Standard Template for a Candidate Demonstration Project

Note: the questions with asterisk should be filled.

1.* Title of the project:
Development of a long acting dosage form of penicillin for the prevention of recurrent acute rheumatic fever rheumatic heart disease

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.)

Acute rheumatic fever (ARF) occurs as an immune mediated complication of infection with group A Streptococcus (GAS) that in turn leads to long damage to the heart (rheumatic heart disease; RHD). Recurrent GAS infection and ARF causes cumulative heart damage that causes the majority of the burden of RHD. Recurrent infection can be prevented by prophylactic penicillin treatment, breaking the cycle of worsening RHD, but unfortunately this requires painful injections at least four weekly for a minimum of 10 years. ARF and RHD are however diseases of poverty, with overcrowding, poor hygiene and lack of access to health care the major determinants of developing both ARF and RHD.[1] In these settings, providing monthly penicillin injections over a prolonged period is logistically impossible. This project will develop a long acting form of penicillin treatment that will last for at least six months to provide a practical and less painful method of preventing RHD and decreasing the significant worldwide burden of disease from this preventable condition.

ARF and RHD are type III* diseases affecting at least 15 million people worldwide.[1] An estimated 95% of cases of ARF occur in developing countries.[1] Of those people with RHD, 79% live in developing countries, with the remainder occurring in those in socioeconomically deprived and Indigenous communities in high resource settings.[2]

*A November 2012 discussion document suggested that RHD be considered a type II disease based on relative disability-adjusted life year (DALY) burden attributed by the Global Burden of Disease (GBD) project.[3] As participants in GBD Expect Group for RHD we are in the process of improving modeling of the DALY burden of RHD in low-middle income countries.

4.* The suggested health technology that project seeks to develop:
(e.g. medicine; diagnostic test; medical device; vaccine etc.)
The project will develop a long acting, affordable formulation of penicillin for the prevention of recurrent ARF and RHD, thereby providing a practical and less painful way of preventing unnecessary morbidity and mortality from RHD.
5.* Project summary:

ARF is a post infectious, immune mediated complication of infection with the bacteria Group A Streptococcus (GAS) that in turn leads to heart damage (RHD).[4] Recurrent GAS infection in patients with previous ARF leads to cumulative heart damage that causes most of the burden of RHD. Penicillin can prevent this recurrent infection and worsening of RHD, but current drug formulations are not appropriate for long term use. ARF and RHD occurs in developing settings where overcrowding, poor hygiene and lack of access to health care leads to frequent and severe GAS infection.[4] ARF occurs most commonly in children and young adults.[5] Consequently, RHD impacts on young adults in their most economically productive years, and through the associated morbidity and premature mortality, has a huge impact on society.[5] There is no cure for established RHD; costly, largely palliative, heart surgery is a last resort.[6] This project aims to prevent the suffering and unnecessary deaths caused by RHD by developing a novel penicillin formulation that will prevent recurrent GAS infection and ongoing heart damage in patients with ARF.

Penicillin is currently administered via monthly, painful intramuscular injections of benzathine penicillin G (BPG) for at least 10 years.[7] This is logistically difficult and expensive, especially in developing world settings. Further, even when regular BPG injections are delivered, the quality and global supply of BPG is sub-optimal.[8] Generic formulations have been associated with lower than expected serum concentrations of penicillin after administration, as well as practical concerns such as blocking in the administering needle.[9, 10] Hence most patients at risk of RHD do not receive adequate penicillin prophylaxis, and patients continue to suffer with, and die of, preventable heart disease.

This project will develop a method of penicillin administration that last for at least 6 months thereby providing a practical, affordable, pharmacologically stable and less painful method of treatment compared to monthly injection, allowing maintenance of adequate serum penicillin levels. For penicillin prophylaxis to be adequate, serum penicillin levels must be maintained above the minimum inhibitory concentration (MIC) of GAS. GAS is exquisitely sensitive to penicillin, and GAS resistance to penicillin has never been reported despite prolonged use in extremely large numbers of people. These features support the theoretical application of long acting, slow release formulations for the secondary prophylaxis of ARF. Our current work is focused on combining penicillin with existing slow release technologies that are being tested in rat models to determine which formulations provide the optimal release kinetics. This application relates to the ongoing clinical development of this technology, namely phase one and two safety studies and pharmacokinetic equivalence studies, followed by phase three efficacy studies. Following this, it is planned that the long acting penicillin formulation would be rolled out to those requiring secondary prophylaxis with phase four studies providing the ongoing surveillance for this technology. Ultimately, a long acting penicillin formulation would revolutionize management of RHD worldwide by vastly increasing the number of patients successfully treated, thereby preventing RHD and ultimately decreasing mortality from this disease.
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 provide some basic level information)

RHD is the most common acquired heart disease of young people in the developing world. At least 15 million people live with RHD, of whom 79% are from developing countries, with the remainder accounted for by the Indigenous populations of developed countries. Recent analysis and data from the Global Burden of Disease (GBD) project suggests that the true burden of disease is much higher, with nearly 30 million prevalent cases. The annual incidence of ARF in 5-15 year olds ranges between 10/100,000 (high resource settings) and 374/100,000 (low resource settings). The peak incidence of ARF is between 5 to 15 years with RHD presenting in late adolescence and early adulthood. In developing countries up to 70% of patients die before 26 years of age. Mortality from RHD has been conservatively estimated at 1.5% annually but measured at up to 12.5%. RHD accounted for 1,430 DALYs in 2010, equivalent to one quarter the burden of all malignant disease.

The only proven intervention to stop the progression of RHD is secondary prophylaxis with penicillin. This intervention is limited by the requirement for monthly, painful intramuscular injections for at least a decade. Adherence to secondary prophylaxis regimes is poor; most programs are unable to deliver the threshold of 80% of scheduled injections to more than half of people. Even in developed countries, administration of penicillin has proved to be beyond public health capabilities. Novel and concerted attempts to improve adherence have made little impact over a number of decades.

The novel technology proposed herein will provide a longer acting formulation of penicillin, facilitating the prevention of severe RHD by providing reliable, effective secondary prophylaxis, interrupting the cycle of recurrent ARF causing progressive RHD. Further, this technology would reduce the individual and health system burden of prophylaxis delivery and address the safety and quality concerns around BPG.

(Maximum 400 words)
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.”)

ARF and RHD is a disease of poverty. The only proven intervention that prevents the progression of heart disease is penicillin over a prolonged period. Despite the need for, and availability of penicillin, it is to date not been formulated in such a way as to be deliverable to those in need in developing world countries. This project aims to combine established slow-release technologies to provide an improved formulation of penicillin that can be used for the prevention of RHD.

This improved penicillin formulation is being developed by a novel collaboration between research experts, pharmaceutical specialists and project management experts. As we move forward to the clinical phase of this project it is hoped that many more collaborative partners, especially WHO, can be engaged to ensure that this product is affordable, suitable and deliverable to those most in need.

Affordability of the implant to developing world settings in paramount to the success of this project. Through a segmented market approach to funding, engagement of philanthropic organizations currently involved in RHD management, developing world manufacturers and with the input of the WHO this project will deliver this much needed intervention to those with ARF/RHD worldwide.

As an adjunct to this project, a health economic analysis of the impact of untreated ARF/RHD will be undertaken. Part of this work will better estimate the cost of inadequate secondary prophylaxis delivery. Modelling the savings from improved secondary prophylaxis with a long acting penicillin formulation will help inform price setting and potentially facilitate release of government funds.

(Maximum 300 words)
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.)

Rheumatic fever received a scant 0.1% of global funding for neglected diseases between 2007 and 2011.[17] Innovation in BPB formulations has been hampered by the small market for RHD prophylaxis and a shift towards new antibiotics for other indications.[8, 18] BPG was developed in 1951 and is a WHO Essential Medicine, but despite this, access to quality assured supplies is limited in many countries.[19] [8] A branded, liquid, cold-chain dependent formulation is available in high income settings. This represents a minority of the global demand for BPG however, and a scant segment of an already small market. Powdered formulations are produced by an array of generic manufacturers for use in resource limited settings. This fragmented market complicates quality assurance and consumer confidence. Significant concerns about quality and safety of these formulations exists. Provider and patient fears about adverse drug reactions hamper delivery of secondary prophylaxis in many settings. The powdered formulation is difficult to suspend in solution and requires a large gauge needle, contributing to painful injections and frequent needle blockages. A novel formulation would address these challenges by providing a quality assured product backed by recent and reliable safety data.

(Maximum 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)

To prevent RHD, blood levels of penicillin must be sustained above the MIC for GAS, interrupting the cycle of recurrent infection, ARF and worsening RHD. Injectable BPG currently provides the most safe and effective way to sustain penicillin levels, but is limited by the requirement for at least monthly dosing. The ongoing worldwide burden of RHD is attributable to a failure of drug delivery rather than of penicillin itself. A sustained release formulation that sustains penicillin concentrations above the GAS MIC for a prolonged period will be a considerable advance in RHD control.

Sustained release drug formulations have been successfully developed and applied in the setting of contraceptives and anti-psychotics, where they have proved reliable and safe. These technologies have now been applied to penicillin.

Penicillin for RHD prophylaxis is an ideal candidate for sustained release formulation; low levels of penicillin are needed over an exceptionally long period as GAS killing is dependent on the duration of exposure rather than the peak concentration of penicillin in the blood, with an estimated 2600mg penicillin required per year. Scitech, a pharmacology company, have developed several slow release coating polymers compatible with penicillin. These have
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 need for an improved penicillin delivery mechanism is widely acknowledged. The potential for new product innovation was identified in pharmaceutical literature from 2006.[20] In 2011 a summary of research priorities in rheumatic fever and rheumatic heart disease identified the inadequacy of existing BPG supplies and highlighted the role of an implantable penicillin formulation.[21] The World Heart Federation identified supply of high quality penicillin as one of five targets for global control of RHD in its Position Statement of 2012 [22] Preliminary research to map proprietary, safety and quality issue surrounding BPG was published this year, confirming widespread inadequacies.[8, 23] The second Rheumatic Heart Disease Forum was held in February 2013, encompassing 150 clinicians, researchers and advocates from 38 countries. Delegates reiterated the challenges of BPG and called for urgent innovative solutions.[24]

The mechanism of action of penicillin is mediated by cumulative bacterial exposure to the drug over a period of time (time dependent killing). This makes it an ideal antibiotic to administer in a long acting formulation. Such technology may be applied in other settings where long term antibiotics are needed, namely in the treatment of syphilis and prevention of...
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?)

A national collaborative team has been established to include expertise in project leadership, Indigenous health, RHD, regulatory-compliant pharmaceutical development, drug formulation, and testing of drug depot formulations via in vivo pharmacokinetic analysis. The project is being overseen by Prof. J. Carapetis, Telethon Institute for Child Health Research (TICHR). Technical and pharmacology expertise is being provided by an independent not-for-profit company with expertise in progressing drugs from concept to market. Monash Institute for Pharmaceutical Science is providing pharmacological input, and Scitech have been engaged to supply slow release polymers. Clinical trials will be conducted by a clinical research organization.

(Maximum 100 words)

12. **Who could potentially manufacture the final product?**

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

It is most likely that the final product will be produced by a manufacturer that specialises in generic drug production. There are several generic and semi-generic manufacturers who may be appropriate for this, including; Dr. Reddy's, Biocon, Teva Pharmaceuticals and Mayne Pharmaceuticals. Manufacturers would be engaged via a model appropriate to the group: co-development partnering, licensure, contract manufacture. The decision on the approach and the partner will be based on cost, probability of execution, experience, corporate culture, speed of manufacture, quality of work and compliance with current good manufacturing practices.

(Maximum 100 words)

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

Guidelines for control of RF and RHD were published by WHO in 2001 (Technical Report Series 923).[6] The RHD program ended in 2001 when it was subsumed by competing priorities. Through this project, it is hoped that WHO will provide renewed momentum for RHD control. A targeted update of the 2001 global guidelines to incorporate the indications and implementation approach for a novel penicillin formulation would be a valuable opportunity to strengthen global implementation. It is also hoped WHO would provide support and guidance to obtain prequalification for the long acting formulation. Support for

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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?

The pharmacological formulation of penicillin into a delayed release preparation has commenced. Three polymers (polylactic-co-glycolic acid, polylactic acid and polycaprolactone) have been applied as coating to a penicillin core to allow sustained release. Detailed pharmacokinetic studies of these preparations is now underway. Planning of clinical trials, including consultation with regulatory authorities regarding the requirements for licensure for this orphan drug indication is also underway.

Penicillin formulation: Timeframe - 10 months.
Milestones:
1) In vitro studies demonstrating release profiles in a bio-relevant medium
2) In vivo studies of formulations in the rat model to determine likely plasma concentrations over time in humans
3) Good Laboratory Practice toxicology studies (2 species) of implant

Economic analysis: Timeframe - 1 year.
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 controlled release polymer technology provided by Scientec Pty Ltd is the subject of granted patents in a number of jurisdictions where manufacture and sale is proposed, including Australia, US and India. If this technology is incorporated into the end product, a licence for use will be sought from Scientec. The provision of a perpetual full and unfettered licence to utilise Scitech’s background IP for applications in developing countries and disadvantaged populations has been discussed, and Scientec has been agreeable to this proposition.

The accessibility of the constitutive components of the implant is of paramount importance. Accordingly, if other alternative technologies are required, a perpetual full and unfettered licence to do all things necessary to utilise the relevant background IP for applications in developing countries and disadvantaged populations will be sought. This project will not use technology or engage with organisations if this cannot be reasonably achieved.

With regard to management of the IP and related assets, patent protection for the implant will be sought if applicable. We will ensure this does not become a barrier to patients accessing the implant in developing countries. Strategies under consideration include fully precluding IP barriers to generic provision by not patenting in developing countries, or by filing and abandoning patents, and the early publication and wide dissemination of results to reduce opportunities for interfering patents.

By seeking patent protection in developed countries monopoly rights can be exercised to price the product at a premium for use in developed populations (see below). Revenue generated will be used to subsidise the price of the implant in developing countries, thereby ensuring product access. Further, we intend to provide open access licences to any patents for use in applications relevant to developing countries (for example, a product for use against helminth infections).
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)

It is anticipated that sustainable access to this product for the use in secondary prophylaxis for ARF/RHD would be supported by market segmentation between developed and developing settings. In the developed world recurrent GAS infection is a significant problem for example for new military recruits. Long acting penicillin is also likely to be useful in developed world settings for use in the treatment of syphilis, recurrent cellulitis and may prove useful for the prevention of recurrent pharyngitis in children. By charging market value for these users, the price for developing world populations can be kept affordable. The impact of ARF/RHD on the Indigenous population of developed countries such as Australia and New Zealand is significant. An advanced commitment to purchase the improved penicillin formulation will be sought from these countries to provide assurance to potential manufacturers.

To optimise accessibility for at developing world populations, existing supply chains for BPG will be used. The most reliable supplies of BPG are currently purchased via UNICEF or the International Dispensary Association. Delivering novel penicillin formulations through these existing purchasing mechanisms would minimize distribution costs. Worldwide, humanitarian heart surgery missions are already investing in treatment of RHD and represent an additional market. These organisations currently lack capacity to prevent the progression of RHD through secondary prophylaxis with antibiotics; partnering with humanitarian providers will ensure the effective treatment of severe RHD.

In order to ensure compliance of the long acting formulation with drug standards, it is planned that WHO prequalification will be applied for.
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.

Initial work around formulating penicillin into a long acting preparation has been funded through seed funding of $200,000 AUD (provided by the Western Australia Department of Health). An application for additional funding via the Australian Heart Foundation is under final review with successful grants announced in November 2013. Following successful formulation, funding for clinical trials for other indications such as recurrent cellulitis and prevention of pharyngitis in military recruits will be sought from industry and independent funding partners. It is planned that some of these routes will support the costs of manufacture, safety and pharmacokinetic studies that can be used to underpin the further clinical trials for secondary prophylaxis in the setting of ARFD/RHD. The necessary clinical trials for providing data of direct relevance to ARF/RHD are likely to require multiple field sites in diverse settings due to the orphan nature of the target condition. Based on similar clinical trials for other orphan diseases, it is estimated that entire clinical trial costs required to get full licensure in all in need countries will be in the region of AUS$2 million. This could be outlined as a staged process depending on available resources. For example, it is estimated that phase I safety and prove of concept studies could be

(Maximum 200 words)

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

Three stakeholders are working on the early preclinical phase of the project. Co-ordination and RHD expertise is provided by TICHR, Australia. Preclinical trials and product development is being conducted by the Monash Institute of Pharmaceutical Sciences in Melbourne, Australia. Pathways to development and licensure are being navigated by Medicines Development a revenue neutral charitable company also in Melbourne. The clinical trial phase will involve recruitment of Trial Steering Committee and Data and Safety Monitoring Board (DSMB) that will provide independent guidance on the design and progress of trials. Governance will be provided by a Project Advisory Team to ensure that the principles and practice of the project support global access to the product. Membership will include institutions charged with reducing the burden of RHD: RHD Australia, (a Commonwealth funded national agency for RHD control), the Pacific RHD Program and other governments. Individual appointments will include people living with RHD, clinical experts in RHD and an access to medicines consultant. It is hoped that the World Heart Federation, WHO's partner organization for cardiovascular disease based in Geneva, will

(Maximum 200 words)
19. Have any donor agencies/governments already indicated interest in supporting the project?

The need for improved secondary prophylaxis for ARF/ RHD is widely recognized. The Western Australia Department of Health has already provided seed funding for the project. The governments of Australia and New Zealand have expressed commitment to improving the management of these conditions in their Indigenous populations. To date, financial commitment has been provided at a national and regional level to improve preventative approaches for initial infection and ARF/ RHD registries. It is anticipated that the development of a long acting penicillin formulation would attract similar support.

References:
10. Broderick, M., et al., Serum penicillin G levels are lower than expect in adults within two weeks of administration of 1.2 million units. PLos One, 2011. 6(10): p. e25308.