Global Access for Technology–Enabled Medication Adherence Monitoring and Differentiated Care of Tuberculosis Patients in Resource-Limited Countries

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Executive Summary

Tuberculosis (TB) is the leading infectious disease cause of death globally.[1] The risk of disease relapse, death, and acquired drug resistance for TB increases substantially with irregular adherence to TB therapy. This is true even for patients who "complete treatment."[2] Despite its successes, in resource-limited settings, DOTS' direct observation is burdensome on patients and highly resource-intensive. As a result, more patients are self-administering their medications.[3] As adherence remains problematic in TB,[4] and as more patients are self-administering, new approaches to patient observation, support, and management are urgently needed.

Several approaches to assessing and subsequently managing adherence (questionnaires, pill counts, diaries) are inaccurate, and other reminder and self-reporting approaches (smart phone reminders and SMS messages) have high "patient burden" or tend to significantly overestimate adherence. Therapeutic drug monitoring, or the incorporation of markers into the drug product formulation, is often proposed as a measure of adherence. Such approaches are at best semi-quantitative, as they reflect only recent dosing and are impacted by inter-individual variation in the pharmacokinetics of the drug or marker. In addition, the equipment necessary for analysis is expensive and sophisticated, requiring a meaningful level of technical expertise, usually only available at central laboratories, thus requiring sample processing and shipment.

In both the developed and developing world and in both infectious and chronic disease, new approaches to observation and adherence support are required. To use today's health system resources (human and financial) more effectively, make better progress on improving disease morbidity and mortality rates, and to avoid the catastrophic economic consequences of continued increases in drug resistance, all of the following should occur:

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[1] World Health Organization. *Global Tuberculosis Report 2015.* Geneva: WHO; 2015.

[2] Thomas A, Gopi PG, Santha T, et al. Predictors Of Relapse Among Pulmonary Tuberculosis Patients Treated In A DOTS Programme In South India. *Int J Tuberc Lung Dis.* 2005;9(5):556-561; Vijay S, Kumar P, Chauhan LS, Vollepore BH, Kizhakkethil UP, Rao SG. Risk Factors Associated With Default Among New Smear Positive TB Patients Treated Under DOTS In India. *PLoS One* 2010;5(4):e10043.

[3] Based on a study published in 2012, it was estimated that 52% of Chinese patients were self-administering, 27% were observed by family members, and only 20% were observed by health workers. Hou WL, Song FJ, Zhang NX, Dong XX, Cao SY, Yin XX, et al. Implementation And Community Involvement In DOTS Strategy: A Systematic Review Of Studies In China. *Int J Tuberc Lung Dis*. 2012;16:1433–1440. pmid:23044444; Lei et al., Are Tuberculosis Patients Adherent To Prescribed Treatments In China? Results Of A Prospective Cohort Study. *Infectious Diseases of Poverty* (2016) 5:38 DOI 10.1186/s40249-016-0134-9. (13.9% of patients had dosing observed). We would expect roughly similar percentages in India, given the size of the purely SAT private sector in India and changes in standard of care for DS-TB patients in the public sector in connection with the introduction of daily-dosed FDCs.

[4] Liu, Xiaoqiu, et al. PLoS Med 12.9 (2015): e1001876. (baseline adherence at 70% -- 70% achieved 80% proper dosing implementation). Lei, Xun, et al. *Infectious Diseases of Poverty* 5.1 (2016): 38. (One-third of participants experienced non-adherence, and patients' lost to follow-up was not uncommon – 28%).

- patients should be given **timely and impactful reminders** of when and how to take their medication – which reminders, particularly when used in combination with medication event monitoring, have been shown to positively impact medication adherence;[5]

- patients should be provided (directly and through their providers) with specific, **personalized feedback** about their dosing patterns to determine adherence challenges – which in other disease states has positively impacted adherence;[6]

- health systems should move away from a "one size fits all" approach to **patient-centered adherence management** – leveraging patient-level adherence data to manage patients according to their demonstrated adherence need;[7] and

- the **reach of existing health systems must be increased** – using data-informed, differential patient management to permit access to and effective management of patients and patient medication taking even in remote regions of these countries.

The use of digital medication monitoring technologies as a method for adherence reminding and measurement/observation has proven to be an effective and pragmatic intervention in both developed and developing countries.[8] Electronic

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[5] Liu X, Lewis JJ, Zhang DOTS, Lu DOTS, Zhang S, et al. (2015) Effectiveness of Electronic Reminders to Improve Medication Adherence in Tuberculosis Patients: A Cluster-Randomised Trial. *PLOS Medicine* 12(9): e1001876. https://doi.org/10.1371/journal.pmed.1001876; Systematic reviews of randomized controlled trials have provided significant empirical data on the efficacy of technology-enabled reminders to enhance adherence to prescribed medications, particularly when part of a multi-intervention strategy. Although the evidence indicating that reminders alone improve treatment adherence is less strong, data suggest that use of reminders/monitors integrated with individualized care delivery based upon the adherence record are associated improved adherence. Demonceau J, Ruppar T, Kristanto P, Hughes DA, Fargher E, Kardas P, De Geest S, Dobbels F, Lewek P, Urquhart J *et al*: Identification and assessment of adherence-enhancing interventions in studies assessing medication adherence through electronically compiled drug dosing histories: a systematic literature review and meta-analysis. *Drugs* 2013, 73(6):545-562. Checchi KD, Huybrechts KF, Avorn J, Kesselheim AS: Electronic Medication Packaging Devices And Medication Adherence: A Systematic Review. *JAMA* 2014, 312(12):1237-1247.

[6] Feedback to patients about their adherence patterns is an important factor positively influencing adherence. Vrijens B, Urquhart J, White D. Electronically Monitored Dosing Histories Can Be Used To Develop A Medication-Taking Habit And Manage Patient Adherence. *Expert Rev Clin Pharmacol*. 2014;7:633–644. pmid:25088004; ("A simple intervention involving monthly adherence counseling based on EDM feedback significantly improved mean adherence among Chinese ART patients. We found an impact on adherence that was both very high -- above the 95% threshold -- and sustained, with mean adherence above 95% throughout the 6-month intervention period."); Sabin LL, DeSilva MB, Hamer DH, Xu K, Zhang J, Li Tao, et al. Using Electronic Drug Monitor Feedback to Improve Adherence to Antiretroviral Therapy among HIV-Positive Patients in China. *AIDS Behav*. 2010; 14(3): 580–589. doi: 10.1007/s10461-009-9615-1; Demonceau et al., *Drugs* 2013;73(6):545-62.

[7] Digital medication monitors can be used to identify 'reliable patients,' so that resources can be focused on 'less reliable patients' who will most benefit from focused counseling or selective DOT. Moulding TS: Viewpoint: Adapting To New International Tuberculosis Treatment Standards With Medication Monitors And DOT Given Selectively. *Tropical Medicine & International Health: TM & IH* 2007, 12(11):1302-1308.

[8] Huan S, Chen R, Liu X, Ou X, Jiang S, Zhao DOTS, et al. Operational Feasibility Of Medication Monitors In Monitoring Treatment Adherence Among TB Patients. *Chin J Antituberculosis*. 2012;34:419–424; Liu, Xiaoqiu, et al. PLoS Med 12.9 (2015): e1001876.

reminding-monitoring of actual dosing helps patients know when and how to take their medications. Moreover, such reminder-monitors generate patient-specific dosing histories that support highly impactful patient counseling. Finally, these reminder-monitors provide reliable and actionable data that providers can use to determine whether and to what degree a specific patient is adherent to the prescribed regimen and how best to tailor individualized therapy management plans. To date, however, such digital medication monitors have been expensive, have not been deployed at scale, have largely been used in clinical trial rather than clinical practice, and have primarily been developed for, and used in, developed markets.

Under grant from the Bill & Melinda Gates Foundation, The Arcady Group developed a detailed target product profile ("TPP") for highly accurate, affordable, re-usable, configurable, scalable, TB-appropriate digital medication monitors that provide timely reminders and deliver patient-specific information regarding medication adherence (hereafter, "TB Reminder-Monitors"). This target product profile was subsequently converted into a detailed RFP and accompanying specifications for the development and manufacture of the foregoing TB Reminder-Monitor. Following development thereof, The Arcady Group developed and documented procedures for quality assurance and for comprehensive field-testing of these TB Reminder-Monitors with TB patients and TB providers.

Should in-country programs desire to replicate these development efforts and utilize local sources of supply for digital monitoring technologies, the detailed information included in this document (TPP, QA and testing protocols, implementation recommendations, etc.) can be used to facilitate and shorten the development or sourcing process.

Also set forth herein is information with respect to Wisepill Technologies' evriMED® TB Reminder-Monitor, selected by The Arcady Group for use in Bill & Melinda Gates Foundation-funded trials and demonstrations in China, India, and Africa. These devices are readily available for procurement via Wisepill pursuant to the terms contained in this document.

Another available, scalable solution for which information is included in this document is 99DOTS. Developed by Everwell Health Solutions in Bangalore, India with funding from the Bill & Melinda Gates Foundation, USAID and UKAID, 99DOTS wraps TB medication in a custom envelope. Patients report their adherence using basic mobile phones and toll-free phone calls to numbers revealed only after dispensing their medication.

All of this information is being made available for ease of implementation of new programs and to fulfill global access requirements.

Additional information and resources related to TB medication adherence and monitoring technologies (including important and recently published WHO-issued

Guidelines and WHO Implementation Handbook that address the importance of adherence in TB and the now-approved role of digital medication monitors in promoting such adherence) can be found by visiting thearcadygroup.com/global-access.

The Importance of Medication Adherence in Tuberculosis

Tuberculosis (TB) is now the leading infectious disease cause of death globally.[9] The risk of disease relapse and acquired drug resistance for TB decreases substantially with increasing duration of TB therapy.[10] [11] In addition, multiple studies also show that irregular adherence to TB therapy — even for patients who achieve treatment completion or cure — is significantly associated with increased rates of disease relapse or development of drug resistance. 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.[12] [13]

Challenges with Traditional Approaches to Adherence Monitoring

Despite its success, DOT as implemented currently in resource-limited settings also has limitations. First, facility-based DOT, still the most common model in many countries, is expensive, resource-intensive and highly burdensome on patients, providers and health systems. Facility-based witnessed dosing requires patients to travel to health facilities for every witnessed dose during the intensive phase and at least once weekly during the continuation phase. For many patients, particularly rural patients, this model may result in loss of autonomy, privacy, time, money and jobs.[14]

Second, strategies for witnessed dosing such as DOT are often poorly and inadequately implemented. We know that DOT has not been extended to the private sector in countries such as Nigeria, Indonesia, Bangladesh, and India, where a significant number of TB patients access care and/or receive treatment. A recent systematic review and a standardized patient study in India highlights the very low quality of TB care in the Indian private sector.[15] [16] Available data suggest

[9] World Health Organization. Global Tuberculosis Report 2015. Geneva: WHO;2015.
[10] Thomas A, Gopi PG, Santha T, et al. Predictors of relapse among pulmonary tuberculosis patients treated in a DOTS programme in South India. Int J Tuberc Lung Dis. 2005;9(5):556-561.
[11] Vijay S, Kumar P, Chauhan LS, Vollepore BH, Kizhakkethil UP, Rao SG. Risk factors associated with default among new smear positive TB patients treated under DOTS in India. PLoS One. 2010;5(4):e10043.
[12] Obermeyer Z, Abbott-Klafter J, Murray CJ. Has the DOTS strategy improved case finding or treatment success? An empirical assessment. PLoS One. 2008;3(3):e1721.
[13] Khatri GR, Frieden TR. Controlling tuberculosis in India. N Engl J Med. 2002;347(18):1420-1425.
[14] Sagbakken M, Frich JC, Bjune GA, Porter JD. Ethical aspects of directly observed treatment for tuberculosis: a cross-cultural comparison. BMC Med Ethics. 2013;14:25
[15] Satyanarayana S, Subbaraman R, Shete P, et al. Quality of tuberculosis care in India: a systematic review. Int J Tuberc Lung Dis. 2015;19(7):751-763

substantially lower treatment completion rates (~50%) in private sector facilities when compared to the public sector (>85%), even in the context of public-private partnerships to improve private sector care.[17] Moreover, even in the public sector, patient self-administration is increasingly the norm.[18]

Third, DOT may often generate low quality and inaccurate adherence data. In resource-limited settings, it is relatively easy/common for healthcare workers to mark a patient as having taken a dose, even if the patient did not make it to the health facility that day to take the witnessed dose. Moreover, since most TB programs in resource-limited settings still rely on paper treatment cards, data is typically not easily amenable to aggregation, analysis, or action.

Finally, DOT is expensive and resource-intensive. The model assumes that all patients will in fact be non-adherent and require an equivalent level of monitoring — rather than focusing resources on patients at highest risk for non-adherence and poor outcomes. Thus, DOT alone is not sufficient. New, cost-effective adherence monitoring strategies are needed that can be utilized in the public sector and by private sector clinics with a high volume of TB patients. These strategies can either replace traditional, facility-based DOT or can provide TB patients with a more diverse set of monitoring options, thereby facilitating the goal of "patient-centered care" endorsed by the International Standards for TB Care (ISTC).[19]

WHO Recommendations for Treatment of DS-TB

In April 2017, the World Health Organization released a comprehensive 2017 Update on Guidelines for Drug Susceptible TB treatment.[20] These guidelines make several important points about the importance of TB treatment adherence, about the impact of various adherence interventions, and emphasize the importance of digital technologies in supporting the implementation of the End TB Strategy. Importantly, the guidelines contain the first-ever WHO evidence-based recommendations on the use of, among other approaches, electronic medication monitors to help patients adhere to TB medication and deliver TB care.

- **"... as treatment supervision alone is not likely to be sufficient to ensure good TB treatment outcomes, additional treatment adherence interventions need to be provided."**

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[16] Das J, Kwan A, Daniels B, et al. Use of standardised patients to assess quality of tuberculosis care: a pilot, crosssectional study. Lancet Infect Dis. 2015.

[17] Floyd K, Arora VK, Murthy KJR, et al. Cost and cost-effectiveness of PPM-DOTS for tuberculosis control: Evidence from India. Bulletin of the World Health Organization. 2006;84(6):437-445.

[18] For example, in China, published studies indicate that only approximately 20% of China TB patients are managed pursuant to conventional DOT, with over 50% self-administering. Hou, DOTS. et al., INT J TUBERC LUNG DIS 16 (11): 1433–1440, http://Dx.Doi.Org/10.5588/Ijtld.12.0080

[19] TB CARE I. International Standards for Tuberculosis Care , Edition 3. TB CARE I, The Hague, 2014

[20] World Health Organization, Guidelines For The Treatment Of Drug-Susceptible Tuberculosis And Patient Care, 2017 Update ISBN 978-92-4-155000-0.

- **Treatment outcomes are "significantly improved" when adherence interventions are combined with either DOT or SAT.** "When patients receiving combined treatment adherence interventions along with DOT or SAT were compared to those receiving DOT or SAT alone, patients who received combined treatment adherence interventions had higher rates of treatment success, treatment completion, cure and adherence, and lower rates of mortality and loss to follow-up."

- Recommendation 2.1.2. states "A package of treatment adherence interventions may be offered for patients on TB treatment in conjunction with the selection of a suitable treatment administration option."

- Recommendation 2.1.3. states: "One or more of the following treatment adherence interventions (complementary and not mutually exclusive) may be offered to patients on TB treatment or to health-care providers: a) tracers (e.g., communication with the patient including via SMS, telephone (voice) calls, or home visits) or **digital medication monitor**; b) material support to patient; c) psychological support to patient; or d) staff education."

- The Guidelines define a "digital medication monitor" as "a device that can measure the time between openings of the pillbox. The medication monitor can give audio reminders or send SMS to remind patient to take medications, along with recording when the pillbox is opened."

These guidelines expressly approve the use of digital medication monitors to improve TB treatment outcomes and suggest communication and collaboration with organizations that have initiated programs and established infrastructure.

Criteria for Evaluation of Adherence Interventions

Desired Impact

Despite the existence of effective TB treatments and despite significant increases in financial support, obstacles to effective disease management remain. Even patients who are properly diagnosed and have access to appropriate treatment regimens will have positive health outcomes only if they take their medications as prescribed. As summarized above, it is clear that witnessed dosing methods such as DOT are not the answer. We require new adherence interventions that (i) are more patient-centric, (ii) generate accurate and actionable data, and (iii) are highly cost-effective. More specifically, to use today's health system resources (human and financial) more effectively, make better progress on disease morbidity and mortality, and

avoid the catastrophic economic consequences of continued increases in drug resistance, all of the following must occur:

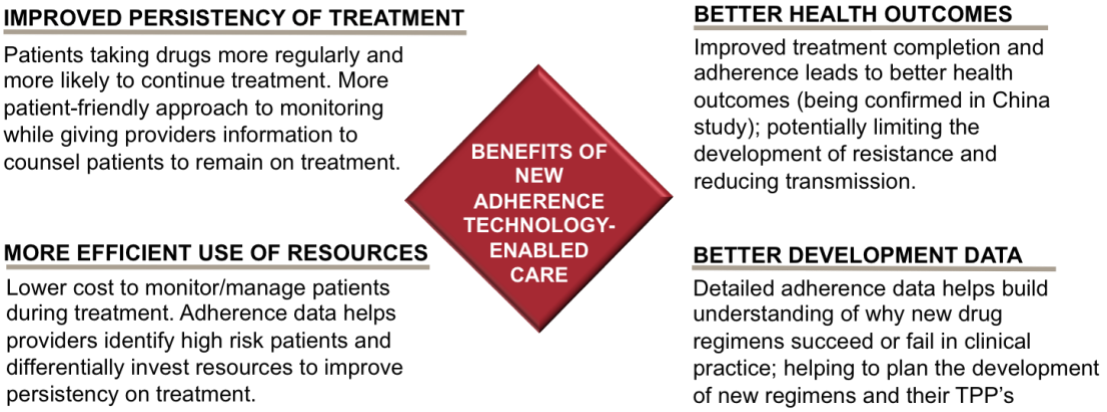
- Patients should be given custody of their medication but their self-administration should be electronically observed and their detailed dosing histories electronically compiled;

- Patients should be given timely and impactful reminders of when and how to take their medication – which reminders, when used in combination with adherence monitoring devices, have been shown again to positively impact medication adherence;

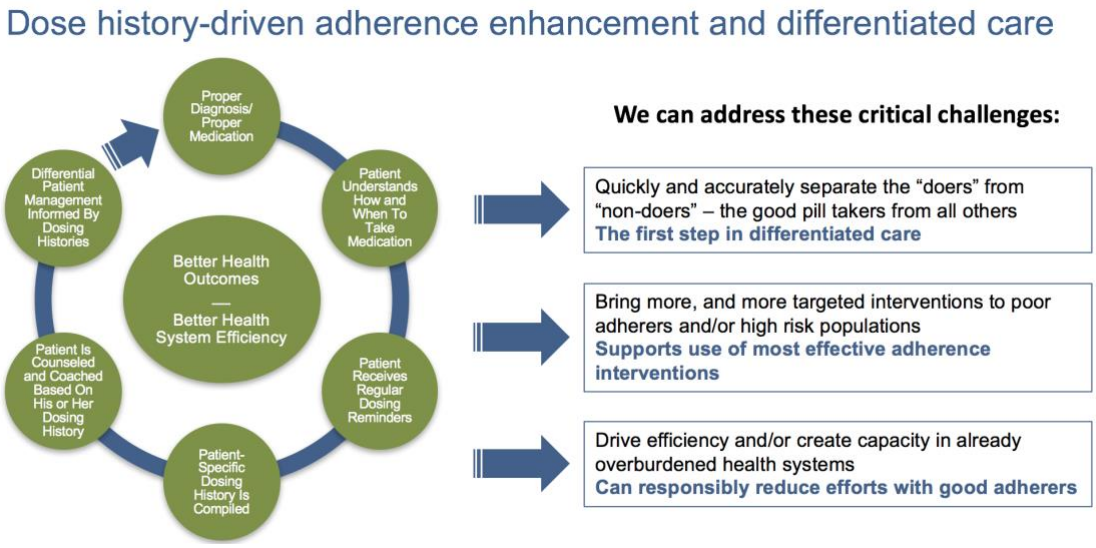
- Patients should be provided (directly and through their providers) with specific, personalized feedback about their adherence challenges – which in TB and in other disease states has positively impacted adherence and persistence (retention in care); and

- Health systems must move away from a "one size fits all" approach to evidence-based, patient-centered differentiated care — leveraging patient-level adherence data to manage patients according to their demonstrated adherence need and resistance/transmission risk profile.

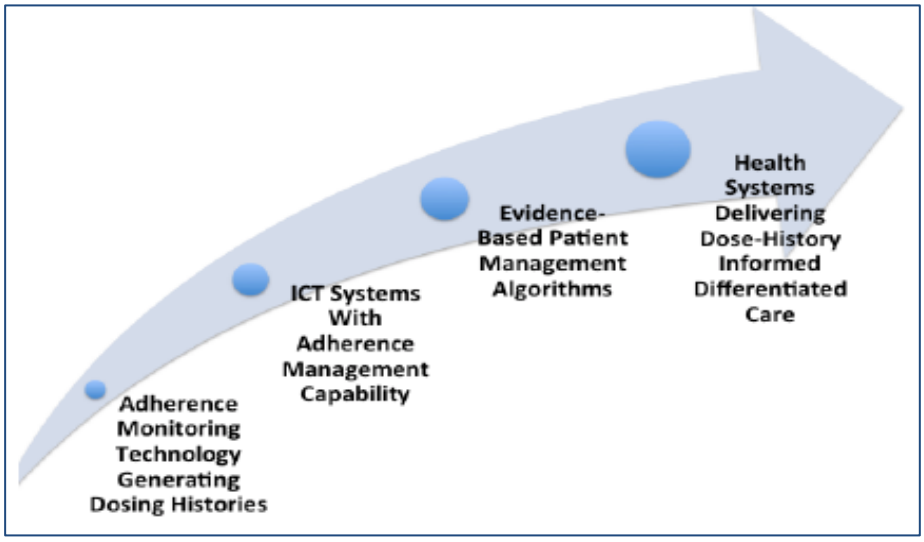
Meeting these criteria will enable benefits for patients and providers, which include those shown in the figure below:



The following graphic illustrates the shift toward more patient-centered differentiated care and the benefits thereof from a patient, disease management and health system perspective:



In order to achieve this vision, an intervention needs to have the following sequential and integrated elements:



Evaluative Criteria

Evaluative Criteria for various adherence monitoring technologies can further be defined along the following dimensions:

Evaluative criteria	Description
Feasibility	• Relative ease of implementation and operation of the technology within existing health systems, technology infrastructure, and supply chains.
Acceptance / Burden	• Relative satisfaction of patients and providers with the technology. • Should include an understanding of (i) cultural or other barriers to uptake (e.g. VDOT for women/ girls), (ii) how this relative satisfaction changes over time, and (iii) how this burden affects both uptake and persistence with respect to the technology.
Accuracy	• For monitoring technologies, the extent to which the technology's "event" (e.g., self-reported medication ingestion) is correlated with actual event (e.g., medication ingestion).
Effectiveness	• Extent to which the technology is able to generate or elicit the intended action, behavior, or event (e.g., improvement in average adherence). • Should include information on the extent to which the effect persists over time. • Ultimate "effect" to be evaluated would be actual health outcomes (e.g. current China RCT)
Affordability	• The total cost of the technology as implemented and used by patients/providers – in relation to (i) cost of treatment regimens, and (ii) total cost of treatment.
Cost Effectiveness	• An assessment of cost-effectiveness/comparative cost-effectiveness (mean and incremental costs per death and DALY averted) of the proposed technology-enabled intervention versus standard of care in the relevant context, i.e., disease burden, budget/costs of the resource-limited setting.
Available TPP	• Availability of a WHO TPP for the product/device.

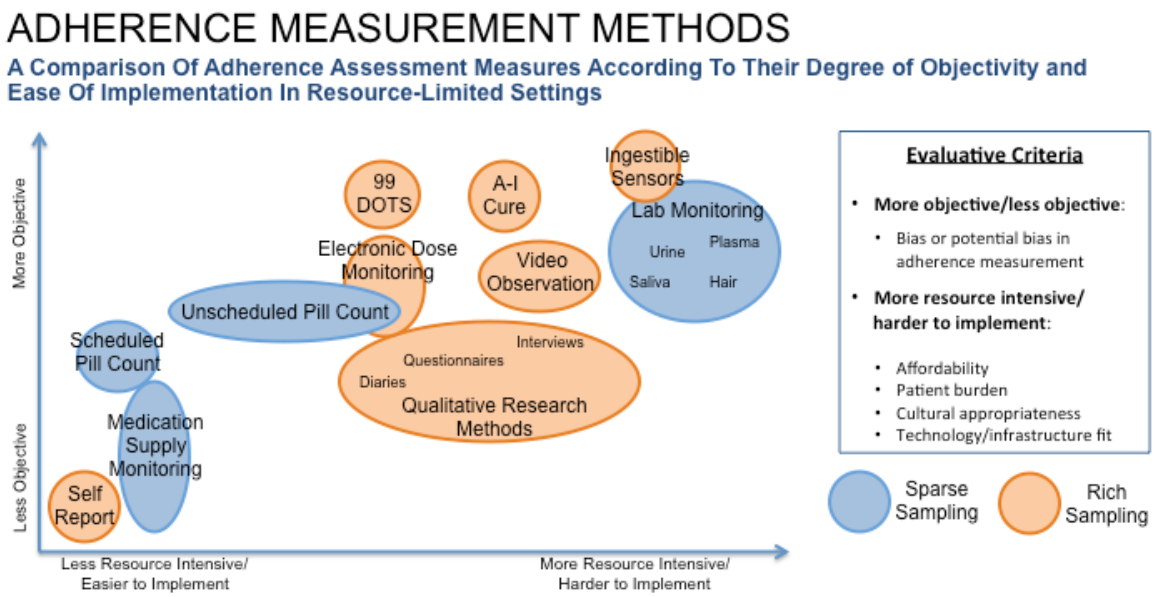
Assessment of Available Adherence Interventions

There exist a wide range of processes (such as pill counts, patient diaries, patient questionnaires) designed to measure patient medication adherence. Each of these, however, has been shown to be highly inaccurate – with a positive bias of at least 20%. In addition to these processes, there are a wide range of apps and products designed to organize medications, to remind patients to take medications, and/or to register or report medication-taking events. Unfortunately, few if any of these solutions are well suited to the unmet need in TB treatment in resource-limited settings. Medication organizers have no reminding or monitoring feature. Medication reminder systems lack any or at least accurate medication event monitoring. Automated medication dispensers are prohibitively expensive and not designed for developing market environments. Finally, while electronic medication organizers, smart medication packages, and smart ingestible devices[21] are all interesting potential solutions, few, if any, are at all suitable (i.e., affordable, suited for existing supply chains and package formats – blisters versus loose fill), or

[21] Ingestible sensors are unquestionably accurate, as they eliminate any doubt as to whether the medication has in fact been ingested. In addition, they have the unique ability to monitor each individual pill in a multi-pill regimen – which might be particularly valuable in instances such as MDR-TB where adherence is important and particularly challenging. However, while solutions like Proteus have been available for years, this technology has not been scaled, has not to our knowledge been demonstrated or used with multi-therapy regimens, and remains very expensive. This remains a technology, however, that if affordable and if deployed in resource-limited setting should be of real interest and impact in TB treatment.

available in resource-limited settings) for multi-pill, variably-dosed, FDCs dispensed in blister format.

The following graphic compares various adherence measurement methods based on objectivity and ease of implementation in resource-limited settings:



These technologies have further been assessed against the defined evaluative criteria:

Evaluative criteria	99DOTS	MERM	EMBRYYO	VDOT	Validated/AI VDOT	Ingestible Sensors
Feasibility	Satisfactory data India, Myanmar Abstract Published	Satisfactory data China Published. Non-RCT	In process Non-RCT	Satisfactory data (?) Kenya – 13 patients Published. Non-RCT	Not tested in high burden countries	Not tested in high burden countries
Acceptance / Burden	Satisfactory data India, Myanmar Abstract Published	Satisfactory data China (India, 2017) In Review. Non-RCT	In process Non-RCT	Not yet tested in high burden countries	Not tested in high burden countries	Not tested in high burden countries
Accuracy	In process with NIRT 600 patients -- India. Non-RCT	Satisfactory data China Published. Non-RCT	Not tested in high burden countries	Not tested in high burden countries	Not tested in high burden countries	Not tested in high burden countries
Effectiveness	Planned - India Retrospective Study Non-RCT	Satisfactory data China Published --RCT	Not tested in high burden countries	Not tested in high burden countries	Not tested in high burden countries	Not tested in high burden countries
Affordability	Satisfactory data India, Myanmar	Satisfactory data China	Not tested in high burden countries	Not tested in high burden countries	Not tested in high burden countries	Not tested in high burden countries
Cost Effectiveness	In process India Non-RCT	In process China, India RCT	Not tested in high burden countries	Not tested in high burden countries	Not tested in high burden countries	Not tested in high burden countries
Available TPP	No	Yes (But BMGF Developed, Not WHO)	No	Yes (WHO Developed/ Endorsed)	No	No

Existing and Planned Evidence Base for Electronic Dose Monitors

The following chart highlights the existing and planned evidence base evaluating the usability and effectiveness of electronic medication event reminder-monitor technologies in resource-limited settings:

	Study/Publication	Principal Investigator	Design/Device	Primary Objective
Complete	Operational feasibility of Medication Monitors in Monitoring Treatment Adherence Among TB Patients *Chin J Antituberculosis. 2012; 34:419–424 (425)*	Huan Shitong (Beijing University)	Feasibility study of 432 TB patients in China China MERM	To explore the operational feasibility of using medication monitors to monitor treatment adherence in TB patients by comparing the medication monitors' records with those of patients' urine tests for traces of TB drugs.
	Effectiveness of Electronic Reminders to Improve Medication Adherence in Tuberculosis Patients: A Cluster-Randomised Trial *PLoS Med 12.9 (2015): e1001876.*	Xiaoqiu Liu (China CDC)	CRT of 4,137 TB patients in China China MERM	To determine the percentage of patient-months where at least 20% of doses (equivalent to missing three of 15 doses) were missed ("poor adherence").
	Usability of the Medication Event Reminder Monitor System (MERM) by Providers and Patients to Improve Adherence in the Management of Tuberculosis *Manuscript in review.*	Liu Xiaoqiu (China CDC)	Usability study of 40 patients and providers in China evriMED (Wisepill MERM)	To examine the robustness and usability of the MERM along the subdimensions of user performance, satisfaction, and acceptability to both TB patients and TB providers in a rural setting in China.
Underway	Using Biomarkers to Predict TB Treatment Duration	Clifton E. Barry III (NIAID) Xiaoqiu Liu (China CDC)	Randomized, Noninferiority trial of 620 TB patients in South Africa and China evriMED (Wisepill MERM)	To demonstrate noninferiority of treatment success rates 18 months after starting treatment in subjects who meet the early treatment completion criteria at 4 months but continue on treatment to 6 months (Arm B) or stop treatment at 4 months (Arm C).
	Cluster randomized trial of a medication monitor in the treatment management of patients with pulmonary tuberculosis	Liu Xiaoqiu (China CDC)	CRT of 3,000 TB patients in China evriMED (Wisepill MERM)	To compare, among drug sensitive pulmonary TB adult patients, a composite poor outcome measured 18 months from the start of treatment between intervention and control arms.
	Economic Evaluation of MERM in China	Anna Vassall (LSH&TM)	Cost-effectiveness evaluation in China evriMED (Wisepill MERM)	To assess affordability, cost-effectiveness outcomes, and equity outcomes as part of the CRT of a medication monitor in the treatment management of patients with pulmonary TB.

	India Adherence Tool Validation, Demonstration and Scale: Evaluation of Pill-In-Hand Adherence Monitoring Tools	Ramnath Subbaraman (Brigham & Women's Hospital)	Interviews, Pilot Study, Home visits of 600 TB patients in India evriMED (Wisepill MERM) and 99DOTS	To evaluate the accuracy, acceptability, feasibility and costs of 99DOTS for monitoring adherence to daily TB therapy among drug-susceptible TB patients in the RNTCP.
Underway	PHOENIx: Protecting Households On Exposure to Newly Diagnosed Index Multidrug-Resistant Tuberculosis Patients NOTE: Devices NOT BMGF-Funded	Nishi Suryavanshi (BJ Medical College CRS)?	Randomized Phase III trial of 3,452 high-risk TB household contacts in up to 10 high-burden countries	To assess the efficacy of 6 months of daily delamanid (novel intervention arm) versus 6 months of isoniazid preventive therapy (control comparison arm) in high-risk household contacts of adult pulmonary MDR TB cases.
	A randomised open-label trial to evaluate the efficacy of periodic high dose rifapentine and INH for three months compared to continuous INH preventive therapy in HIV-infected and TB-infected adults	Gavin J Churchyard (The Aurum Institute)	Randomised open-label trial of 3600 HIB/TB Co-infected patients in South Africa, Mozambique, Malawi and Ethiopia	To compare the efficacy of annual high dose periodic rifapentine and INH (p3HP) to continuous INH (cINH) among HIV-infected, tuberculosis infected adults without evidence of active TB.

Gates Foundation Funded Work and Deliverables

Under grant from the Bill & Melinda Gates Foundation, The Arcady Group developed a detailed target product profile ("TPP") for highly accurate, affordable, re-usable, configurable, scalable, TB-appropriate digital medication monitors that provide timely reminders and deliver patient-specific information regarding medication adherence (hereafter, "TB Reminder-Monitors"). This target product profile was subsequently converted into a detailed RFP and accompanying specifications for the development and manufacture of the foregoing TB Reminder-Monitor. The Arcady Group also developed and documented procedures for quality assurance and for comprehensive field-testing of these TB Reminder- Monitors with TB patients and TB providers. These materials, particularly the TPP, were used by Arcady's selected supplier, Wisepill Technologies, to develop two versions of the desired TB Reminder - Monitors, the evriMED® TB Reminder-Monitor, selected by The Arcady Group for use in Bill & Melinda Gates Foundation-funded trials and demonstrations in China, India, and Africa. Additional information about the evriMED devices is set forth below. Set forth in Appendix I hereto, in fulfillment of The Arcady Group's global access obligations are this TPP and these testing protocols.

Also set forth below is information relating to another Gates Foundation-funded monitoring technology, Everwell Health Solutions' 99DOTS, an ultra low cost, highly scalable approach to adherence monitoring that has been widely scaled with DS-TB and TB-HIV patients in the public and private sectors in India.

An Available, Scalable Solution: Wisepill Technologies' evriMED

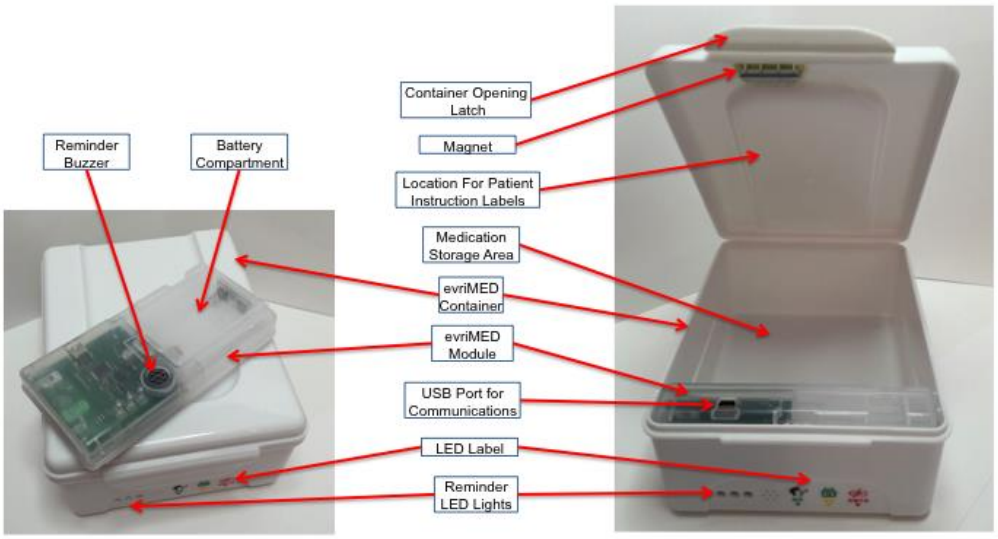
Product Profile

Developed with funding from the Bill & Melinda Gates Foundation, and currently in use in clinical trials and in clinical practice in several resource-limited countries, evriMED is an affordable, scalable, TB-appropriate digital medication monitor. Using a unique, modular approach that permits customization of the container for DS-TB, MDR-TB and TB-HIV patients, the evriMED device is a highly-accurate, low patient burden, adherence monitoring technology. http://DOTS.evrimed.com

The salient technological features include:

- Suitable for use with blister packaged TB medications.
- Modular construction to reduce cost and permit container customization.
- Significant billboard space to communicate to patients and allow for region-specific customisation.
- Simple data acquisition using a magnetic sensor to detect container opening.
- Programmable Alert Mechanisms consisting of:
    - Three (3) LED Lights: Green - Dose Alert; Yellow – Refill; Red - Low Battery
    - An Audible tone to indicate that a dose is due
- Two versions available: basic (monthly data transfer via USB) and real-time (using highly available and affordable 2G capability).
- Affordable and reusable -- less than 10 USD per patient based on conservative reuse assumptions.
- Very low patient burden -- no recharging required.
- Easily integrated into existing open source and national health data systems.

Below is a labeled image of an evriMED module and container. The container can be made of injection molded plastic (as shown) or corrugated paperboard (above with "Sample Instructional Materials for Patients and Providers").



Adherence Analysis through Backend System

Clinicians access a dashboard showing daily adherence records (example below). Each row represents a patient and each red rectangle represents a missed dose. Clinicians can quickly differentiate patients who are potentially capable of self-administration and those who require a higher touch outreach model.

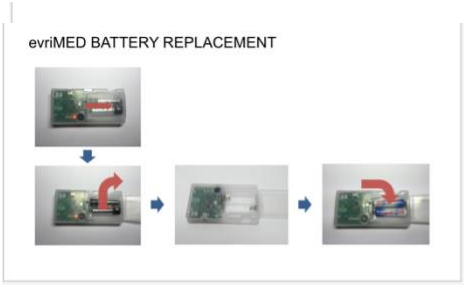
The evriMED® technology provides highly patient-centric adherence monitoring, reminders of dosing and refill, supports enhanced adherence counseling, and enables differentiated care to drive health-system efficiency and improve treatment outcomes.

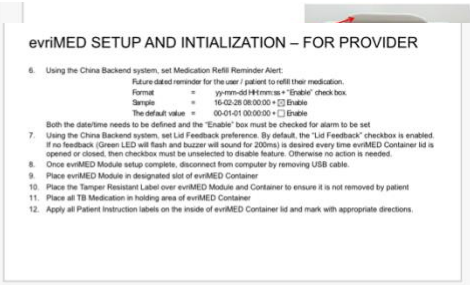
Sample Instructional Material for Patients and Providers

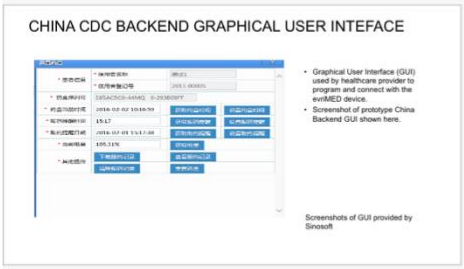
Labels and instructional materials that are region and regimen-specific provide guidance for patients on proper self-administration. The examples below highlight communication and customization opportunities:

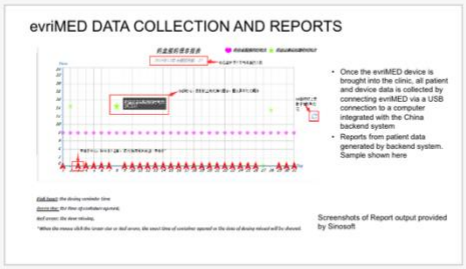
evriMED User Guides

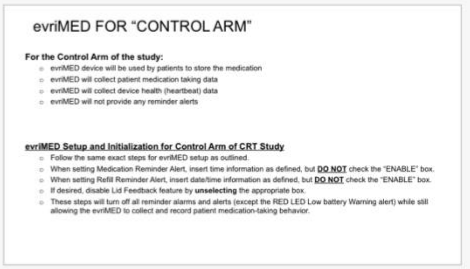
China user guide example - English

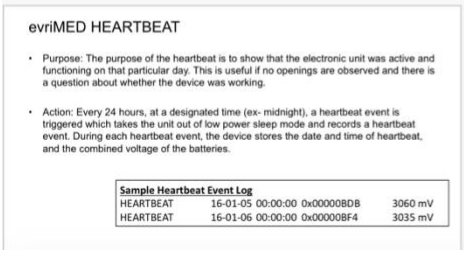


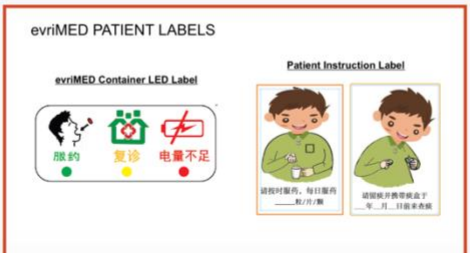












India User Guide Example

Available Backend System Options

evriMED® programs are designed to integrate both with Wisepill's proprietary back-end system and with other national health systems (e.g., India's e-Nikshay system). evriMED is also fully integrated with the 99DOTS platform, that presents another mechanism for back end system support and analytics. See Appendix II for further details on evriMED and 99DOTS integration.

For smaller pilots or evaluations, even simpler software has been developed for licensure. Additional information available at http://DOTS.evrimed.com.

evriMED Price Matrix

	Unit Increments (Combined Basic and Real-Time)	Basic Version Per Unit Price	Real Time Per Unit Price	Basic Version Application-Integration (Web hosting and viewing of Basic Unit data)	Real Time Version Wisepill System Integration (Web hosting and viewing of Real Time Unit data)	Minimum Order Quantity Units
A	Up to 15,000	USD 12	USD 18	$0.5 per month per device	$1.0 per month per device	2,000
B	15,000 to 25,000	USD 11.50	USD 17.50	$0.4 per month per device	$0.8 per month per device	2,000
C	25,000 to 50,000	USD 10.50	USD 16	$0.3 per month per device	$0.6 per month per device	5,000
D	50,000 – 100,000	USD 9.25	USD 14.50	$0.2 per month per device	$0.4 per month per device	10,000
E	Over 100,000	USD 8	USD 14	$0.1 per month per device	$0.3 per month per device	10,000

The Basic Version of evriMED includes the following components that are not part of price matrix:

- AA Batteries
- USB Cable
- Patient medication instruction cable
- Shipping and handling fees
- Taxes, VAT and custom fees

- Certification and/or regulatory approval fees as required from new jurisdictions

The Real Time version of evriMED requires the following components that are not part of the price matrix:

- Lithium Polymer battery
- Battery Charger
- USB Cable
- Patient medication instruction cable
- Shipping and handling fees
- Taxes, VAT and custom fees
- Certification and/or regulatory approval fees as required from new jurisdictions

Wisepill agrees to accept orders that are below the defined MOQ and may assess an additional "below minimum fee" charge for those orders not to exceed 20% of defined price.

Program Implementation Guidelines

- Digital medication monitors provide affordable, scalable, low patient burden electronic assistance to, and observation of, self-administering patients. They are approved for use by WHO and are available for purchase as, in essence, a "pillbox" for TB medications (DS or MDR-TB).
- These monitors have been extensively tested and are in use in India and China. A "users group" is being established as a way for NTP managers to obtain and share information and experiences. In particular, this users group can share and provide information on ICT integration of digital medication monitors and on the differentiated care algorithm.
- Because supply chains and ICT systems vary from country to country, it is recommended that digital medication monitors first be piloted in country before scale-up. It is anticipated that technical assistance will be provided to assist in both in country piloting and scale-up.

Company Profile: Wisepill Technologies, Ltd.

Wisepill develops and manufactures technologies that enable monitoring and measurement of patient medication-taking behavior. Wisepill solutions are cost-effective, scalable, and widely accepted by patients. Founded in South Africa in 2007, Wisepill medication dispensers have been used in more than 20 countries and 40 research trials. To learn more, please visit wisepill.com.

An Available, Scalable Solution: Everwell Health's 99DOTS

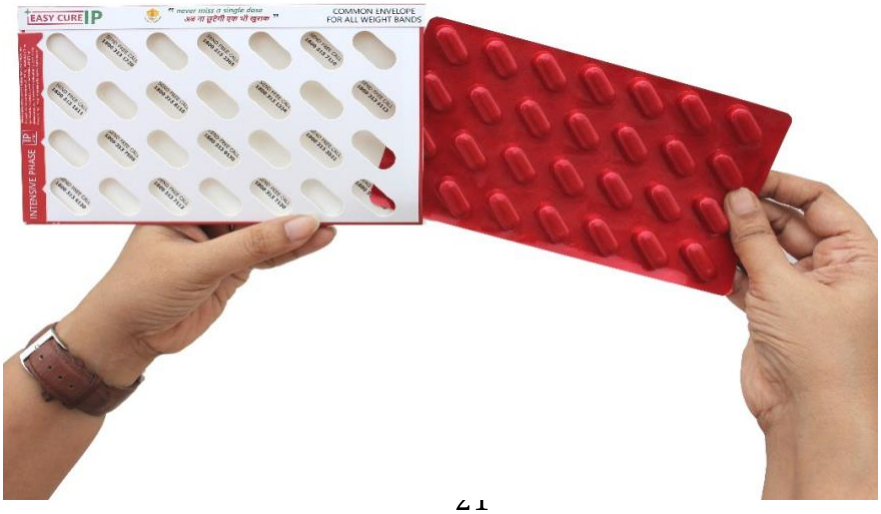
Product Profile

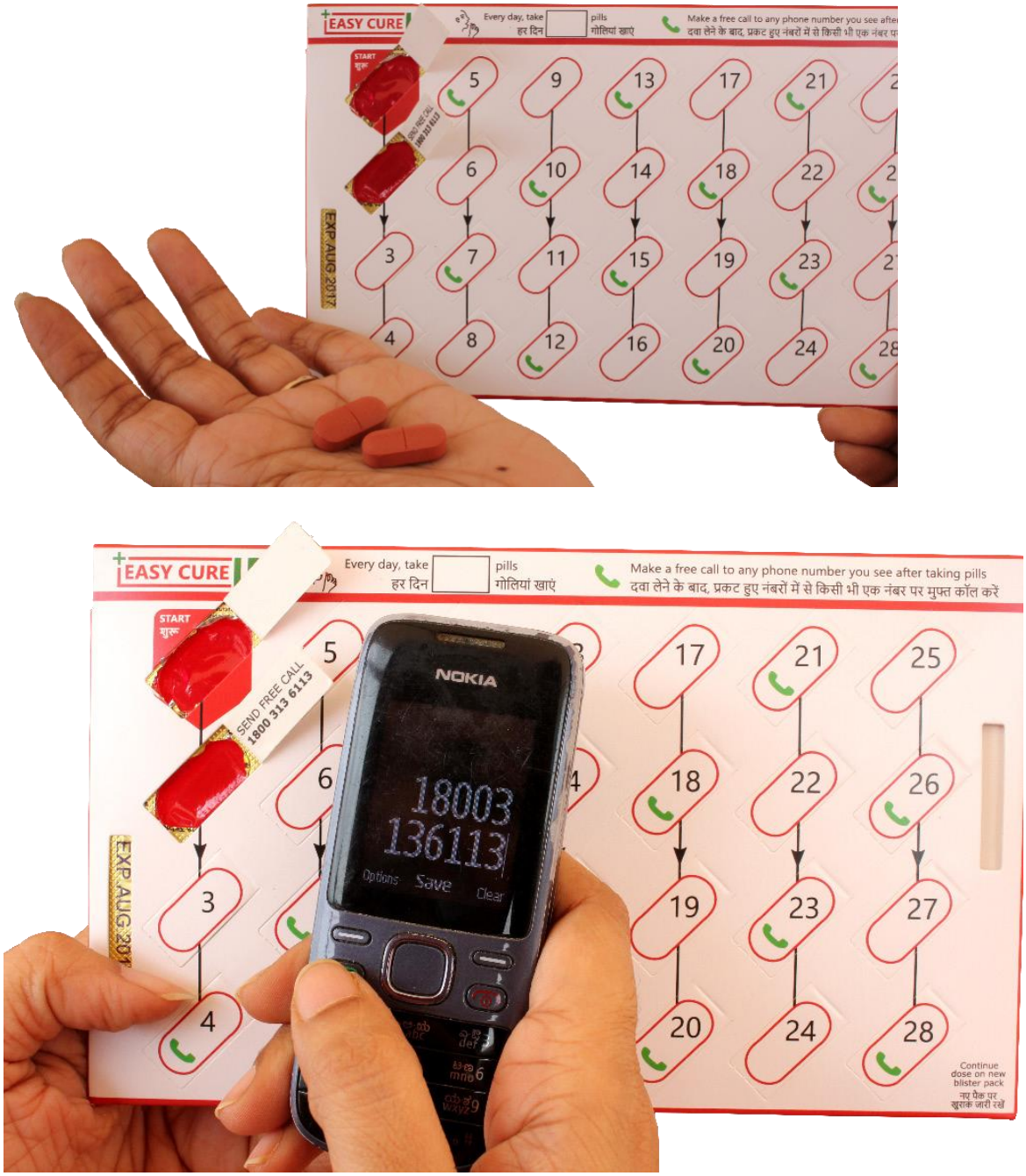
Developed by Everwell Health Solutions in Bangalore, India with funding from the Bill & Melinda Gates Foundation, USAID and UKAID, 99DOTS wraps TB medication in a custom envelope. Patients report their adherence using basic mobile phones and toll-free phone calls to numbers revealed only after dispensing their medication. With more than 50,000 patients enrolled, primarily in India, 99DOTS is an affordable, scalable, TB-appropriate medication monitoring technology. 99DOTS.org

The salient technological features include:

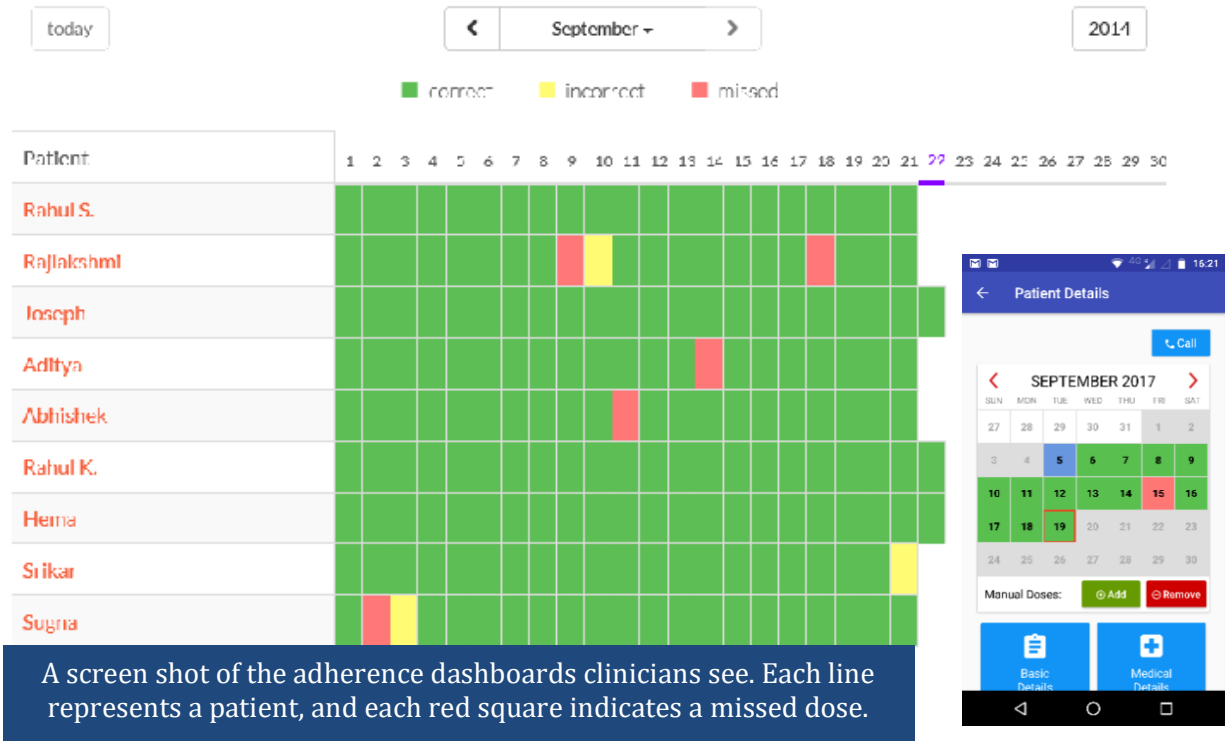
- Inexpensive and easily integrated into existing drug manufacturer supply chains.
- Calls are completely free for patients and can be made from any phone - mobile, land line, shared.
- Any call from a registered patient number is marked as a dose taken.
- Numbers are not unique, but appear in an unpredictable sequence - ensures "pill-in-hand" adherence. More accurate / verifiable than "mere" self-reporting via SMS or call.
- Healthcare providers can monitor the adherence of individual patients or groups of patients.
- Automatic alerts and reminders to patients and supervisors for non-adherent patients.
- The platform prioritizes patients based on their reported adherence for immediate follow-up.
- The 99DOTS platform can also integrate with other adherence monitors, enabling providers to manage patients on a single platform, independent of which monitoring technology the patients are using.

Below are images of 99DOTS envelopes:





Unpredictable numbers are revealed when pills are expressed. Patients call the number from a registered phone.



A screen shot of the adherence dashboards clinicians see. Each line represents a patient, and each red square indicates a missed dose.

Available Back-end System

The 99DOTS back-end system has been made open source and globally accessible. The zip file with the source code of 99DOTS can be found here: **https://drive.google.com/open?id=0Bxk4-v1kc8kYeWVyZlVGRmg0OGs.**

Pricing & Program Implementation Guidelines

- Digital medication monitoring technologies such as Everwell's 99DOTS, provide affordable, scalable, low patient burden assistance to, and observation of, self-administering patients.
- 99DOTS envelopes are not patented and specifications for them can be made available to those wishing to independently source.
- 99DOTS been extensively tested and is in use at scale in India for DS-TB patients. The 99DOTS platform utilizes an open source ICT system with robust reporting and proven ability to integrate with national ICT systems and other monitoring technologies.
- To deploy 99DOTS envelopes and adherence technologies, contact Andrew Cross with Everwell Health Solutions at andrew@99dots.org. Everwell is experienced and excited to work with interested partners to develop the highest quality, lowest cost implementation of 99DOTS for each country context. Exact costs vary by country, but in countries where 99DOTS has been deployed, the cost (including 99DOTS platform) is approximately US$5-6 per patient course (generally 6 months).

Company Profile: Everwell Health Solutions

Everwell Health Solutions is a healthcare technology startup company based in Bangalore that focuses on leveraging technology to improve adherence to anti-Tuberculosis medication through an innovative mHealth project called 99DOTS. Their mission is to use appropriate technology to empower patients to self-monitor their adherence, and enable programs to identify in real time which patients require additional outreach. To learn more, please visit everwell.org.

Additional Information

For additional information and resources related to TB medication adherence and monitoring technologies, please visit thearcadygroup.com/global-access.

The Arcady Group Profile & Contact Details

Company Profile

The Arcady Group helps organizations and businesses address global health issues, enhance patient and disease management, and improve the effectiveness and the efficiency of health systems. We turn science into action – enhancing patient management and health system delivery in some of the world's most challenging disease states and in some of the most health-care challenged regions of the world. The Arcady Group has served as both consultant to, and grantee of, the Bill & Melinda Gates Foundation, working on matters relating to TB medication adherence and differentiated care in China, India, and Africa.

The Arcady Group holds no financial interest in Wisepill, the evriMED device, Everwell or 99DOTS.

Contact Details

For more information, visit thearcadygroup.com or reach out to:

Bruce V. Thomas
Founder & Managing Director
bruce.v.thomas@thearcadygroup.com
+1 804-339-7028

Appendix I

Target Product Profile (TPP) of a TB Reminder-Monitor

The following chart can be used to evaluate or source an Electronic Dose Monitor:

Operating Environment	● Large temperature range (5-40°C). ● Broad humidity (to 95% non-condensing) and altitude ranges. ● Direct sun light to low light. ● Dusty conditions. ● Intermittent electrical access.
Performance and Accuracy	● >95% accuracy in event capture, ● Captures >1000 dosing events, ● Clock precision +/- 90 seconds per week, ● >95% accuracy in dosing history transmission.
Design Considerations	● To support both high cost-effectiveness and multiple use cases, we believe that the Monitor must be designed as a two-part, integrated solution: the "Container" (which holds and stores the medication) and the "Monitoring Technology" (removable, portable aspect containing the data capture, storage and transfer elements as well as other essential electronics). ● Designed to require little to no patient engagement – e.g., battery charging, phone calls, etc. ● Designed to be low cost and highly cost-effective. ● Designed to be highly intuitive operation for target population (patients and providers).
	● The Container would likely be paperboard but can also be injection-molded plastic. ● The Container could be of myriad sizes and shapes depending on the use case and amount and format of the medications involved. The only requirement would be that the Container would need to be designed to securely house the Monitoring Technology. ● The Monitoring Technology could and should be standard to permit scaled manufacturing and low cost. It should be "plug and play" into the myriad Container formats described herein. ● The foregoing "two part, integrated" design principle is critical, we believe, to increasing as much as possible the addressable market (via supporting myriad use cases) while decreasing as much as possible the per unit cost.
Child Resistant	● No
Senior Friendly	● Yes – to the extent that the package is easy to operate. Will not require testing protocol for senior friendly validation.
Anti-tamper	● Yes – standard available tamper-evident features such as tape seals.
Waterproof	● Water-resistant – suitable for high humidity environments.
Medication accommodation	● A wide range of medication doses (from one week, to one month, to two months, and up to six months medication). ● Suitable for use with multiple medications (e.g., MDR-TB, XDR-TB, and pediatric DS-TB treatments).
Portability	● Highly portable. Monitor contains a removal electronic module, the Monitoring Technology, which is highly portable and discrete and holds all the dosing history and adherence data needed by health care providers.
Durability	● Monitor able to survive the entire dosage period including any transportation of the Monitor required in the use thereof or in

	the transfer of data therefrom.
Reusability	● Monitoring Technology re-usable (i.e., removable from Container, battery removable and replaceable, with minimal loss of accuracy/reliability for original and one additional patient/user). ● Monitoring Technology can be removed from the Container and incorporated into another Container. ● Monitoring Technology battery easily removable and replaceable with no damage to Monitor. ● Monitoring Technology re-usable for 3 additional patients/users (assuming patient treatment is approximately 6 months).
Data Capture	● Record patient medication dosing history by capturing time and date Monitor is opened to access medication. Event captured via a simple well-established technology such as a microswitch or magnetic trigger sensor, with components that can be easily integrated in the Monitor. ● Mechanism to eliminate false indications/events (Example of such mechanism: all events detected within a 5 min period are recorded as one event). ● On a daily basis the Monitoring Technology will run a simple diagnostic and record results to ensure the device is functional and no major malfunction has occurred. This data will be transmitted via long-range wireless data transfer protocol and/or via USB transfer protocol.
Data Storage	● Storage of medication dosing history capturing one daily dosing event for up to a six-month period. ● Memory can be manually erased/cleared when Monitoring Technology is prepared for re-use with another patient. ● Minimum memory size = 8 MB ● Non-volatile memory that does not lose data due to loss of power (ex- FRAM, EEPROM, other non-volatile flash memory).

Data Transfer	● "Periodic" data transfer via long-range wireless data transfer with periodic batch transfer of real-time monitored data occurring twice per week.
	● Backup data transfer protocol via Micro USB (3.0) – high data transfer rates (up to 4.8 Gbits/s) with low power consumption to be used in the event primary transfer method fails.
	● Suggested long-range wireless transfer: Low power consumption GSM/GPRS Module that can be programmed to transfer data in batches twice a week.
	● Specs:
	  ● Frequency Bands: between 850 MHz and 1900 MHz.
	  ● Power consumption: Idle Mode ~<7.0 mA, Average communication ~350 mA, Maximum communication ~2000mA.
	  ● Requires SIM card.

Digital Alerts	● Three different visual (LED) alerts:
	  ● Medication Dosing Alert to remind patients of dosing
	  ● Malfunction Alert to indicate failures, like low battery.
	  ● Medication Refill Alert
	● Audible Alert (buzzer) to indicate Medication Dosing
	● Alerts are easily and remotely programmable.

Power Source	● Disposable battery (Lithium-Ion AA) with a minimum life of 1 month. ● Fast/efficient battery replacement without the need of special tools.

Back-end system integration requirements

Medication Monitoring Device - Basic Version

Data transfer to occur from the medication monitoring device via a USB connection to computer that will integrate patient data into the existing back-end system. This transfer will include data collected from monitoring patient behavior (date and time of patient medication taking) as well as a daily diagnostic report that demonstrates the device remains functional each day. Medication monitoring device manufacturer must provide exact specifications on the format and the computer language code of the data transfer packet that will be transferred via a USB cable. Medication monitoring device manufacturer must also assist back-end developers to program and create a software adapter plug-in that will allow the existing back-end system to accept the data packet and integrate into the patient database.

Medication Monitoring Device - Real Time Version

Data transfer to occur from the medication monitoring device via wireless telecommunication network to servers that will integrate patient data into the existing back-end system. This data transfer will be sent as a data packet which will include the data collected from monitoring patient behavior (date and time of medication taking) as well as a daily diagnostic report that demonstrates the device remains functional each day. Medication monitoring device manufacturer must provide exact specifications on the format and the computer language code of the data transfer packet that will be transferred wirelessly. The medication monitoring device manufacturer must also develop and provide the appropriate API (Application Program Interface) that will allow the existing back-end system to accept the data packet and integrate into the patient database.

Quality Requirements & Testing Protocols

Summary of QA Criteria

The following table highlights suggested quality checks and tests that should be conducted to ensure the TB Reminder-Monitor meets all defined and expected technical and quality requirements.

	Requirements	Quality Assurance Evaluation Procedure
Container Requirements	● Can accomodate 1 month of anti-tuberculosis fixed-dose combination (FDC), ● Patients can open the box and then take out the medication.	● Verify dimensions of Container. Ensure that Container is able to hold one month of FDC medication. ● Evaluate the ease of use and access for patient to take medication in and out of Container. ● Verify that the box closes securely and is not opened when shaken, vibrated, dropped, or turned upside-down.
	● Internal and external materials	● Test box surface for sticker adhesion

	are designed to facilitate placement of labels or stickers.	and whether sticker remains secure on surface. ● Ensure adhesion remains good in high humidity conditions and when the box is subjected to vibration.
Functional Requirements	● Separate and distinct alerts for daily dosing, monthly refill, and low battery via LED lights and sound.	● Conduct functional tests (as suggested in section A below) by setting alerts and verifying function for all scenarios and all types of reminders. **Please reference Section A for functional testing protocol.**
	● Field-level medical workers set medication reminders based on patients' needs (should be able to customize dosing reminder times and refill/visit reminder date).	● Obtain configuration software from supplier and evaluate the ease in understanding device programming/reprogramming procedures and amount of training required.
	● To identify the date and time each time patient opens and closes the Container, and record such dosing events: - Record accuracy shall be ≥99%, weekly recording clock error ≤ ±90 seconds. - Record number of medication incidents more than1500 articles.	● Verify accurate data capture with repeated opening and closing of container as outlined in **Section A functional testing**. ● Measure maximum capacity of memory. Request supplier to provide device sample with a minimum of 1500 events recorded to demonstrate full capacity. ● Verify accuracy of date and time against recorded events captured during Functional Test **(Section A)**.
	● Battery-powered: at 4℃~40℃ environment, batteries should be guaranteed for more than two months of normal use WITHOUT recharging. ● Should have the function of automatically detecting and recording each day the charge remaining and generate a low battery level alert when less than 5 days battery power reamins. ● Health care workers should be able to replace the battery without the use of special tools.	● Measure battery output voltage after stored in cold environment after set period of time. ● Test if low battery alert activated appropriately measures and records battery voltage on a regular basis. ● Evaluate battery replacement mechanism, and that it does not require special tools. ● Conduct a Reverse Polarity test: plug the batteries in the wrong way in battery holder and the electronics should remain undamaged. ● Conduct high-voltage protection test: components are protected from voltage surges.
	● Daily dosing events and device status automatically recorded and stored for download or for "real-time" delivery.	● Verify dosing events and device status automatically and accurately captured and stored.
	● Device should use non-volatile memory storage media, and data storage memory can only be deleted manually/cleared. ● When the battery/power supply is removed for up to 120 seconds, device maintains	● Test time clock and data retention: disconnect the battery for 30, 60, 120 seconds and make sure that the clock and data is preserved. ● Evaluate method of deleting/clearing memory.

	date/time fidelity.	
	● Device should automatically connect, sync, and download data via Micro USB.	● Check device connectivity to a PC: connect via USB to a computer that does not have the configuration software and verify that PC recognizes the device.
Quality requirements	● Container quality --- test items should include, but not be limited to temperature cycle tests, constant hot and humid test, drop test, vibration test, test of solar radiation, repeated pressing 500 tests, repeated 50 times test.	● Conduct **Environmental Testing protocol as outlined in Section C**.
	● Plastic suitable for food and pharmaceutical packaging, plastic such as polypropylene copolymer resin. ● Wear-resistant, hygienic, easy to disinfect.	● Verify what type of resin used in plastics: - Must be suitable for food and pharmaceutical packaging - Must be wear-resistant - Must be hygienic - Must be easy to disinfect
	● Anti Fall: 1M fall to a hard surface, to work correctly: - Keep the overall structural integrity - To protect internal electronic components and drugs from damage - Normal opening and closing - Not to lose event capturing, or any impact on the accuracy of data collection	● Drop test of plastics and cartons of shipped plastics can be conducted by **protocol outlined in Section B.**
	● Anti vibration:10 ~ 55Hz And amplitude 0.35mm: - Appears intact and working properly (no "panic" or "unplanned downtime"), - Able to adapt to standard transport environment.	● **Environmental testing as outlined in Section C.**
	● Other: Normal working in these defined conditions - Temperature: -30 ℃~ +40℃; - Humidity: 0 ~ 95% ; - Able to adapt to the dusty environment.	● Conduct **Functional Tests (Section A) of Devices after Environment Test (Section C**)
Software Specifications	TB Reminder-Monitors must be accompanied by and operate with electronic software systems, for use on stand-alone client software that (i) can initiate patients on TB Reminder-Monitors (including setting of alarms/reminders), and (ii) can record, store, and deliver patient medication event information.	● Supplier must provide a software/application to configure device and manage patient data. ● Verify that device captures and provides appropriate patient data. ● Verify specifications as defined regarding reminders and dosing event delivery.

Detailed Testing Protocols

Device Functionality Test Protocol

Each TB Reminder-Monitor should be passed through a thorough functional evaluation to determine the quality of the device and the consistency of quality maintained between samples provided for evaluation. This functional testing protocol will evaluate the overall essential functions of the TB Reminder-Monitor. This protocol will also test that the reminder LEDs, buzzers and sensors are in good functional condition. A step by step functional test is outlined below:

- Plug in TB Reminder-Monitor to a computer to determine ease of connecting with new software:
  - First plug in device to a computer that does not have the configuration software. PC should recognize the device.
  - Then plug the computer into a computer that does contain the configuration software. PC should recognize the device.

- Using configuration software, set medication alarm and medication refill alarm

- Once medication alarm is set, test device response under different user scenarios:
  - Record if medication alarm (LED and Buzzer) is activated as programed.
  - Once medication alarm is ON, open container box. Record time container box is opened.
  - Reset medication alarm, and wait till medication alarm turns ON. Do not open the container box. Once medication alarm turns OFF, wait for first follow-up alarm. Once follow-up alarm is ON, open container box. Record time container box is opened.
  - Reset medication alarm, wait till medication alarm turns ON. Do not open the container box. Wait till first follow-up Alarm is ON. Do not open the container box. Wait till second follow-up Alarm is ON. Open container box. Record time container box is opened.
  - Repeat steps for as many follow-up alarms possible for the device. Record time container box is opened each time.
  - Reset medication alarm. Open container box before medication alarm is ON. Close container box and wait to see if medication alarm turns ON. If medication alarm turns ON, note that this effect is not desired.
  - Evaluate Container to see if it accounts for patient "fiddle." Very quickly open and close the container lid and verify if this is recorded as an event. If patient does not have enough time to take medication while Container is open, then this should not be recorded as an event.

- Upon completion of the medication alarm functional test, plug device to computer and review event log. Ensure accurate time stamps of Container opening against recorded time during testing.

- Once medication refill alarm is set, test to see if alarm turns ON as programmed.

Container Drop Test Protocol

This procedure outlines the steps necessary to determine the durability of Container units in their final use condition against improper handling or abuse in transit. The testing procedure is as follows:

- Once all units have passed visual inspection, insert the fully assembled Module into the Container and confirm correct orientation for snap retention into the Container.

- Drop height as described in the table below. Drop the Container flat on all six sides, unless instructed otherwise.

  Sequence Drop Height 1 through 3 until no failures: n=6
  - Height 1 = 76 cm
  - Height 2 = 63 cm
  - Height 3 = 45 cm

- Re-inspect all units visually, reporting any defects.

- If defects are found, investigate possible causes and corrections.
- Unlatch and re-latch the units three cycles to verify that they still function properly and have seal integrity.

- Record the number of test units evaluated, the number and types of defects that were found, and anything unusual detected during the test.

- Pack the TB Reminder Monitors in the appropriate cartons and tape the cartons shut

- Drop the carton from specified heights (see above) onto each of the six sides

- Re-inspect all units visually, record the number of test units, report the number and types of defects, report anything unusual that was detected.

Device Environmental Testing Protocol

1. Thermal Shock Test

- Test Conditions:
  High temperature: 50 ℃
  Low temperature: -40 ℃
  Temperature change rate: 0.5 ℃/min
  Test duration: 10h
  Retention time at high, low and room temperatures: 30 min

- Thereafter, conduct Functional test (Section A, above) after environmental condition test, determine if the functions of the TB Reminder-Monitors continue to function to specification, including medication alert, information transmission to the platform and its accuracy.

2. Constant Damp Heat Test

- Test Conditions
  Temperature: 40 ℃
  Humidity: 85% RH
  Test duration: 10 DOTS

- Thereafter, conduct Functional test (Section A, above) after environmental condition test, determine if the functions of the TB Reminder-Monitors continue to function to specification, including medication alert, information transmission to the platform and its accuracy.

3. Drop Test

- Test Conditions
  Drop height: 1m;
  Test method: Repeat natural drops on hard surfaces, 10 drops/box.

- Thereafter, conduct Functional test (Section A, above) after environmental condition test, determine if the functions of the electronic pill boxes continue to function to specification, including medication alert, information transmission to the platform and its accuracy.

4. Vibration Test

- Test Conditions
  Frequency of sinusoidal vibration: 10 – 55 Hz;
  Amplitude of sinusoidal vibration: 0.35mm;
  Test duration: 0.5h/axis
  Test axes: XYZ axes

- Thereafter, conduct Functional test (Section A, above) after environmental condition test, determine if the functions of the TB Reminder-Monitors continue to function to specification, including medication alert, information transmission to the platform and its accuracy.

5. Solar Radiation Test

- Test Conditions
  Radiation intensity: 0.51W/m^2@340nm
  Chamber temperature for light cycle: 40 ℃
  Chamber temperature for dark cycle: 25 ℃
  Test duration: 24 DOTS (radiation for 20 DOTS, pause for 4)

- After test, inspected if there were obvious sun cracks or softening in appearance. In addition, conduct Functional test (Section A, above) after environmental condition test, determine if the functions of the TB Reminder-Monitors continue to function to specification, including medication alert, information transmission to the platform and its accuracy.

Field Test/Pilot Study Protocol

Objective

TB Reminder-Monitors have proven to be an effective and pragmatic intervention for adherence reminding and measurement in China. The field test/pilot study outlined below seeks to examine the usability of TB Reminder-Monitors in both the patient as well as the provider populations in other regions. Specific objectives related to patient and provider use are to evaluate (i) user (patient and provider) performance of the TB Reminder-Monitors, and (ii) user (patient and provider) acceptance/satisfaction with the TB Reminder-Monitors.

Participant Demographics Selection

At least 40 adult participants should be enrolled and participate in the study. A total of 20 participants should be patients diagnosed with pulmonary tuberculosis (TB) ("Patient Participants") and a total of 20 participants should be health care providers ("Provider Participants"). Ideally, a mix of urban versus rural, geographic coverage, gender, socio-economic status should be reflected in the patient and provider populations. Demographic data (age, gender, literacy level, living conditions, basic information on medication management for patients taking other medication, IT experience, other co-morbidities) should be collected from Patient Participants and Provider Participants by means of questionnaires completed at the time of inclusion. Once selected, Patient Participants receive basic information about the importance of adherence, basic instructions about correct use of the TB Reminder-Monitors, and an explanation for how the TB Reminder-Monitors will help them to remember to take their medications as prescribed and attend any

additional examinations. Patient Participants should sign an Informed Consent Form ("ICF") prior to enrollment indicating that they agree to the terms of participation including: (i) obtaining their drugs from the dispensary, (ii) attending their sputum examination at the designated intervals at the dispensary, (iii) accepting supervision from the health workers, and (iv) using and keeping the TB Reminder-Monitors e as directed.

The following **inclusion** criteria should be used for Patient Participants:

- at least 18 years old
- newly-registered active TB patients (smear-positive or smear-negative)
- being on TB treatment for at least 6 months
- willing to participate in the study for 3 weeks
- conscious without any mental disease
- conscious without any communication impairment (mental, visual, auditory or speech)
- without any motor skill or dexterity impairment that would prevent operation of the TB Reminder-Monitors
- expressed intent to live locally during treatment
- willing to use the TB Reminder-Monitors for a period of 3 weeks
- willing to answer questions at the time of inclusion and at the end of the test period
- willing to provide voluntary written informed consent to participation in the research

The following **exclusion** criteria should be used for patient participants:

- mental health issues
- MDR-TB patient
- visual, auditory, dexterity, or speech disability
- patients who are not self-administering their treatment or are otherwise not responsible for their own medication

Once selected, Provider Participants will receive basic information about the importance of adherence, basic instructions about the protocol and how correct use of the TB Reminder-Monitors and the associated ICT System will help their patients take their medications as prescribed and will help providers more effectively and differentially manage their patients. Participants will sign the ICF prior to enrolment indicating that they agree to the terms of participation including: (i) use of the TB Reminder-Monitors in their practice for 3 weeks, and (ii) answering end of study questions.

The following **inclusion** criteria should be used for Provider Participants:

- licensed medical provider treating TB population in study region
- willing to implement the MM Device and associated ICT System into their practice for a period of 3 weeks

- willing to answer questions at the time of inclusion and at the end of the test period
- willing to provide voluntary informed consent to participation in the research
- technical and ICT familiarity and capability sufficient to use effectively the MM Device and associated ICT System.

The following **exclusion** criteria should be used for Provider Participants:

- mental health issues
- visual, auditory, dexterity or speech disability
- lack of sufficient technical and ICT familiarity and capability

Methodology

Overview

This field/pilot study contemplates a "multi-method component design" which includes a combination of quantitative and qualitative research methods to evaluate the various aspects of usability. The study consists of four different sets of one-on-one testing sessions, two for patients (one at patient initiation/training and the other after three weeks of use) and two for providers (one at initial/training and the other after three weeks of use). Each of the sessions lasts approximately 30-45 minutes.

In order for the patients to use the TB Reminder Monitors correctly, the user must be able to complete two critical steps: understand the reminders and intended action, and properly access medication from the TB Reminder Monitors. These activities should be broken down into the series of consecutive actions that are necessary to reach the desired result and each should be separately analyzed. The researcher should assess the various actions as correctly or incorrectly carried out. The researcher should also note down how long the user took to carry out the steps correctly. After the participant correctly carries out all of the critical steps, he or she will be given a scale on which to indicate how difficult it was to use the TB Reminder Monitors. This scale will be designed appropriately based upon patient literacy and language considerations.

In order for the providers to use the TB Reminder Monitors correctly, the user must be able to complete two critical steps: load the TB Reminder Monitors with medication and program reminders accordingly, and download data off of the TB Reminder Monitors. Each of these steps should be systematically analyzed as a series of consecutive actions that are necessary to reach the desired result. The researcher should assess the various actions as correctly or incorrectly carried out. The researcher should also note down how long the user took to carry out the steps correctly. After each participant correctly carries out all of the critical steps, he or she should be given a scale on which to indicate how difficult it was to use the TB Reminder Monitors. This scale will be designed appropriately based upon patient literacy and language considerations.

After patients and providers have used the TB Reminder-Monitors for three weeks in real-world settings, semi-structured interviews are used to gain information on the satisfaction with and acceptability of the TB Reminder Monitors. The researcher prepares a list of 19 questions as a guide during the interviews. The order of the questions is not fixed and is, among other things, dependent upon the answers of the test subject. After the interviews, the participants are given 9 questions to answer on a form with the purpose of quantitatively measuring satisfaction and acceptability. The users answer on a 5-point Likert scale (1-5), whereby higher scores indicated a more positive experience.

Date Collection and Coding

The data collection and coding for this study are intended to collect sufficient and appropriate data to facilitate identification and understanding of the root causes of any use events or deficiencies with TB Reminder Monitors. A use event refers to any instance in which the product is not used as the designer intended or does not act as the user expected. Both subjective and empirical data will be collected, as described below.

Empirical Data

Data, such as successful or failed performance of tasks, will be measured directly rather than from participant opinions. Tasks and questions are scored either as "OK" or "Other". A score of "OK" means that the task or question is completed successfully without issue. A score of "Other" requires root cause probing to identify the source of the issue.

Subjective Data

Participants are asked a series of subjective feedback questions at the end of the session. Additionally, participants provide comments on a number of product likes, dislikes, and improvements throughout each of the sessions. All of this subjective data will be qualitatively coded and categorized to best identify patterns in the data.

Data analysis

Evaluating practical usability

The total time duration required to carry out all of the steps for using the TB Reminder Monitors should be expressed per patient as the number of required seconds. The median time, interquartile distance and range should be calculated for the entire group, as well as separately for the patients and for the providers.

Based on this list, with a systematic analysis of all the steps concerning the correct usage of the TB Reminder Monitors, the actions per patient can be dichotomized (*i.e.,* step carried out correctly = 1; step carried out incorrectly = 0). A total score can be calculated per person. The proportion of test subjects who make mistakes should be calculated separately for each step. The scores on the preference scale that assessed the degree of difficulty of use are expressed as a median score for the entire group, as well as separately for the patients and for the providers. These

insights and data will identify operational and acceptance issues between users (patients and providers) and the TB Reminder Monitors.

Evaluating satisfaction and acceptability

The scores on the preference scale that assesses the satisfaction and acceptability will be expressed as a median score for the entire group, as well as separately for the patients and for the providers. The answers to the various questions from the semi-structured interview during the second appointment (after the testing period) will be studied in detail to derive, via an analysis of content, various themes from these answers. A record will be kept of how many times a certain answer came up in the semi-structured interviews for the entire group, as well as separately for the patients and for the healthy volunteers. Two independent researchers, who will then subsequently compare their results, should carry out these processes.

Conclusion

This field/pilot study will permit the systematic evaluation in pragmatic settings of the usability of the TB Reminder Monitors. This type of electronic monitoring device has been validated as an effective and pragmatic intervention for adherence reminding and measurement. However, critical to successful use of such devices in improving patient medication adherence is the ability for providers and patients to effectively use the devices. To optimally design and deploy an electronic monitoring device, one must consider patient and provider usability, satisfaction, and acceptability. Accordingly, through the implementation of a combination of quantitative and qualitative research methods, this study will elicit evidence on usability in view of user performance, satisfaction, and acceptability information.

Appendix II

Electronic Medication Monitors: Ensuring Pill-in-Hand Adherence at Low Cost

Two available, low-cost, scalable technologies can ensure that TB patients make a full recovery. Supported by a unified ICT platform and mobile application, these complementary solutions enable responsive, patient-centered care across a diversity of low-resource environments.

99DOTS

Medication is wrapped in custom paper envelopes with hidden phone numbers printed on the inside. Patients place free calls to the revealed numbers to show that drugs are taken.

- Very low cost
- Fosters patient engagement
- Deployed at scale in low-resource setting
- Learn more at 99dots.org

Provided by everwell

evriMED

A reusable electronic monitoring device is housed within a flexible printed paperboard container and passively registers when a patient opens the container to take medication.

- Does not depend on phone access
- Supports complex MDR-TB regimens
- Deployed at scale in low-resource setting
- Learn more at evrimed.com

Provided by wisepill

Simple, Flexible, Robust

Both solutions have demonstrated feasibility and acceptance in low-resource environments. 99DOTS envelopes can be added at any point in the medication supply chain. evriMED boxes can be printed and customized for any TB treatment regimen.

Personalized, Data-Driven Care

Healthcare providers visualize real-time adherence information on a computer or phone. Algorithms automatically identify patients that need prioritized attention and follow-up. Unified ICT platform supports both 99DOTS and evriMED, and is interoperable with others.