Digital Medication Monitors To Support Patient-Centric Observation, Adherence Support, and Differentiated Care of Tuberculosis Patients in Resource-Limited Settings
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Background

Product Use Summary/Medical Need.
Tuberculosis (TB) is now 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:

- patients should be given **timely and impactful reminders** of when and how to take their medication – which reminders, particularly when used in

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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.

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 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

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\(^7\) 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.

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.

**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. 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, digital 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."

- **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."

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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.

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. 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.

In fulfillment of The Arcady Group’s global access obligations in connection with grants received from the Bill & Melinda Gates Foundation, set forth herein are three sections, or documents, that contain this TPP and these testing protocols. 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:

Section 1: A Target Product Profile of an Electronic Dose Monitor
Section 2: QA Requirements & Testing Protocol
Section 3: Field Test/Pilot Study Protocol
Section 4: evriMED®: An Available, Scalable Solution

SECTION 1: Target Product Profile (TPP) of an TB Reminder-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 aqueous-coated containerboard 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.

<table>
<thead>
<tr>
<th>Child Resistant</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Senior Friendly</td>
<td>Yes – to the extent that the package is easy to operate. Will not require testing protocol for senior friendly validation.</td>
</tr>
<tr>
<td>Anti-tamper</td>
<td>Yes – standard available tamper-evident features such as tape seals.</td>
</tr>
<tr>
<td>Waterproof</td>
<td>Water-resistant – suitable for high humidity environments.</td>
</tr>
<tr>
<td>Medication accommodation</td>
<td>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).</td>
</tr>
<tr>
<td>Portability</td>
<td>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.</td>
</tr>
<tr>
<td>Durability</td>
<td>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.</td>
</tr>
<tr>
<td>Reusability</td>
<td>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).</td>
</tr>
<tr>
<td>Data Capture</td>
<td>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.</td>
</tr>
</tbody>
</table>
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.

### SECTION 2: 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.

<table>
<thead>
<tr>
<th>Container Requirements</th>
<th>Requirements</th>
<th>Quality Assurance Evaluation Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Can accomodate 1 month of anti-tuberculosis fixed-dose combination (FDC), Patients can open the box and then take out the medication.</td>
<td>• 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</td>
</tr>
<tr>
<td>Functional Requirements</td>
<td>• Internal and external materials are designed to facilitate placement of labels or stickers.</td>
<td>• Verify that the box closes securely and is not opened when shaken, vibrated, dropped, or turned upside-down.</td>
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<td>-------------------------</td>
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<td>--------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>• Test box surface for sticker adhesion and whether sticker remains secure on surface.</td>
<td>• Ensure adhesion remains good in high humidity conditions and when the box is subjected to vibration.</td>
</tr>
<tr>
<td></td>
<td>• Field-level medical workers set medication reminders based on patients' needs (should be able to customize dosing reminder times and refill/visit reminder date).</td>
<td>• 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.</td>
</tr>
<tr>
<td></td>
<td>• To identify the date and time each time patient opens and closes the Container, and record such dosing events:</td>
<td>• Verify accurate data capture with repeated opening and closing of container as outlined in Section A functional testing.</td>
</tr>
<tr>
<td></td>
<td>- Record accuracy shall be ≥99%, weekly recording clock error ≤ ±90 seconds.</td>
<td>• Measure maximum capacity of memory. Request supplier to provide device sample with a minimum of 1500 events recorded to demonstrate full capacity.</td>
</tr>
<tr>
<td></td>
<td>- Record number of medication incidents more than 1500 articles.</td>
<td>• Verify accuracy of date and time against recorded events captured during Functional Test (Section A).</td>
</tr>
<tr>
<td></td>
<td>• Battery-powered: at 4℃~40℃ environment, batteries should be guaranteed for more than two months of normal use WITHOUT recharging.</td>
<td>• Measure battery output voltage after stored in cold environment after set period of time.</td>
</tr>
<tr>
<td></td>
<td>• 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 remains.</td>
<td>• Test if low battery alert activated appropriately measures and records battery voltage on a regular basis.</td>
</tr>
<tr>
<td></td>
<td>• Health care workers should be able to replace the battery without the use of special tools.</td>
<td>• Evaluate battery replacement mechanism, and that it does not require special tools.</td>
</tr>
<tr>
<td></td>
<td>• Conduct a Reverse Polarity test: plug the batteries in the wrong way in battery holder and the electronics should remain undamaged.</td>
<td>• Conduct high-voltage protection test: components are protected from voltage surges.</td>
</tr>
<tr>
<td></td>
<td>• Daily dosing events and device status automatically recorded and stored for download or for “real-time” delivery.</td>
<td>• Daily dosing events and device status automatically and accurately captured and stored.</td>
</tr>
</tbody>
</table>
|                         | • Device should use non-volatile memory storage media, and data storage | • Test time clock and data retention: disconnect the battery for 30, 60, 120
| Quality requirements | • Memory can only be deleted manually/cleared.  
  • When the battery/power supply is removed for up to 120 seconds, device maintains date/time fidelity.  
  • Device should automatically connect, sync, and download data via Micro USB.  
  • Evaluate method of deleting/clearing memory.  
  • 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.  
  • 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.  
  • Plastic suitable for food and pharmaceutical packaging, plastic such as polypropylene copolymer resin.  
  • Wear-resistant, hygienic, 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  
  • 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.  
  • Other: Normal working in these defined conditions  
    - Temperature: -30 °C~ +40°C;  
    - Humidity: 0 ~ 95% ;  
    - Able to adapt to the dusty environment.  
  • Conduct Environmental Testing protocol as outlined in Section C.  
  • Conduct Environmental testing as outlined in Section C.  
  • Environmental testing as outlined in Section C.  
  • Other: Normal working in these defined conditions  
  • Conduct Functional Tests (Section A) of Devices after Environment Test (Section C)  
  • 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.  
  • Other: Normal working in these defined conditions  
    - Temperature: -30 °C~ +40°C;  
    - Humidity: 0 ~ 95% ;  
    - Able to adapt to the dusty environment.  
  | 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:
  o First plug in device to a computer that does not have the configuration software. PC should recognize the device.
  o 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:
  o Record if medication alarm (LED and Buzzer) is activated as programmed.
  o Once medication alarm is ON, open container box. Record time container box is opened.
  o 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.
  o 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.
  o Repeat steps for as many follow-up alarms possible for the device. Record time container box is opened each time.
  o 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.
  o 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.
  o 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 ºC
     - Low temperature: -40 ºC
     - Temperature change rate: 0.5 ºC/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 ºC
     - Humidity: 85% RH
     - Test duration: 10 h

     • 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/m²@340nm
     Chamber temperature for light cycle: 40 °C
     Chamber temperature for dark cycle: 25 °C
     Test duration: 24 h (radiation for 20 h, 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.

**SECTION 3: 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 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 will 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 will 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 will 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.

**Data 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
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.

SECTION 4: An Available, Scalable Solution- evriMED

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. It meets all of the technical specifications set forth in Section 1 hereof, and it has successfully passed both the quality assurance and the field/pilot test processes described in Section 2, and 3 hereof. evriMED® also is highly scalable and affordable, with special pricing available for global health use. Detailed information (including contact information) about the evriMED® device can we found at http://www.evrimed.com.

The salient technological features of evriMED® include:

- Suitable for use with blister packaged TB medications.
• Modular construction to reduce cost and permit container customization – including versions suitable for DS-TB, MRD-TB, and pediatric DS-TB treatments.
• Significant billboard space to communicate to patients and allow for region-specific customization.
• Simple data acquisition using a magnetic sensor to detect container opening.
• Programmable Alert Mechanisms consisting of:
  o Three (3) LED Lights: Green - Dose Alert; Yellow – Refill; Red - Low Battery
  o 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.

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.

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) or other well-constructed adherence management systems (e.g., 99DOTS). For smaller pilots or evaluations, even simpler software has been developed for licensure. Additional information available at http://www.evrimed.com.
Additional Information
For additional information and resources related to TB medication adherence and monitoring technologies, please visit thearcadylgroup.com/global-access.