**PROTOCOL**

**TITLE:**  DrOTS: Drone Observed Therapy in Madagascar

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**A. SPECIFIC AIMS**

1. To assess the adequacy and acceptance of the introduction of new technological approaches (i.e. drones, video-based curricula and Medication Event Reminder-Monitors) in TB control and prevention as introduced by the Drone Observed Therapy System (DrOTS) at the levels of the beneficiaries (patients, communities) and the health care providers (community health workers, medical staff, program implementers);
2. To evaluate the performance of the new technologies with regards to processes and outcomes;
3. To assess the outcomes and impact of the integrated interventions for the population concerned based on the standardized TB indicators (additional case notification and treatment initiation, adherence and success).

**B. BACKGROUND AND SIGNIFICANCE**

Tuberculosis (TB) is a preventable infectious disease caused by organisms of the *mycobacterium tuberculosis* complex. It remains a leading cause of mortality and morbidity worldwide, accounting for an estimated 1.4 million deaths in 2015 [1]. The End TB Strategy, endorsed by the World Health Organization (WHO), aims at a 95% reduction of TB-deaths and a 90% reduction of the TB incidence rate by 2035 [2]. The strategy builds on three pillars: (1) integrated, patient-centered care and treatment; (2) bold policies and supportive systems; and (3) intensified research and innovation [2].

# C. PRELIMINARY STUDIES

The use of drones for humanitarian purposes, such as health care delivery, is a recent development on which little scientific literature exists to date [3]. There is a momentum to explore the potential of drones in health care delivery in Africa, where three pioneering drone projects are at running at a pilot stage: (i) in Ghana, for delivery of vaccines [4]; (ii) in Rwanda, for delivery of blood for transfusions [5]; and (iii) in Malawi, for transportation of HIV samples in children [6]. In 2014, Médecins sans Frontières tested the collection of sputum samples for TB diagnosis in remote areas in Papua New Guinea and considered it a useful method of connecting remote areas to the health system; however, the drone technology was yet insufficient for purpose [7]. To date, there is only one cost, one cost-effectiveness and one acceptability study assessing health care delivery in low-income countries. The impact on health outcomes and acceptance of the technology in remote areas has not yet been assessed [6, 8, 9]. An evidence base regarding if and how drones have potential in health care delivery in different settings is largely yet to be established.

The use of mobile phones or tablets for data collection, diagnosis algorithms and remote diagnosis has developed rapidly over the past few years [10-12]. These technologies have been primarily used by trained health care personnel. Here, the goal is to target community health workers (CHWs) with simple video-based instruction and training curricula. This extends from the concept that laypeople can learn to perform simple tasks and activities by watching “how-to” videos on YouTube. There is reportedly a lack of evidence whether such technology targeted to CHWs has an impact on disease outcomes, let alone when targeted to patients directly. [10]

The MERM device combines a medication reminder system (i.e. by audio or visual signals) with an electronic monitoring system that records times when the medication box is opened. Reminder systems have been found to significantly improve treatment adherence across different regimens or patient backgrounds [13, 14]. Facility-based directly observed treatment short course (DOTS) has been implemented as the main approach to improve TB treatment adherence without sufficient evidence that it was effective [15]. Meanwhile, community-based DOTS was found to promote successful treatment in low- and middle-income settings [16, 17]. The MERM technology combines the successful reminder and monitoring systems with a patient-centric approach [2]. In one study, the use of technology was shown to improve adherence by 40%, and up to 50% when combined with a text message-based follow-up system [18]. However, the combination of the technology with a drone-supported remote treatment initiation and follow up system has not be evaluated to date.

**D. RESEARCH DESIGN AND METHODS**

1. **Rationale/overview**

In line with the National Strategic TB Plan and the End TB Strategy, the DrOTS-project offers integrated, patient-centered care and prevention and addresses bottlenecks of the pathway from exposure to cure through three innovative technologies and interlinked interventions in a rural, remote setting of Madagascar. The three innovative technologies employed are:

1. **Drones** that are based at a diagnostic and treatment center and transport sputum samples as well as TB drugs to and from remote villages [4].
2. A **video-based training curriculum** that instruct community health workers (CHWs) in taking sputum samples of suspected TB cases for TB diagnosis.
3. The **Medication Event Reminder-Monitor (MERM)**, a box containing TB drugs that audio-visually reminds patients to take medication and records the times it is opened to support observation of treatment adherence.

We aim to assess the feasibility of using these technologies, both as individual units and as a comprehensive treatment system that can be integrated into the existing framework of TB treatment in Madagascar.

1. **Research Site**

The study will be piloted in Ifanadiana district, located in the south-central highlands of Madagascar. The bulk of the population is scattered in remote villages with about 300-500 inhabitants each. These villages are accessible only by footpaths that take many hours to traverse. The communities are characterized by a young age distribution, low literacy levels, high poverty levels and low access to sanitation and safe drinking water. The DrOTS project will be gradually implemented across 36 randomly selected villages, which are within the drone flight range of 30 km from the Centre ValBio research center.

1. **Study sample**

Male and female adults or children age 15+ years with full cognitive ability that have been diagnosed with TB will be included in the study. Patients with drug-resistant TB will be excluded from the study. We assume that 5% of all individuals presenting symptoms (primarily a productive cough) will test positive for tuberculosis. Assuming an average village population of 250, and 10% of the population presenting a productive cough, approximately 115 participants will be expected to test positive and be eligible to participate in the study. However, due to limited information in the study area regarding tuberculosis and an anticipated large number of undiagnosed cases, incident rates may vary.

1. **Screening**

Screening will occur at the village level. Following a presentation to the village conducted in conjunction with the village elder, individuals with chronic cough will be instructed to attend a screening clinic the following morning. At that clinic, held in the privacy of a hut or tent, a health team worker using standard evaluation criteria set by the national TB program will identify subjects.

1. **Procedures**

In brief: (1) Upon identifying a suspected TB case according to above screening procedures, a health worker activates an emergency satellite beacon that sends a signal to the local diagnostic and treatment center. (2) Upon receiving the signal, the diagnostic and treatment center launches a drone to the village containing a sputum sample cup and a mobile device. (3) In the village, the mobile device plays an instructional video directing the health worker to collect sputum. (4) Once the sputum sample is taken, the drone flies the sample back to the diagnostic and treatment center where it is tested for TB using GeneXpert MTB/RIF assay diagnostic test. A quality assurance program for microscopy and molecular diagnosis will be established with the Institut Pasteur de Madagascar (IPM; Antananarivo, Madagascar) to ensure for accurate diagnosis in the context of new technology (GeneXpert MTB/RIF) implementation in NTP laboratories. (5) If the sample is found positive for *M. tuberculosis*, the patient will be delivered a one-month dose of first-line TB drugs via drone. The drugs will be contained in a MERM, which records daily opening times. (7) Every month, the drone flies into the village to collect the empty MERM and delivers a new, filled box. Data from the MERM will be analyzed; the opening times are used as a proxy for treatment adherence. (8) At key points in the study, health workers will also be instructed to collect urine samples for assessment of drug toxicities and consumption. These samples will be tested using urinalysis and TB-drug dosing tests. If drug toxicity is suspected, the patient will be asked to provide a blood sample for CBC/LFT testing.

Aim 1 will be addressed through two cross-sectional questionnaire surveys: at baseline, prior to DrOTS-project implementations and at end line, after implementation in all 36 villages. Interviews will be conducted in the villages with (a) all TB cases identified; (b) randomly selected community members; (c) CHWs; as well as with (d) health care providers; and (e) representatives from the National TB Control Program.

Aim 2 will be assessed by the performance indicators of each technology that are recorded on a continuous basis by the DrOTS-project implementers. Drones, mobile devices playing the video-based curriculum and the MERM will be under scrutiny for operational data, cost, functionality, failures, accidents, etc.

Data from the routine health information system (HIS) will be collected in monthly intervals in the affected diagnostic and treatment center and across the NTP. Furthermore, TB prevalence data will be collected by the health team going to the field. Importantly, data collected within this project relevant to the NTP will be channeled back into the routine HIS of the district.

The data collected in aims 2 and 3 will be utilized for cost-effectiveness analysis of the drones-based TB case finding and treatment provision as compared to the routine approach currently implemented by the National TB Control Program. In order to cross-check MERM data, monthly urine samples will be collected from TB cases to test for bilirubin (an indicator of drug hepatotoxicity) and drug (i.e. isoniazid) metabolites (an indicator of drug consumption) [19]. Urine samples will be collected at the time of drug delivery and transported alongside the MERM by drone.

**E. STATISTICS**

All interviews will be administered via structured questionnaire including closed- and open-ended questions hence applying a mixed-method approach gathering quantitative and qualitative data. Questionnaires will be designed in collaboration with the NTP and pre-tested. Depending on outcomes of the pre-testing, in-depth interviews could be considered more appropriate in certain target groups. Open Data Kit (ODK) software will be used for data collection.

The processes and outcomes of the technology will be assessed by monthly routine reporting, e.g. hours flown, hours logged, as well as incidence reporting, e.g. failure of MERM. ODK as well as an SQL Based Database system will be used to record data.

A series of standardized process and outcome indicators for TB will be assessed. ‘Additional case notifications’ is the typical primary outcome measure of TB interventions and refers to TB cases that would not have been notified in the absence of an intervention [20]. To assess this and other indicators, two case-control analyses will be performed: First, a step-wedge design will be applied to compare pre- and post-intervention measurement using the target villages as their own control, while gradually implementing the interventions in the villages [21]. By recording, at the level of the diagnostic and treatment center, the origin villages from which new cases arise, we can compare the endpoints by village before and after implementation and calculate additional yield [22]. Second, baseline trend data from the three years before the DrOTS-project initiation from intervention as well as a matching number of non-intervention rural villages in the district will be obtained from the diagnostic and treatment center. The non-intervention villages will be randomly selected and serve as an additional control group. Hence, intervention and non-intervention villages from the same district will be compared based on their case notification trend data prior to intervention and after intervention [22].

**F. FUNDING STATUS, DETAILS**

The Global Health Institute (GHI) at Stony Brook University (New York, USA), as a lead applicant, together with the Institut Pasteur Madagascar (IPM; Antananarivo, Madagascar), as a consortium partner, have been awarded funding for the ‘DrOTS: Drones Observed Therapy in Remote Madagascar’-project from TB Reach. The funding begins in April 2017 for a period of 18 months.

**G. HUMAN SUBJECTS RESEARCH PROTECTION FROM RISK**

**Risk to Subjects**

This study poses minimal risks to the subject. Suboptimal treatment and adherence can cause MDR TB [19, 23]. The project uses the best knowledge, high standard treatment and best available technologies to minimize risk of MDR TB development.

**Adequacy of Protection Against Risks**

All sputum testing will be proof-tested by IPM laboratories to ensure quality control and accurate diagnosis during GeneXpert technology implementation in NTP laboratories. Remote surveillance will be provided to subjects through MERMs and blood and urine examination. Additional medical monitoring will be provided in accordance to standard tuberculosis care and routine visits by the Centre ValBio health team over 6 months of treatment. The team will consist of a doctor specializing in TB as well as a nurse. The health teams will regularly visit TB cases to observe disease progression (e.g. coughing frequency). If a situation arises in which remote care is inadequate, or the subject needs urgent care, healthcare workers will help transport the subject to a health care facility.

**Potential Benefits of Proposed Research to the Subjects and Others**

Upon successful implementation, we foresee the following benefits from the DrOTS system:

1. The use of drones to deliver diagnostic and treatment materials will allow faster provision of care.
2. By easing the burden of travel to health clinics, study subjects will have easier access to treatment materials, leading to a higher rate of treatment completion.
3. MERMs will improve medication adherence by alerting subjects when the container is unopened to take the daily dose of medication.
4. MERMs will provide doctors with a comprehensive summary of the frequency of opening the medication storage box, correlating with the frequency of medication ingestion. This information allows the treating physician to provide more patient-centric care.
5. The video training system will improve patient comprehension of treatment protocols and encourage proper method in following treatment by providing pertinent information regarding their illness and treatment.

**Importance of the Knowledge to be Gained**

The information obtained from this study will contribute overall to the improvement of rural healthcare in the following ways:

1. Facilitate the analysis of a comprehensive remote healthcare system. Particularly, we will be able to advance delivery and remote monitoring of tuberculosis. An assessment of population-specific response to the innovative technologies introduced in DrOTS can provide feedback to improve socialization and fine-tune features to be appropriate for the intended audience;
2. Conduct a cost-effectiveness analysis to optimize the system for further use. Analyses will be developed based on flight frequency, distance, and time among other parameters to understand the financial burden of implementing the DrOTS program;
3. Reduce the transmission of TB through education and treatment of infected individuals, and therefore reduce the TB burden on rural communities;
4. Establish a paradigm for using drones to deliver healthcare to remote areas of the world, bringing medical care directly to patients who are otherwise unreachable.

**H. DATA SAFETY MONITORING PLAN (for more than minimal risk studies)**

N/A

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