develop affordable yet high quality field deployable single multiplex point-of-care test (POCT) for major febrile illnesses prevalent in the tropical and subtropical countries. To achieve the final goal, we have proposed three parallel subprojects which are 1) Generation of high quality multi-country sera panel for major febrile illnesses. Evaluation of POCT with clinical samples from tropical and subtropical countries (SEARO region) is prerequisite as regional background antibody titers must be determined to tune the cut-off value; 2) Generation of pathogen specific diagnostic intermediates (antigen/antibodies) and development of high quality lateral flow based multiplex POCT; 3) Generation and evaluation of affordable handheld mobile phone based test reader which will improve both the sensitivity and specificity of the test.

5.* Project summary:

Acute fever or acute febrile illness (a rapid onset of fever and symptoms such as headache, chills or muscle and joint pains) is common in the tropics and sub-tropics and can be caused by very diverse pathogens[1-3]. Differential diagnosis of these etiologies based on clinical criteria alone is not possible as clinical signs and symptoms of most of these infections are very similar and the correct diagnosis is only possible by using pathogen specific diagnostic tests. For patient treatment and management, differential diagnosis of causative agent is required [1-3]. In low income countries, many preventable deaths occur because of delayed or lack of correct diagnosis. In last few years, extensive efforts to control malaria are resulting in positive outcome. In fact, non-malarial febrile illnesses (NMFI) cause more deaths than malaria even in malaria-endemic countries and in the absence of accurate or available diagnostics for NMFI, many non-malarial fevers are treated as malaria which is contributing in the generation of artemisinin resistance [1, 2, 4, 5]. Based on these facts, availability of multiplex test which can quickly identify a pathogen from a group of pathogens that cause the similar symptoms is of paramount importance not just from medical standpoint but will also have much greater public health relevance[1].

There are many state of the art diagnostic platforms and techniques available which can be used for multiple target screening in a specimen e.g. advanced multiplex nucleic acid tests, array based immunoassays and bead/flow based assays [6-8]. Unfortunately, these platforms are not suitable for most of the developing countries as these tests tend to involve
complex equipment, are expensive and not proven to be robust in field situation where constant power supply is problem and regular maintenance is a challenge. In the resource-limited settings, the impact of diagnostic tests that can be provided at immediate point-of-care is potentially even greater, because the alternative to a POC test (POCT) may be no diagnostic support at all [8]. Based on these facts, in this proposal, we have decided to use simple field deployable lateral flow formats, which with some innovation, can be used for the generation of multiplex test for at least 5-6 major high-burden pathogens responsible for AFI in tropical and subtropical regions of the world especially SEARO region. Based on literature search, infectious diseases which cause major burden of AFI and also amenable to multiplexing include Malaria, Dengue, Typhoid/Paratyphoid, Chikungunya, Leptospirosis and Scrub Typhus [1-3, 5, 9]. These are the diseases that are proposed to be targeted by multiplex POCT.

Despite the strong need, no multiplex POCT is available in market which can be used in resource limited settings for the detection of multiple etiologies of AFI. Although, individual (singleplex) POCTs for the chosen infections (Dengue, Malaria, Typhoid/Paratyphoid, Chikungunya, Scrub Typhus, Leptospirosis) are commercially available but most of these tests are of poor quality. Only the POCTs for malaria (because of FIND/WHO extensive evaluation program), and to some extent Dengue NS1 Ag, fulfill WHO ASSURED criteria [1, 5, 10]. The POCTs for infectious diseases developed in developed countries are often imported by developing countries but these tests are generally very expensive and also do not perform to the mark in the developing countries. Major reasons for poor performance of available tests are: 1) Not sufficient financial incentive to develop high quality rigorously evaluated tests for developing countries; 2) Use of poor quality antigen/antibodies; 3) lack of knowledge about specific target(s) of particular pathogen which causes problem of cross-reactivity; 4) Lack of evaluation using local clinical specimen (inappropriate cutoffs) ([8, 10, 11]. Because of the problems in available singleplex tests, we also propose to generate high quality diagnostic intermediates/reagents for each pathogen. Here, we also propose to generate, affordable handheld mobile phone based test reader which will improve both the sensitivity and specificity of the test as the reader will remove the subjectivity involved in reading the test line or dot.

**Strategy:** The strategy will involve parallel/simultaneous detection of IgM antibodies against particular pathogen and pathogen specific antigen in whole blood or serum. For *Plasmodium falciparum* and *P. vivax*, antigen will be detected. For Dengue, both antigen and IgM will be detected. For *S. Typhi/ Paratyphi A, Leptospira spp., Orientia tsutsugamushi* and Chikungunya virus only IgM antibodies will be detected. We will utilize fused strip approach for multiplexing as this approach allows incorporation or removal of any target from the panel, without affecting the performance for other targets. This is very important as the prevalence of different pathogens varies between regions. Another advantage of fused strip approach is that it’s an open system and can be manufactured by many diagnostic companies present in developing countries without any IP issues related to the platform. In this project, we will also develop a mobile based assay reader which will improve both the sensitivity and specificity of the test as the reader will remove the subjectivity involved in interpreting the results. The reader will also remove dependence on colloidal gold tracer which is not very sensitive. The proposed reader will also be capable of transmitting data to central server which will help in disease surveillance and will have greater public health significance. The high quality multi-country sera panel for major febrile illnesses will also be generated in this project. Evaluation of assay using clinical samples from developing world/SEARO region is prerequisite as regional background must be determined to tune the cut-off value [10]. The whole project will be guided by the WHO ASSURED criteria. THSTI, India will play role of coordinator (nodal point) for this project.

6.* **Public health need 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
Effective treatment requires correct diagnosis, but many febrile illnesses have similar signs and symptoms. In the absence of field deployable POCTs, healthcare workers use an empirical approach to the treatment of a fever. This leads to inappropriate use of anti-bacterial drugs (promoting antimicrobial resistance) and unfavorable clinical outcomes. POCTs for malaria are increasingly available; however negative malaria test result does not provide guidance for alternative diagnosis of the patient [1]. In the absence of multiplex tests for AFI, non-malarial fever cases in many endemic regions are still treated as malaria. Undifferentiated fever is also one of the most common reasons for hospitalization in low-income countries. The identification of disease causing agents is of utmost importance, not only to patient and healthcare providers, but the pathogen identification also has public health relevance that goes beyond an individual patient [8]. Some of the major public health impacts of proposed multiplex tests are:

1. Accurate diagnosis and etiology based treatment and management will result in favorable clinical outcomes and will prevent severe illness and deaths in developing world.
2. Etiology based treatment will prevent overuse and misuse of antibiotics and anti-malarials, thus ultimately reducing the onset of antibiotic and antimalarial drug resistance.
3. The use of handheld/mobile phone connected reader will alert the public health system in the early stage of epidemic which may help to curb the spread of pathogen by public health interventions.
4. The multiplex POCT combined with mobile reader will also generate surveillance data and this kind of data will help in setting the public health priorities for malarial and NMFI e.g. need for vaccination, vector control, drug resistance.
5. The proposed system will also help in clinical trials of vaccines for malaria and NMFI in terms of determining the sites for trial (overall burden of different febrile illnesses) and also in determining the efficacy of vaccines.

Based on literature search, the infections which are mainly responsible for AFI in tropical and subtropical part of the world especially SEARO region and also amenable to multiplexing include Malaria, Dengue, Typhoid/Paratyphoid, Chikungunya, Leptospirosis and Scrub Typhus.

Epidemiology
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 delinkage 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.”)

Open platform: The lateral flow platform is being proposed for the development of a multiplexed POCT for six pathogens. The major advantage of this format is that it is available in the public domain and is free from IP issues. Importantly, the tests in this format can be manufactured by companies from developing countries. The proposed multiplexing approach also allows the incorporation or removal of any target from the panel, without affecting the performance for other targets.

Product Development Partnerships: For the present project, the public players such as WHO-TDR, DBT could be partnered in consortium mode with BMGF and various NGOs for various stages of product development. In the initial discussions, some of the agencies mentioned have
already shown interest in the concept along with ministry of health, Govt. of India.

**Delinking the cost of R&D from the product price:** De-linkage of the R&D cost from the product price is a radically new approach and is profoundly different from that which seeks to sustain R&D through legally enforced time-limited monopolies on new products. De-linkage eliminates monopolies on final products and permits a much more decentralized system of manufacturing, distributing and marketing. In the proposed project, the de-linkage component is already in-built to large extent, since this will essentially be a public-funded project.

**Field testing and validation:** This will be carried out by a consortium of stakeholders including hospitals/clinicians from SEARO countries including those mentioned in point number 11. These will essentially be the partners who engage in creation of a well-defined sera panel for this purpose. This activity will be coordinated from THSTI with support from WHO-TDR and FIND.

### 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.)*

There are not sufficient financial incentives to develop high quality rigorously evaluated tests for developing countries. Because of this reason even the singleplex test available for individual pathogens are of poor quality. One major reason of poor performance is that these tests are generally not validated on clinical specimen from different geographical regions and use inappropriate cutoffs. Most of the singleplex tests for selected pathogens are manufactured in developed countries and therefore are very expensive. There is no multiplex POCT available, as this kind of test requires lots of R&D efforts and rigorous testing and generally useful for particular geographical areas. Because of the problems mentioned above we are proposing the development of high quality, field deployable multiplex POCT for six pathogen which are major cause of fever in tropical and subtropical region of the world especially SEARO region.

*(Approximately 200 words)*

### 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)*

The feasibility of achieving the goals of the proposed project is very high both scientifically and technically as the partners in the project have all relevant expertise, know-how and prior experience to perform the proposed tasks. In past ICGEB has developed several rapid POCTs for several infections which are in market including test for dengue NS1 antigen and antibody detection. Centre for Biodesign and Diagnostics of THSTI has mandate to develop diagnostic assays and technologies which can be utilized in developing countries. Researchers at THSTI have the know-how and experience for identification of new pathogen specific target and also the development of diagnostic assay. Division of Biotechnology, University of Turku, Finland (DBUT) has more than 20 years’ experience in label technologies, assay development and instrument design. Many assays and technology platforms developed at DBUT are in market. DBUT also has experience in using non-gold labels in lateral flow assay which results in increased sensitivity. Designinnova, India has experience in the development of portable UCP reader for lateral flow strips and it will use this experience for the development of handheld mobile phone based reader. Other partners mentioned in the section 11 also have previous experience and expertise to fulfill the respective tasks. THSTI and ICGEB are already working on dengue, typhoid and leptospirosis diagnostics.
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.)

The proposed project presents unmet needs, which, if fulfilled, will be able to differentially diagnose millions of cases, not only in the SEARO region, but throughout the tropics and sub-tropics. Proper diagnosis will save unnecessary mistreatment with antibiotics and antimalarials where there is no need e.g. viral fever. Importantly, a proper diagnosis will ensure that the correct antibiotic is started promptly and at the correct dosage, thereby discouraging the emergence of resistance. Multiplexing using a lateral flow format is feasible, and a workable plan is proposed. The incorporation of mobile phone based reader will greatly enhance the utility of multiplex POCT not only in-terms of overall test performance but also in-terms of surveillance and will also have other public health impacts.

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?)

As the proposed project has many sub-objectives, the goals can only be achieved by collaborative approach. The Centre for Biodesign and Diagnostics (CBD), Translational Health Science and Technology Institute (THSTI) will coordinate the consortium. THSTI is well placed to carry out multidisciplinary research, as it covers the entire translational pathway for product development. It has an expanding network with clinicians and hospitals where the latter phases of the project can be implemented.

**Generation of well characterized sera panel**

- Centre for Biodesign and Diagnostics, Translational Health Science and Technology Institute, Gurgaon, India (Quality control)
- Faculty Of Medicine, University of Kelaniya, Sri Lanka
- Department of immunology, Department of Gastroenterology, Sanjay Gandhi Postgraduate Institute of Medical Sciences (SGPGI), Lucknow, India (Prospective partner)
- Christian Medical College, Vellore, India (Prospective partner)
- Kasturba Medical College (KMC), Manipal, India (Prospective partner)
- Fortis Hospital, Delhi/Gurgaon (Prospective partner).
- Center for Emerging and Neglected Infectious Diseases, Mahidol University, Bangkok, Thailand (Prospective partner).
- Department of Virology, Haartman Institute, University of Helsinki, Helsinki, Finland (Traveler’s sera panel)
- Partners from other countries may also be included.

**Development of handheld reader**

- DesignInnova, New Delhi, India (Reader development)
- Division of Biotechnology, University of Turku, Turku, Finland (Reader development and evaluation)
- Recombinant Gene Products group, International Centre for Genetic Engineering and Biotechnology, New Delhi, India (Evaluation)
- Centre for Biodesign and Diagnostics, Translational Health Science and Technology Institute, Gurgaon, India (Evaluation)
Generation of pathogen specific reagents
- Centre for Biodesign and Diagnostics, Translational Health Science and Technology Institute, Gurgaon, India
- Recombinant Gene Products group, International Centre for Genetic Engineering and Biotechnology, New Delhi, India
- Division of Biotechnology, University of Turku, Turku, Finland

Assay development and multiplexing
- Centre for Biodesign and Diagnostics, Translational Health Science and Technology Institute, Gurgaon, India
- Division of Biotechnology, University of Turku, Turku, Finland

Field Evaluation
- Centre for Biodesign and Diagnostics, Translational Health Science and Technology Institute, Gurgaon, India (Quality control)
- Faculty of Medicine, University of Kelaniya, Sri Lanka
- Department of immunology, Department of Gastroenterology, Sanjay Gandhi Postgraduate Institute of Medical Sciences (SGPGI), Lucknow, India (Potential partner)
- Christian Medical College, Vellore, India (Potential partner)
- Kasturba Medical College (KMC), Manipal, India (Potential partner)
- Fortis Hospital, Delhi/Gurgaon (Potential partner).
- Center for Emerging and Neglected Infectious Diseases, Mahidol University, Bangkok, Thailand (Potential partner).
- Department of Virology, Haartman Institute, University of Helsinki, Helsinki, Finland (Traveler’s sera panel)
- Partners from other countries may also be included.

Manufacturing and marketing
- J Mitra & Co. Pvt Ltd, India (Potential partner)
- Tulip group of diagnostics, India (Potential partner)
- Trivitron (Ani Labsystems) Finland/India (Potential partner)

Evaluation of kits (product) manufactured by diagnostic companies
- FIND with partners involved in sera panel generation and field evaluation

12. Who could potentially manufacture the final product?
Multinational company? Local production? Joint venture? How the decision will be made about the producer?

As we are going to use an open platform (lateral flow) for test development, many diagnostic manufacturers in developing countries have capacity and proven track record for manufacturing. In the initial discussions many local manufacturers have shown interest in the concept and on successful completion of this project these companies may manufacture the test. Some of the prospective manufacturers are J Mitra & Co. Pvt Ltd, India, Tulip group of diagnostics, India and Trivitron (Ani Labsystems), Finland/India. For manufacturing of reader, two local companies have shown interest in the initial discussions. While local production will ensure that the cost of the product will remain low and therefore affordable, a joint venture would be the preferred pathway if another WHO Region would want to develop a similar product, and the two product development efforts could be clubbed together. This could be decided by a joint meeting of all the stakeholders from the various regions in a common forum, preferably organized and coordinated by the WHO and FIND.
13. What could be the role of WHO, if any, in this demonstration project to bring this venture to fruition?

It is envisaged that WHO would play a very crucial role for the successful implementation of this project. WHO is very well placed, with its unique knowledge of disease situation in different regions. It also has a vast experience with development of recommendations on a country, regional as well as global basis. WHO can also get the various stakeholders on board including donors and health ministries of different countries.

The design and assembly of the reference panel is the most crucial element for the development and evaluation of diagnostic assay. WHO-TDR has prior experience and expertise in the generation of specimen panel for diagnostic evaluation. We require WHO-TDR technical support for quality control and distribution of sera panel required during 1) development of the assay; 2) validation of tests post technology transfer and manufactured by different companies to meet QC for bulk purchase by each country for use in their health system. Endorsement of high quality test by WHO will also be very crucial as this will help end-user choosing the right product.

(Approximately 200 words)

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?

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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 main platform to be used in the project is the lateral flow. This platform is in public domain and being used by diagnostic manufacturers around the globe. The other component of the POCT is obviously the immuno-reagents (antigen and antibodies) and detection labels. These reagents need to be of highest quality and standard. Importantly, standardization and optimization will be carried out in-house. In the limited search, we didn’t find any major IP issue or need for licensing in the technology. If patenting issues arise in future, the Biotechnology Industry Research Assistance Council (BIRAC), an enterprise of the Department of Biotechnology (DBT), Govt. of India, will help in this matter as they have patent experts in-house.

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)

De-linkage of R&D cost from product cost: As mentioned before, if the R&D cost can be de-linked from the product cost, then this will ensure lower price of the final product and therefore greater affordability.

Bulk Procurement: It is envisioned that the final product will be introduced into the public health system. The idea of having the Ministry of Health on board is to have assurance that this diagnostic test, if successfully developed, will be taken-up by the public health system. Therefore, in this type of scenario, it is envisaged that the diagnostic kit will be bulk-Procured for streamlined supply to the public health system.

Advance Market Commitment: Since the final product is being targeted to public health system, the Governments will be in a position to give assurance, in the form of an advance market commitment (AMC) that a certain volume of product will be utilized by the public sector. Therefore, the company who will manufacture the product without having to worry about the sustainability of its product, since a large bulk will be procured by the public sector. The AMC will ensure a robust supply chain.

Storage and Prescription: These diagnostic kits would ideally be stored at room temperature, thereby circumventing the need for a cold-chain.

Dispensing and Compliance: These diagnostic kits would be dispensed from primary health centers (PHCs). The so-called “last mile” delivery will be implemented by Accredited Social Health Activists (ASHAs), who have been instrumental in the National Rural Health Mission (NRHM) of the Govt. of India. They will ensure patient compliance. In other countries also similar kind of approach may be applied.

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 type of international project involves multiple stakeholders. One of the most crucial elements in the implementation of the project involves the smooth flow of funds. Some innovative strategies could be adopted if there are multiple sources of funding. Importantly, since the various places will be physically separated there will be a need to link them up. An innovative model exists in this regard – “The Pearls on a String”. What is essentially done in this model is to devise strategies to link these “pearls” with a string. This type of strategy will ensure that the various scattered “strengths” are properly linked-up. This will not only ensure better governance and coordination, but will also ensure smooth flow of funds.

An innovative form of financing can also be instituted after the product is developed and which will ensure better penetration and uptake of the product. A mechanism should ensure that the product is made available to selected organizations at lower cost with a lower profit margin. Since acute febrile illnesses are very common affliction, the lower profit margins will in the long run be compensated by the sheer volume or bulk of the ordered tests. This type of strategy has already been implemented for GeneXpert test for diagnosing TB. Therefore, this innovative financing strategy could well pay off in case of POCT for acute febrile illness also.

The estimated cost of this project would be around 20 million USD.

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

Proper governance and coordination is the key to the successful implementation and outcome of any
R&D project. Therefore, a proper governance structure needs to be put in place. Whether the existing institutional framework will be able to support this kind of R&D endeavor, or there needs to be a revamping of the governance structure in order to cater to the increased workload during the implementation phase of the project, needs to be carefully looked-into, debated and evaluated. There will probably be a need for a nodal officer for the project, who will be the ideal link and contact point for the WHO as well as other stakeholders. The nodal officer will constantly be appraised by the PI of the latest research findings, progress of the project as well as the current status of the project with particular reference to the pre-determined timeline. Importantly, the nodal officer will be one of the key players who will ensure that the timeline is being properly adhered-to. It is envisaged that this will lead to a better modus operandi and much better coordination amongst the various stakeholders that will lead the project to a fruitful and timely conclusion.

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

The parent funding agency of THSTI, namely the Department of Biotechnology (DBT), Govt. of India, has shown keen interest in supporting the project. DBT funds projects in the area of Biotechnology product development, and has a brilliant track record of funding major projects in these areas of scientific endeavor. Importantly, DBT has a number of bilateral collaborative initiatives not only within the country (with the Indian Council of Medical Research [ICMR]), but also with foreign countries (Indo-Finnish, Indo-Swedish etc.). Therefore, DBT is in an ideal position to take up this project, especially with collaborations with foreign nations that WHO might identify. Importantly, ICMR, which is a century-old organization and has a vast experience in carrying out product-testing activities in field settings, could be roped-in to fund the testing activities that will arise down the line in the product development pipeline. Moreover, the Ministry of Health and Family Welfare, it goes without saying, is the major nodal agency that has taken a keen interest in the project since its conceptualization stage. Therefore, there are a number of government agencies that could potentially support this R&D endeavor.

References

8. Microbiology, A.A.o., Bringing Lab to the patient: developing point-of-care diagnostics for resource limited settings, A. Reid, Editor 2012: Washington, DC.


