TB REACH Wave 6
Improving TB Treatment Adherence And Outcomes

Background

The strategy of witnessed dosing, or directly observed therapy (DOT), was designed to reduce non-adherence and has contributed to substantial improvements in TB treatment outcomes. Despite this success, the implementation of DOT has severe limitations. Facility-based DOT requires patients to regularly travel to health facilities, resulting in the loss of autonomy, privacy, time, and money.[1] As a result, DOT is often poorly and inadequately implemented, and even in public sector facilities, most patients are asked to self-administer their medication. This presents a particular challenge for TB management, as irregular TB treatment adherence is associated with disease relapse and development of drug resistance even among patients who achieve treatment completion or cure.[2] DOT is also costly for health systems and the approach inefficiently allocates resources by assuming that all patients will be non-adherent, rather than focusing resources on patients at highest risk for non-adherence and poor outcomes. Although many countries report high treatment success rates, the reported figures rates are likely overestimated since there is a lack of true adherence monitoring. In this environment, many people with TB still fail to sufficiently adhere to and/or successfully complete their treatment, particularly in certain key populations and patient types.

New adherence monitoring approaches are needed to either replace traditional, facility-based DOT or to provide patients with a more diverse set of monitoring options, thereby facilitating differentiated, patient-centred TB care.[3] **This Category of funding is designed to evaluate innovative approaches and technologies that are aimed at improving TB medication adherence (both dosing implementation and persistence) and treatment outcomes for TB infection, drug-sensitive TB and drug-resistant TB.**

Monitoring and Evaluation (M&E)

All TB REACH grants (regardless of their Category) are evaluated using a standard M&E framework; please read the dedicated M&E Concept Note to learn more about how TB REACH will monitor and assess the impact of your proposed intervention(s). In short, TB REACH will measure changes in either interim or final TB treatment outcomes. Due to short project timelines and the initiative's focus on patient impact, TB REACH recommends that applicants focus their activities on one type of person receiving TB treatment (either for TB infection, drug-sensitive TB or drug-resistant TB), rather than trying to evaluate gains across multiple patient types and regimens. Given the nature of TB treatment outcome reporting to NTPs, it is almost certain that the collection and reporting of patient-level data will be necessary. Improvements in the regularity of taking TB medicine (dosing implementation) may also be measured, although every project must still use interim or final TB treatment outcomes as its primary evaluation end point.

Area of Focus: Digital Adherence Monitoring Technologies

Several technologies have emerged which can supply healthcare workers with accurate, real-time, and detailed dosing histories for people on TB treatment. This information is extremely powerful, as it gives healthcare workers an opportunity to make data-driven decisions about to whom, when and how differentiated care and targeted adherence interventions can be provided. For example, individuals with a documented history of intermittent dose skipping or those who have skipped several consecutive doses can be followed up with targeted counselling on the phone and/or during a home visit. While at the same time, individuals who show consistent consumption of doses can continue self-administering their medication between routine healthcare system interactions (e.g. smear testing, clinical evaluation, medicine pick up, etc) because they are at lower risk of poor treatment outcomes. At present, few TB programs can make informed

decisions about which patients need either more or less intensive follow up to maximize treatment success rates, and in reality, health system resources are spread thinly and inefficiently across all patients on treatment regardless of their risk for poor outcomes.

As a reminder – from lessons learned in Wave 5 – be sure to present the roll out of digital adherence monitoring technologies in a patient-centred fashion which does not aim to entirely replace healthcare worker interactions, but rather to differentiate TB care so those most in need receive adequate attention. If these tools are presented as either replacing or reducing healthcare worker interactions with patients, they will not be well received by our independent Proposal Review Committee (PRC). In addition, be sure that the roll-out of these tools are cost-appropriate (e.g. rationally related to the cost of TB medications) and suitable for use in resource-limited settings.

The below paragraphs describe a handful of digital adherence monitoring technologies which are areas worthy of further investigation and possible investment by TB REACH.

99DOTS (https://www.99dots.org/) Product Profile

99DOTS is an unobtrusive, inexpensive adherence monitoring approach first piloted on a large scale in India. Patient medications (pill blisters) are packaged in a custom, secondary envelope with a series of unpredictable, hidden phone numbers that are revealed each time a patient takes his/her medication. Patients are asked to call the revealed numbers to let healthcare workers know that they have taken their medication. The use of these unpredictable, hidden numbers is intended to increase the accuracy of self-reported information by confirming that the medication is 'in hand.' Information is sent to an open source IT platform, which has a mobile app, allowing providers to view patient dosing histories and to receive alerts. The platform can also been integrated with country's notification systems and other adherence monitoring technologies (see the Electronic Dose Monitor section below), which creates the potential for two-way interactions by sending SMS messages with custom-tailored medical advice or counselling. Even without the two-way IT dialogue, the detailed dosing history this technology creates can facilitate evidence-based, differentiated care and targeted adherence counselling. At present, no peer-reviewed studies about the roll out or impact of 99DOTS have been published in the scientific literature, but over 48,000 TB patients have been enrolled in a deployment in India and Myanmar. This technology is low-cost (less than USD 5 per patient for 6 months) and when scaled up, has the potential to be even lower cost. In addition to the impact of this technology on interim or final treatment outcomes (the expected primary objective of all successful TB REACH grants), several key implementation and operational research questions must be addressed as this technology begins to roll out in other areas.

Feasibility
- What percentage of patients have regular access to their own mobile phone, a shared mobile phone or land line?

Acceptance
- How will patients respond if/when phones are shared with family members?
- Will providers be willing to use the 99DOTS mobile app both to register patients and to access dosing history data to differentially manage patients?

Persistence
- Will patients continue calling with every dose, especially after they become asymptomatic and/or establish good medication taking habits?

Accuracy
- How accurate is 99DOTS in monitoring whether patients did in fact take their doses – or that they took doses at the time they called? Does this accuracy change over time?

Scalability
- Is 99DOTS cost-effective compared with the standard of care in most high TB burden countries (self-administration), rather than DOT?
- Are sufficient toll free phones lines available for a scaled deployment?
- Is there sufficient standardization of medication format (blister size) and sufficient printing capability/capacity to support 99DOTS scaled deployment?

- How can NGOs initiate and lead the roll out this technology when scale is only likely to be achieved by NTPs?

Electronic Dose Monitors (https://www.evrimed.com/) Product Profile

Various electronic dose monitors have been used for decades to monitor and improve medication adherence, primarily outside the TB community. The Wisepill evriMED devices are robust, low patient-burden, and adaptable, and have been deployed and evaluated in China and India. Pill blisters (of varying sizes/shapes) can be stored in the device and every time it is opened, data are sent to a server, permitting remote electronic 'observation' of medication taking. Audio and visual reminders of both dosing and refill can also be enabled/disabled on certain device models to remind patients to regularly take their medication and/or return to the clinic for examination or refill. Dosing history data are either downloaded directly to a desktop app via USB or sent directly to an IT platform managed by Wisepill, which can be configured to automatically share data with other integrated IT platforms. As with 99DOTS, the detailed dosing history collected for individual patients allows healthcare providers to make informed decisions about differentiated care and targeted adherence counselling. Published studies from China have evaluated the approach's accuracy,[4] acceptance among patients and providers,[5] and its ability to improve TB treatment adherence.[6] An ongoing trial in China will evaluate the approach's impact on health outcomes impact and cost-effectiveness.[7] Despite these evaluations, and in addition to the impact of this technology on interim or final treatment outcomes, several key implementation and operational research questions remain about the roll out and impact of these devices.

Feasibility
- Are evriMED devices robust enough to be reused? If yes, how many times?
- Will there be an issue of theft?

Acceptance
- Particularly in areas of high TB stigma, will patients be willing to use a medication monitor box?
- If there are several family members taking TB treatment, how will the evriMED devices function, particularly with respect to audio/visual reminders?
- Will patients who travel frequently be willing to use the medication monitor and, if so, will they be willing to carry it with them during travel?
- Will providers be willing to access and utilize medication monitor-generated dosing history to differentially manage patients?

Accuracy
- How accurate is the medication monitor in determining whether patients did in fact take their doses?

Sustainability
- Are evriMED devices cost-effective compared with the standard of care in most high TB burden countries (self-administration), rather than DOT?
- How can certain key populations at risk for poor treatment outcomes be prioritized for roll out?

Video Observed Treatment (VOT) SureAdhere Product Profile emocha Product Profile

VOT is a derivation of DOT whereby the observation of dose taking is achieved with real-time video and/or video recording. The technology eliminates the need for healthcare workers and patients to be in the same physical space and allows for virtual observation at times convenient for the patient's schedule, reducing some of the costs and barriers associated with treatment adherence. In addition to creating a detailed dosing history, the transmission of videos has the potential to generate real-time data on a patient's wellbeing (e.g. medication side effects, etc). The combination of quantitative and qualitative data can lead to very tailored, differentiated care and adherence counselling. Several different VOT platforms are commercially available, including emocha's miDOT, SureAdhere, aiCure, and others. Several studies have described the roll out of this technology [8-10], but none have been published from a high TB burden country or resource-limited setting where self-administered treatment is the standard of care. Despite many potential advantages, this adherence technology has the highest patient burden of those described in this concept note, and there are

several key implementation and operational research questions which applicants should consider when conceiving VOT approaches.

Feasibility	• How will this technology roll out in areas where smart phone penetration and data connectivity are not universal? • What infrastructure is required for health systems and health workers to support this approach and to what extent is this infrastructure already in place?
Acceptance	▪ Will patients, particularly adolescent girls and women, be willing to film their faces in areas where TB stigma is commonplace? ▪ Will patients be willing to incur the cost of data plans to transmit videos? ▪ Will providers/healthcare workers be willing to conduct video reviews every day when this is potentially more work compared to self-administered treatment?
Persistence	• Will patients continue filming themselves/transmitting videos as they begin to feel better and their treatment adherence is well established?
Accuracy	▪ In light of potential increases in healthcare provider workloads, what is the risk that video reviews are falsified?
Sustainability	• Is VOT cost-effective compared with the standard of care in most high TB burden countries (self-administration), rather than DOT?

SMS Reminders

The World Health Organization's 2017 guidelines for drug-susceptible TB treatment indicate that 'mobile telephone interventions' positively impact TB treatment outcomes.[11] However, there is a growing body of evidence that automated SMS reminders alone do not significantly improve TB treatment outcomes.[6,12-13] Given these results and the funding available in Wave 6, TB REACH's independent Proposal Review Committee (PRC) is unlikely to select applications which propose using SMS reminders as a standalone intervention, unless there is a clear justification how the activities and expected impact are different from the published literature.

Other adherence monitoring technologies

Many other technologies exist which are aimed at improving medication adherence and TB REACH would be open to funding their roll out in TB programs as long as impact assessments were conducted using TB REACH's M&E framework. In particular, proposals that involve digital tools or other automated/semi-automated mechanisms to use patient-level adherence information to inform and enhance adherence counselling would be of interest.

Other Non-Technological Approaches

Although the Wave 6 call for proposals has a stated area of focus on the use digital adherence monitoring technologies, TB REACH will still continue to accept proposals and may fund applicant-proposed, non-technological approaches for improving TB treatment outcomes. Though, it will be extremely important to justify how other adherence approaches and/or their evaluation are *truly innovative* to access funding. For example, what is the differential impact and cost-effectiveness of food baskets compared with unconditional cash transfers?

Conclusion

The Stop TB Partnership and many others are optimistic that digital adherence monitoring technologies can improve adherence (dosing implementation), persistence on treatment and eventually TB treatment success rates by facilitating data-driven, differentiated TB care. There are still many implementation and operational

research questions which TB REACH Wave 6 funding is well positioned to answer as these technologies begin to roll out and scale up in high TB burden, resource-limited settings.

References

1. Sagbakken M, Frich JC, Bjune GA, Porter JD (2013) Ethical aspects of directly observed treatment for tuberculosis: a cross-cultural comparison. BMC Medical Ethics 14(25). DOI: 0.1186/1472-6939-14-25
2. Cadosch D, Abel zur Wiesch P, Kouyos R, Bonhoeffer S (2016) The Role of Adherence and Retreatment in De Novo Emergence of MDR-TB. PLOS Computational Biology 12(3): e1004749. DOI: 10.1371/ journal.pcbi.1004749
3. TB CARE I. International Standards for Tuberculosis Care, Edition 3. TB CARE I, The Hague, 2014. http://www.who.int/tb/publications/ISTC_3rdEd.pdf
4. Huan S, Chen R, Liu X, Ou X, Jiang S, Zhao Y, et al. Operational feasibility of medication monitors in monitoring treatment adherence among TB patients. Chin J Antituberculosis. 2012;34:419–424.
5. Liu X, Blaschke T, Thomas B, De Geest S, Jiang S, Gao Y, et al. (2017) Usability of a Medication Event Reminder Monitor System (MERM) by Providers and Patients to Improve Adherence in the Management of Tuberculosis. International Journal of Environmental Research and Public Health 14(10): 1115. DOI: 10.3390/ijerph14101115
6. Liu X, Lewis JJ, Zhang H, Lu W, Zhang S, Zheng G, et al. (2015) Effectiveness of Electronic Reminders to Improve Medication Adherence in Tuberculosis Patients: A Cluster-Randomised Trial. PLoS Med 12(9): e1001876. DOI: 10.1371/journal.pmed.1001876
7. A trial of an electronic pill box with reminders for patients taking treatment for tuberculosis. DOI: 10.1186/ISRCTN35812455
8. Wade VA, Karnon J, Eliott JA, Hiller JE (2012) Home Videophones Improve Direct Observation in Tuberculosis Treatment: A Mixed Methods Evaluation. PLoS ONE 7(11): e50155. DOI: 10.1371/journal.pone.0050155
9. Garfein RS, Collins K, Muñoz F, Moser K, Cerecer-Vallu P, Raab F, et al. (2015) Feasibility of tuberculosis treatment monitoring by video directly observed therapy: a binational pilot study. International Union Against Tuberculosis and Lung Disease 19(9): 1057-1064. DOI: 10.5588/ijtld.14.0923
10. Chuck C, Robinson E, Macaraig M, Alexander M Burzynski J (2016) Enhancing management of tuberculosis treatment with video directly observed therapy in New York City. International Union Against Tuberculosis and Lung Disease 20 (5): 588-593. DOI: 10.5588/ijtld.15.0738
11. World Health Organization (2017) Guidelines for treatment of drug-susceptible tuberculosis and patient care (2017 update). http://www.who.int/tb/publications/2017/dstb_guidance_2017/en/
12. Mohammed S, Glennerster R, Khan AJ (2016) Impact of a Daily SMS Medication Reminder System on Tuberculosis Treatment Outcomes: A Randomized Controlled Trial. PLoS ONE 11(11): e0162944. DOI: 10.1371/journal.pone.0162944
13. Hermans SM, Elbireer S, Tibakabikoba H, Hoefman BJ, Manabe YC (2017) Text messaging to decrease tuberculosis treatment attrition in TB-HIV coinfection in Uganda. Patient Preference and Adherence 2017(11): 1479-1487. DOI: 10.2147/PPA.S135540