PROTOCOL

TITLE: DrOTS: Drone Observed Therapy in Madagascar

INVESTIGATORS: Peter Small, MD; Joe Brew, MPH

A. SPECIFIC AIMS

1. To assess the adequacy and acceptance of the introduction of new technological approaches (i.e. drones, MERMS, video-based curricula) 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 (World Health Organization, 2016). 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 (Oxlade & Menzies, 2016; The Lancet Respiratory Medicine & Medicine, 2014). 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.

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 (Lichtman & Nair, 2015; Martini, Lynch, Weaver, & van Vuuren, 2016; Ruiz Estrada & Estrada, 2017). There is a momentum to explore the potential of drones in health care delivery in the developing world. In Africa, four pioneering drone projects are at running at a pilot stage: (i) in Ghana, for delivery of vaccines; (ii) in Rwanda, for delivery of blood for transfusions; (iii) in Malawi, for transportation of HIV samples in children (Mbuya, Rambaldi, & Chaham, 2017; Phillips N, Blauvelt C, Ziba M, Bancroft E, Wilcox A, 2016); (iv) in Madagascar, for transportation of TB lab specimens and medicine. 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 (Eichleay M, Mercer S, Murashani J, Evens E, 2016; MSF, n.d.). 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 (Eichleay M, Mercer S, Murashani J, Evens E, 2016; Haidari et al., 2016; Phillips N, Blauvelt C, Ziba M, Bancroft E, Wilcox A, 2016). 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 (Alepis & Lambrinidis, 2013; Graber, Byrne, & Johnston, 2017). These technologies have been primarily used by trained health care personnel. However, there is high potential for already trained health care personnel to use video curricula as a tool for patient education. There is reportedly a lack of evidence whether such technology in the hands of CHWs has an impact on disease outcomes (Källander et al., 2013). The combination of video 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 two innovative technologies and interlinked interventions in a rural, remote setting of Nepal. The two 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 (UNFPA, n.d.).
2. A **medication reminder box (Medication Event Reminder-Monitor; MERM)**, which stores daily medicine, reminds the patient to take them, and records when the box is opened;

3. A **video-based training curriculum** that instruct community health workers (CHWs) in taking sputum samples of suspected TB cases for TB diagnosis.

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 Nepal.

2. Research Site

The study will be piloted in Pyuthan district, located in the west-central highlands of Nepal. 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 12 villages, which are within the drone flight range of 25 km from the district hospital.

3. Study sample

Male and female adults age 16+ 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. Given that the estimated TB incidence in Nepal is 154 per 100,000, we expect approximately 350 incident cases in Pyuthan district in one year, or 115-120 during every four month period. Given that we expect to have the entire district covered for about 4 months (subject to flight permissions), we anticipate approximately 115 cases. However, due to limited information in the study area regarding tuberculosis and an anticipated large number of undiagnosed cases, incident rates may vary.

4. Training

Prior training: This study will rely on local CHWs as the primary points of contact with participants. The cadre of CHWs who will carry out study activities have all already worked as CHWs for the Nepali Ministry of Health, and undergone the training required of the Ministry for TB-related diagnostic and treatment activities. They are trained and competent in active TB case detection, contact tracing, diagnostic support and referral protocols, and treatment initiation and adherence monitoring.

Training in consenting and assessing capacity to consent: CHWs will receive specialized training for consenting and assessing the capacity to consent of potential study participants. CHWs will be training on engaging potential study subjects in conversation about the study, asking non-leading questions about the study's aims, risks, benefits, and activities, and ensuring that the responses reflect a clear understanding of the study’s characteristics, and especially, risks. CHWs will also be trained and tested on certain “hard lines” regarding capacity for consent: (i) that the study subject does not have a previously established legal or medical surrogate; (ii) that the subject has the ability to understand and answer “yes” or “no”; (iii) that the subject understands the information relevant to the study, including procedures and the consenting process; (iv) that the subject understands the possible risks and benefits resulting from participation in the study and implications on their lifestyle. CHWs will taught to always first make clear that participation in the study is entirely optional and refusal to participate will incur no negative consequences. The final part of the consent and capacity assessment workshop will include CHW-pair observations in which the workshop facilitators act as potential patients, one CHW seeks to assess capacity to consent and then seeks consent, and the other CHW observes and writes up a critique. The critiques are then shared, and the roles swapped. Following this exercise, the entire group reconvenes and reviews areas of confusion, ambiguity or difficulty.

Training on use of video-based curricula: This project will provide CHWs with video-based curricula for them to show to participants as a means of enhancing patient education. In order to fully prepare the CHWs for using video-based tools, CHWs will undergo a workshop prior to project initiation in which they are instructed on both the technical aspects of using video curricula as well as its social aspects. On the technical front, they will learn to navigate the local file system of their android systems in order to load and view videos and adjust settings; socially, they will be taught to identify instances where a patient may not understand the video, may prefer to not watch video at all, or may need certain components of it reinforced through further conversation.

Training on protocol adherence: All individuals who may interact with the study in any way (CHWs, drone pilots, mechanics, laboratory technicians, physicians) will undergo a training workshop in protocol adherence prior to study commencement. This workshop will provide an overview of the protocol, give a detailed listing of potential scenarios which may affect the different roles and how to address them, and provide materials (including contact information) regarding the flow of information in the potential case of a deviation from the protocol.

General health education: In regards to more general health education, CHWs will undergo a review workshop to supplement/reinforce their previous MOH training on TB diagnostics and care. This workshop will be carried out in collaboration with the MOH so as to ensure that national healthcare guidelines are adhered to at all steps of patient interaction, and that all contingencies (“lost” cases, symptom developments, etc.) are understood and addressed within the framework of the MOH’s guidelines.

5. 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.

6. Procedures

In brief: (1) Upon identifying a suspected TB case according to above screening procedures, a health worker obtains informed consent, then 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 (in the case that the health worker does not already have a video-enabled 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 Birat Nepal Medical Trust (BNMT) to ensure for accurate diagnosis in the context of new technology (GeneXpert MTB/RIF) implementation in NTP (National Tuberculosis Program) laboratories. (5) If the sample is found positive for *M. tuberculosis*, the patient's HCW will be delivered a one-month dose of first-line TB drugs via drone, as well as an EvriMed MERM; the HCW will train the patient on MERM use, and will also provide additional video training and conversational engagement to ensure full patient understanding of the diagnosis, the disease, the medication, the MERM, and the treatment protocol. (6) 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, and mobile devices playing the video-based curriculum 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 adherence data collected by the CHW, 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 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 and storage.

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. 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. See below table:

Indicator	**Explanation**	**Method**
Additional case notifications	Does the DrOTS approach lead to more cases notified?	Step-wedge implementation of DrOTS by “wave” over villages. Geographical areas matched with self pre-post DrOTS. Simple count of additional cases, adjusted for time, in the pre-post periods.
Medical staff receptivity	Are medical staff receptive to DrOTS technology?	Qualitative interviews with key medical staff and semi-structured focus group discussions. Analysis using open coding.
Patient receptivity	Are patients receptive to DrOTS technology?	Qualitative interviews with key medical staff and semi-structured focus group discussions. Analysis using open coding.
Impact on notification rate	Does the DrOTS program cause a higher TB notification rate?	Using step-wedge implementation structure, comparison in form of 2x2 stratum (indicator on one row, population or person-time on the other), with uncertainty quantified via Mantel-Haenszel method. In the case of the detection of significant time-contingent confounding variables, binomial logistic regression to adjust for time-varying confounders (such as weather’s impact). Outcomes to be calculated are the odds of a certain indicator event (ie, a case being detected, a detected case being treated, a treated case adhering to treatment at n months, and a treated case completing treatment) as a function of (a) DrOTS vs. DOTS protocol and (b) potential confounding variables.
Impact on case detection rate	Does the DrOTS program cause a higher case detection rate?	
Impact on treatment initiation rate	Does the DrOTS program cause a higher initiation rate?	
Impact on treatment adherence rate	Does the DrOTS program cause a higher treatment adherence rate, relative to those in DOTS?	
Impact on treatment completion rate	Do participants in DrOTS have a higher treatment completion rate than those in DOTS?	
Impact on TB incidence	Is TB incidence affected by DrOTS?	2 methods: - Comparison of incidence of TB using the step-wedge

Indicator	Explanation	Method
		implementation of DrOTS by "wave" over villages, in which each village is its own "control" (in the sense that each village enters into the panel data with both before and after observations). Analysis using binomial logistic regression to calculate odds of developing TB as a function of pre/post intervention status. - Comparison of incidence of TB between DrOTS implemented areas and non-DrOTS implemented areas using the "synthetic control" approach in which non-DrOTS areas (which are far enough geographically to not be at risk of "positive spillover" from the DrOTS project) are aggregated as a counterfactual with which to compare and thereby estimate project effect. The synthetic control approach is a quasi-experimental method which is similar to difference-in-differences comparison, but weights the relative "contribution" of control districts as a function of their epidemiological and demographic similarity to the intervention area
Cost	How much do project operations cost?	Itemization and categorization of all project expenses, including in-kind contributions, in Nepali Rupees and US Dollars.
Cost-effectiveness	Relative to the counterfactual standard of care (DOTS) is DrOTS cost-effective?	Comparison of costs of the DrOTS project with costs of the MoH-administered DOTS approach, with QALY and DALY outcomes so as to take into account potential differences in effectiveness. Variables to be reported include unit costs of differential diagnostic and treatment approach, patient costs subsequent to different treatment completion rates, days off work averted, cost of time averted, hospitalizations, etc.
Generalizability of cost-effectiveness	At what distances, incidence rates, elevations, costs, etc. would DrOTS be cost-effective?	Incremental cost-effectiveness ratios will be calculated under different hypothetical coverage scenarios, notification rates, case detection rates, etc. Cost variations as a function of drone type, travel distance, crash rate, etc. will be calculated. The purpose of this analysis will be to use project data to generate a model applicable to all geographies which takes into account altitude, distance, vehicle costs, staff wages, and disease epidemiology to provide a rough estimate of DrOTS vs. DOTS implementation costs.
Generalizability of program	Are operational lessons applicable elsewhere (permissions, flight paths, villager receptivity, privacy issues, etc.)?	Qualitative analysis reported in narrative format outlining project development, obstacles, collaborations, facilitators, and hindrances.

'Additional case notifications' (the first indicator in the above table) 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]. This is the primary outcome measure of interest in regards to the use of drones. The impact of DrOTS on rates and disease incidence is relevant to the MERMS and video education components of the project.

The step-wedge implementation design, in which we can gather data on outcomes both prior to and following the implementation of the DrOTS program, allows for the use of binomial logistic regression for all binary events, from which we can extract odds ratios to compare DrOTS and DOTS. Since target villages are effectively their own control thanks to the gradual implementation of the intervention as a "wave" across villages, the number of confounding factors should be low and limited only to those which are time-variant [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].

The impact of the program on TB incidence is of general scientific interest, but is also extremely relevant to subsequent cost-effectiveness analyses. Accordingly, for this metric, we will employ not only logistic regression using the step-wedge generated data, but also a second method for the purposes of redundancy and robustness. The synthetic control method will rely on data both form this project as well as that from the NTP. We will compare incidence in the intervention areas with a hypothetical counterfactual (the "synthetic control"), which is an aggregation of non-intervention areas which are weighted as a function of their epidemiological and demographic similarity to the intervention area.

F. FUNDING STATUS, DETAILS

The Global Health Institute (GHI) at Stony Brook University (New York, USA) has been award a grant from the Nick Simons Foundation to "support the Pilot and Implementation Phases of the DrOTS Program designed to integrate new drone, electronic communication and monitoring technology into the Nepali government's health system to develop scalable ways to reach the unreachable in remote Nepal". The funding begins in January 2018 for a period of 24 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 CHW check-in and blood and urine examination. Additional medical monitoring will be provided in accordance to standard tuberculosis care and routine visits by the Birat Nepal Medical Trust 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. CHW follow-up will provide doctors with a comprehensive summary of medication adherence and side effects. This information allows the treating physician to provide more patient-centric care.
4. 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

I. LITERATURE CITED

Alepis, E., & Lambrinidis, C. (2013). M-health: supporting automated diagnosis and electronic health records. *SpringerPlus*, *2*(1), 103.

Eichleay M, Mercer S, Murashani J, Evens E. (2016). Using unmanned aerial vehicles for development: perspectives from citizens and government officials in Tanzania. *FHI 360*.

Graber, M. L., Byrne, C., & Johnston, D. (2017). The impact of electronic health records on diagnosis. *Acta Radiologica: Diagnosis*, *4*(4), 211–223.

Haidari, L. A., Brown, S. T., Ferguson, M., Bancroft, E., Spiker, M., Wilcox, A., … Lee, B. Y. (2016). The economic and operational value of using drones to transport vaccines. *Vaccine*, *34*(34), 4062–4067.

Källander, K., Tibenderana, J. K., Akpogheneta, O. J., Strachan, D. L., Hill, Z., ten

Asbroek, A. H. A., … Meek, S. R. (2013). Mobile health (mHealth) approaches and lessons for increased performance and retention of community health workers in low- and middle-income countries: a review. *Journal of Medical Internet Research*, *15*(1), e17.
Lichtman, A., & Nair, M. (2015). Humanitarian uses of drones and satellite imagery analysis: the promises and perils. *AMA Journal of Ethics*, *17*(10), 931–937.
Martini, T., Lynch, M., Weaver, A., & van Vuuren, T. (2016). The Humanitarian Use of Drones as an Emerging Technology for Emerging Needs. In *Information Technology and Law Series* (pp. 133–152).
Mbuya, F. E., Rambaldi, G., & Chaham, H. R. (2017). *Getting drones off the ground in Africa*. CTA.
MSF. (n.d.). Innovating to reach remote TB patients and improve access to treatment. Retrieved from http://www.msf.org/en/article/papua-new-guinea-innovating-reach-remote-tb-patients-andimprove-access-treatment
Oxlade, O., & Menzies, D. (2016). Putting numbers on the End TB Strategy—an impossible dream? *The Lancet Global Health*, *4*(11), e764–e765.
Phillips N, Blauvelt C, Ziba M, Bancroft E, Wilcox A. (2016). Costs associated with the use of unmanned aerial vehicles for transportation of laboratory samples in Malawi. *VillageReach*.
Ruiz Estrada, M. A., & Estrada, M. A. R. (2017). How Unmanned Aerial Vehicles UAVVs (or Drones) Can Help in Case of Natural Disasters Response and Humanitarian Relief Aid? *SSRN Electronic Journal*. https://doi.org/10.2139/ssrn.2961576
The Lancet Respiratory Medicine, & Medicine, T. L. R. (2014). The End TB Strategy: a global rally. *The Lancet Respiratory Medicine*, *2*(12), 943.
UNFPA. (n.d.). Drones for Development: Dr.One proof of concept: executive summary.
World Health Organization. (2016). *Global Tuberculosis Report 2016*.