Cost comparison of wirelessly vs. directly observed therapy for adherence confirmation in anti-tuberculosis treatment

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Setting: A US clinic treating patients entering the continuation phase of treatment for Mycobacterium tuberculosis.

Objective: To compare the costs of direct confirmation of treatment using wirelessly observed therapy (WOT) vs. standard of care utilizing World Health Organization-recommended 7-day and 3-day directly observed therapy (DOT).

Design: A model was created comparing the costs between the two types of DOT and WOT, using data from public sources of treatment, personnel costs, patient spending, and interview responses. The model considered public health facility’s cost-to-treat and patient’s cost-to-be-treated. Cost drivers for M. tuberculosis treatment monitoring were identified, and four univariate sensitivity analyses were conducted on selected variables.

Results: The cost of WOT was estimated to be 36% of 7-day DOT, and 71% of 3-day DOT in public health facility’s cost-to-treat. The patient’s cost-to-be-treated with WOT was estimated to be 4% of 7-day DOT and 8% of 3-day DOT. Sensitivity analyses indicated that WOT was likely to provide immediate cost savings over a range of WOT costs, time spent on WOT monitoring, WOT-related treatment failure rates and clinician compensations.

Conclusion: Under several potential cost scenarios, the immediate cost of M. tuberculosis treatment by WOT appears to be substantially less than DOT. Further WOT development for M. tuberculosis treatment appears warranted.

Key words: tuberculosis; continuation phase; cost comparison; directly observed therapy; adherence confirmation

THE WORLD HEALTH ORGANIZATION (WHO) recommends that the 4-month continuation phase treatment for Mycobacterium tuberculosis utilizes directly observed therapy (DOT) at least thrice weekly (3-day DOT), and preferably daily (7-day DOT). While DOT represents the M. tuberculosis treatment standard, its implementation is commonly attenuated due to its cost. Some M. tuberculosis programs in the United States use DOT only for high-risk patients. In many countries, twice- and thrice-weekly DOT is employed despite evidence that daily dosing of M. tuberculosis medication is superior.1,2 Family observation has also been utilized, but has resulted in more unobserved doses, higher rates of non-adherence and lower cure rates than observation by non-family members.3,4

Other surrogates for treatment confirmation have been developed as alternatives to DOT, but all are indirect, offer no near real-time notification capability, and have been shown to be inaccurate or ineffective. These methods have included patient questionnaires, pill counts, electronic pill-bottle caps, prescription refill rate monitoring, and drug concentration monitoring. Patient interviews are vexed by faulty patient recall and a desire to present oneself as having followed the doctor’s orders.4 Counting returned tablets is inaccurate, as patients are known to discard tablets to create the impression of good adherence.5 Electronic pill-bottle caps use cap-opening as a surrogate for drug dosing; however, mismatches between electronic cap opening and actual drug intake have been reported.6–9 Medication possession ratio, a means of determining adherence retrospectively based upon the time between medication refills, cannot capture actual drug utilization, and is impractical when a patient obtains drugs from other than the pharmacy of record.10 Measurement of drug concentration, while considered a clinically attractive surrogate for drug dosing, has been found to be potentially misleading due to ‘white coat adherence’.11 Thus, there remains an unmet need for a reliable and efficient method to confirm M. tuberculosis treatment adherence and course completion.

Wirelessly observed therapy (WOT) is under development as an alternative to DOT for direct confirmation of M. tuberculosis treatment (Figure 1). The
The WOT system directly confirms adherence to oral medication electronically and wirelessly, eliminating the need for direct observation by a health worker and allows anytime, anywhere, objective confirmation of dosing. The current system can identify multiple types and doses of medications ingested simultaneously, and is capable of up to 99% positive detection accuracy when compared to observed ingestion in a study of healthy human volunteers. With over 4.5 billion mobile phones now in use worldwide in industrialized and developing countries, a wireless platform technology is available to potentially reduce costs and to scale operations.

To assess the potential cost savings of WOT, a model was created to compare the costs of standard of care for *M. tuberculosis* treatment monitoring utilizing DOT to WOT for adherence confirmation during the 4-month continuation phase of therapy. The cost analysis results are reported in this manuscript.

**METHODS**

**WOT: description and dose-confirmation strategy**

WOT utilizes ingestible sensors (1 mm² in size) that can be combined with an oral solid formulation to time-stamp pharmaceutical ingestion. When ingested, the sensor readily separates from the medication, is activated by gastric fluid and communicates with an adhesive-backed wearable sensor worn on the user’s torso. The wearable sensor interprets the information as unique to each ingested sensor, and records the type, dose, date and time of medication taken in the monitor’s internal memory. The communication process between the ingestible and wearable sensors is not dependent upon gastric pH or stomach content; it is unnoticed by and not detectable beyond the user. The information stored in the wearable sensor is automatically encrypted and sent wirelessly to a designated mobile device (i.e., a mobile phone) whenever it comes into proximity, for subsequent upload to a secure data server. Patients have control of their data to maintain privacy, and can allow health workers to access their data using a web-based interface. Health workers in turn may utilize the data that are provided by this automated system to confirm drug intake dose by dose, to manage a large number of patients remotely and to certify completion of a course of antituberculosis treatment. It allows health care workers to identify, in near real time, those patients who are non-adherent for more intensive management such as phone call follow-up and/or outreach visits. From the patients’ perspective, they are no longer required to travel to a designated location and be witnessed by a treatment supporter for each dose; they may seek and complete treatment remotely and privately without having to take time off from work to attend DOT.

**Setting and design**

The cost model was developed to compare WOT during the 4-month continuation phase of treatment and two WHO-recommended DOT regimens: 1) the optimal ‘7-day DOT’ strategy requiring patients to adhere to a daily treatment regimen per WHO Recommendation 2.1, and 2) the WHO alternative ‘3-day DOT’ strategy, which mandates a thrice-weekly regimen. WOT was assumed to be utilized every day outside of the clinic, with an addition of a monthly clinic visit for assessment of drug safety. As this was an analysis based on published data and no human studies were conducted, ethics approval was not required.

In 2010, the global *M. tuberculosis* treatment success rate reported by the WHO was 86% (WHO 2010); thus for 7-day and 3-day DOT, a baseline treatment failure rate of 14% was used to estimate the frequency of retreatment. For WOT, the model assumed that WOT had a baseline treatment failure rate approximately 1.5-fold worse in treating *M. tuberculosis* when compared to DOT: a treatment failure rate of 24% was used to estimate the frequency of retreatment, representing a 14% baseline treatment failure rate and an additional 10% baseline technical
inability to use WOT (estimated based on historical experience). In the event of treatment failure, for either DOT or WOT, it was assumed that 1) all costs of the initial M. tuberculosis treatment were incurred, and 2) a patient would be retreated using 4-month, 7-day DOT at the same cost as 7-day DOT.

Costing
Cost items and costs were identified and assessed based on searches of publicly available databases, reports and interviews with public health workers and patients, conducted in 2011 based on US dollars. The cost comparisons were exploratory in nature and reflected best estimates. Specifically, M. tuberculosis medication cost was obtained from a WHO Global Drug Facility (GDF) direct procurement service catalog;14 the numbers of hours spent per DOT session by a health worker and by a patient were estimated from interview responses; the number of DOT sessions in the continuation phase was determined based on WHO treatment recommendations;14 the wage of a patient was assumed to be at US minimum wage level;19 and travel costs were estimated based on nominal cost in the United States. WOT costs were estimated assuming a mature, commercial system; costs included that of tagging drugs with sensors, all WOT equipment, data storage and management, technical training and support for WOT usage and data assessment. As WOT technology has commercial applications in other therapeutic areas besides TB case management, the necessary investment costs to bring the technology to maturity was assumed to be borne by the technology developer for the purpose of this analysis. The time spent to monitor WOT data was estimated as follows: 70% of the patient cohort was assumed to be adherent, requiring 10 min/week for WOT monitoring; 30% of the patient cohort was non-adherent, requiring a total of 45 min/week of follow-up consulting by phone calls and/or outreach visits. This resulted in an average of 22 min/week, 6 h/course of WOT monitoring time per patient.

Sensitivity analysis
Four univariate sensitivity analyses were conducted to compare the marginal cost of 7-day DOT to WOT, and the marginal cost of 3-day DOT to WOT:

1. Frequency of retreatment due to WOT usage, varied from 0% to 100%.
2. WOT cost, varied from US$50, a cost target that represents a mature, commercial WOT system, to US$3200.
3. Hourly compensation of public health workers, varied from US$30, which represents a family observation scenario, to US$30; and
4. Case-work time related to WOT monitoring, varied from 1 h/course to 64 h/course.

Results were plotted graphically to identify cost-neutral points where the values are zero, meaning the two treatment costs are equal. These cost-neutral points were used to establish various scenarios in which WOT would provide cost savings compared to DOT.

RESULTS

Public health facility’s cost to treat
and patient’s cost to be treated

WOT appeared to provide potential cost savings when used as an alternative to WHO-recommended 7-day or 3-day DOT for the 4-month continuation phase of treatment. The costs of 7-day DOT, 3-day DOT and WOT are summarized in Table 1. Overall, health facility’s cost to treat with WOT was estimated to be 36% of 7-day DOT and 71% of 3-day DOT. Patient’s cost-to-be-treated with WOT was estimated to be 4% of 7-day DOT and 8% of 3-day DOT. Estimated public health worker time per subject treated using WOT was 34% of 7-day DOT and 67% of 3-day DOT. Estimated patient time for treatment using WOT was 4% of 7-day DOT and 8% of 3-day DOT.

The leading cost drivers in M. tuberculosis treatment monitoring appeared to be personnel and retreatment costs (Figure 2). With 7-day DOT, personnel and retreatment costs accounted for respectively 86% and 13.5% of the total cost of US$3472; with 3-day DOT these were 73% and 27% of the total cost of US$1772. In contrast, WOT cost US$1273, of which respectively 38% and 61% were personnel and retreatment costs. Based on the ratio of providers’ treatment cost, the model demonstrated that WOT would allow providers to treat respectively 2.7 times and 1.4 times more patients compared to 7-day and 3-day DOT.

Sensitivity analysis
Four univariate sensitivity analyses were conducted to compare the marginal cost of 7-day DOT to WOT and the marginal cost of 3-day DOT to WOT.

DISCUSSION
A hallmark of WOT is the ability to use electronic interaction to replace the frequent, labor-intensive personnel-interactions otherwise associated with DOT for direct dose confirmation. WOT may have particular utility in countries such as China and Mexico, where many M. tuberculosis patients are mobile workers. Currently, these patients often experience treatment interruption and default due to the inability to transfer administratively from one clinic to another.
### Table 1  DOT and WOT cost comparisons

<table>
<thead>
<tr>
<th></th>
<th>7-day DOT</th>
<th>3-day DOT</th>
<th>WOT</th>
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</thead>
<tbody>
<tr>
<td>Public health facility’s cost to treat per patient per course*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>18.15</td>
<td>18.15</td>
<td>18.15</td>
</tr>
<tr>
<td>Personnel cost of conducting in-person DOT</td>
<td>2975.00</td>
<td>1275.00</td>
<td>106.25</td>
</tr>
<tr>
<td>Hourly compensation of a public health nurse</td>
<td>50.00</td>
<td>50.00</td>
<td>50.00</td>
</tr>
<tr>
<td>× number of hours spent per DOT visit</td>
<td>0.50</td>
<td>0.50</td>
<td>0.50</td>
</tr>
<tr>
<td>× number of DOT visits per week</td>
<td>7.00</td>
<td>3.00</td>
<td>0.25</td>
</tr>
<tr>
<td>× number of weeks in continuation phase</td>
<td>17.00</td>
<td>17.00</td>
<td>17.00</td>
</tr>
<tr>
<td><strong>WOT costs</strong></td>
<td></td>
<td></td>
<td>50.00</td>
</tr>
<tr>
<td>Personnel cost of monitoring WOT data</td>
<td>300.00</td>
<td></td>
<td></td>
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<tr>
<td>Hourly compensation of a public health nurse</td>
<td>50.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>× number of hours spent per patient per course</td>
<td>6.00</td>
<td></td>
<td></td>
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<tr>
<td><strong>Retreatment cost</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment failure due to ineffectiveness of <em>M. tuberculosis</em> therapy, %</td>
<td>16</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>+ Treatment failure due to use of WOT, %</td>
<td>16</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>= Treatment failure rate, %</td>
<td>16</td>
<td>16</td>
<td>10</td>
</tr>
<tr>
<td>× 7-day DOT treatment cost</td>
<td>2993.15</td>
<td>2993.15</td>
<td>2993.15</td>
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<tr>
<td>= Retreatment cost</td>
<td>478.90</td>
<td>478.90</td>
<td>778.22</td>
</tr>
<tr>
<td>Cost to treat per patient per course, US$</td>
<td>3472.05</td>
<td>1772.05</td>
<td>1252.62</td>
</tr>
<tr>
<td>Cost ratio of WOT to DOT, %</td>
<td>36</td>
<td>71</td>
<td></td>
</tr>
<tr>
<td>Marginal cost of DOT to WOT</td>
<td>2219.43</td>
<td>519.43</td>
<td></td>
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<tr>
<td>Time spent per patient per course, h</td>
<td>69.02</td>
<td>35.02</td>
<td>23.60</td>
</tr>
<tr>
<td>Time ratio of WOT to DOT, %</td>
<td>34</td>
<td>67</td>
<td></td>
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<tr>
<td>Patient’s cost to be treated per patient per course*</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Loss of wages</td>
<td>862.75</td>
<td>369.75</td>
<td>30.81</td>
</tr>
<tr>
<td>Number of in-clinic visits for treatment monitoring</td>
<td>119.00</td>
<td>51.00</td>
<td>4.25</td>
</tr>
<tr>
<td>× number of hours spent per in-clinic visit</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
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<tr>
<td>× hourly minimum wage in United States</td>
<td>7.25</td>
<td>7.25</td>
<td>7.25</td>
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<td>Transportation cost</td>
<td>476.00</td>
<td>204.00</td>
<td>17.00</td>
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<tr>
<td>Number of trips to and from clinic</td>
<td>238.00</td>
<td>102.00</td>
<td>8.50</td>
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<tr>
<td>× travel cost per trip</td>
<td>2.00</td>
<td>2.00</td>
<td>2.00</td>
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<tr>
<td>Cost to be treated per patient per course, US$</td>
<td>1338.75</td>
<td>573.75</td>
<td>47.81</td>
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<tr>
<td>Cost ratio of WOT to DOT, %</td>
<td>4</td>
<td>8</td>
<td></td>
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<tr>
<td>Marginal cost of DOT to WOT</td>
<td>1290.94</td>
<td>525.84</td>
<td></td>
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<tr>
<td>Time spent by patient per course, h</td>
<td>119.00</td>
<td>51.00</td>
<td>4.25</td>
</tr>
<tr>
<td>Time ratio of WOT to DOT, %</td>
<td>4</td>
<td>8</td>
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*US$ unless stated otherwise.

DOT = directly observed therapy; WOT = wirelessly observed therapy.

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**Figure 2** Cost of confirming *M. tuberculosis* treatment adherence via 7-day DOT, 3-day DOT and WOT. DOT = directly observed therapy; WOT = wirelessly observed therapy. This image can be viewed online in color at http://www.ingentaconnect.com/content/iuatld/ijtld/2012/00000016/00000011/art00014
under the traditional DOT-based strategy. As WOT does not depend on the geographic location of the patient and health provider, it may provide an alternative and feasible means of confirming adherence to prescribed M. tuberculosis treatment.

The cost model developed in this study suggests that WOT may be financially feasible for the continuation phase of M. tuberculosis treatment. Results indicate that the cost of anti-tuberculosis treatment supervision using WOT may be substantially less than that of either 7-day or 3-day DOT. Sensitivity analyses demonstrated that cost savings may be attainable by WOT over a range of provider time spent monitoring adherence using WOT as well as in countries where provider wages are lower than in the United States. Cost savings also appear to be possible even if 1) treatment failure with WOT is several-fold worse than failure with DOT, and 2) all treatment failure were to occur at the very end of treatment, when all treatment costs have been incurred.

In addition to immediate cost savings, WOT may provide several considerable benefits over DOT for patients, health workers, and public health facilities. From the patients’ perspective, WOT may eliminate the need for face-to-face dose confirmation sessions and allow them to seek treatment privately and remotely. Patients would have potentially more productivity and less risk of having their health status revealed, which may be inducements to completing

Table 2  Cost-neutral points identified from four univariate sensitivity analyses

<table>
<thead>
<tr>
<th>WOT provided cost savings over DOT when . . .</th>
<th>7-day DOT</th>
<th>3-day DOT</th>
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<tr>
<td>Figure 3A The cost of WOT was</td>
<td>&lt;$2250</td>
<td>&lt;$550</td>
</tr>
<tr>
<td>Figure 3B The time spent on treatment</td>
<td>&lt;50 h</td>
<td>&lt;16 h</td>
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<tr>
<td>monitoring via WOT was</td>
<td></td>
<td></td>
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<tr>
<td>Figure 3C The treatment failure rate</td>
<td>&lt;85%</td>
<td>&lt;27%</td>
</tr>
<tr>
<td>due to WOT usage was</td>
<td></td>
<td></td>
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<tr>
<td>Figure 3D The hourly compensation of</td>
<td>&lt;$1.2</td>
<td>&lt;$4.5</td>
</tr>
<tr>
<td>health worker was</td>
<td></td>
<td></td>
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</tbody>
</table>

WOT = wirelessly observed therapy; DOT = directly observed therapy.

Figure 3  Univariate sensitivity analyses of selected cost items. A. Sensitivity analysis of the cost of WOT equipment and services. B. Sensitivity analysis of the time spent on WOT data monitoring. C. Sensitivity analysis of the rate of WOT-related treatment failure. D. Sensitivity analysis of the hourly compensation of health care workers. WOT = wirelessly observed therapy. This image can be viewed online in color at http://www.ingentaconnect.com/content/iuatld/ijtld/2012/00000016/00000011/art00014
treatment. From the public health facility’s perspective, WOT may also enable health workers to triage patients efficiently by providing objective, near real-time adherence data for each patient. Health workers could then target their coaching and monitoring efforts at those patients who are non-adherent, while allowing adherent patients to complete their treatment courses independently. Of most importance, WOT has the potential to leverage the ubiquitous mobile technology to expand the reach of M. tuberculosis treatment monitoring to a larger scale than can occur with the current standard of care. A large cohort of patients, including those who live in remote areas, could be monitored effectively using WOT, increasing the patient throughput of a clinic. Public health facilities could avoid those ineffective compromises of less frequent ‘modified-DOT’ and preserve the core principle of DOT, namely objective confirmation of each prescribed dose.

Early clinical evidence suggests that WOT may be feasible for M. tuberculosis case management. To date, there have been more than 14,000 sensor ingestions by more than 250 subjects, including human volunteers and patients with TB and other chronic diseases. Ingestions have occurred twice daily for as long as 12 weeks, and as many as 30 sensors have been ingested in a single day with no adverse effect. Moreover, a prospective, non-randomized pilot study was conducted in 30 TB patients of diverse native origin using an early WOT prototype at two clinics in the United States. Study participants were monitored during 10 daily DOT visits. At each visit, participants co-ingested sensors along with their TB medications for comparison with directly observed records. The WOT system identified 98% (95% confidence interval [CI] 97–99) of the sensors that were co-ingested and successfully differentiated each of the individual sensors ingested. No serious adverse device events or unanticipated adverse device events were observed. The vast majority of the participants found the system concept to be acceptable for daily use as treatment monitoring over several months. Based on the initial clinical experience from the use of WOT in the continuation phase of M. tuberculosis treatment, further expansion could include the use of WOT in the intensive phase of treatment, particularly in countries where DOT is limited and treatment is provided at periodic clinic visits, as well as for other cases of M. tuberculosis such as latent or drug-resistant TB and human immunodeficiency virus (HIV) co-infection.

A limitation of the current cost model is that there is limited clinical experience to date with WOT use in TB patients. It is therefore not possible at the moment to account for longer-term differences in cost. The current cost model attempted to address this limitation by including a sensitivity analysis of hypothetical treatment failure due to WOT. It is anticipated that the model will be updated with actual costs of utilization, clinical outcomes and failure rates of WOT and DOT as they become available from future clinical studies. The current cost model assumed a mature WOT cost of US$50 per patient per treatment course. While this assumption may appear to be optimistic in the immediate future, the cost estimate appears achievable given that the costs of sensors, mobile phones and cloud data storage are already decreasing dramatically.

CONCLUSION

Under several potential cost scenarios, the immediate cost of M. tuberculosis treatment by WOT appears to be substantially less than that by traditional 7-day and 3-day DOT. The findings from this cost analysis provide the impetus for further WOT development for M. tuberculosis management.

Disclosure: KYAY and LDC receive employment from Proteus Digital Health, the developer of wirelessly observed therapy.

References


**CONTEXTE :** Un dispensaire US traitant les patients entrant dans la phase de continuation du traitement pour *Mycobacterium tuberculosis*.

**OBJECTIF :** Comparer les coûts d’une confirmation directe du traitement au moyen du traitement observé par message radiotélégraphique (WOT) par comparaison avec les standards de soins recourant au traitement directement observé (DOT) de 7 jours et de 3 jours recommandé par l’Organisation Mondiale de Santé.

**SCHEMA :** On a créé un modèle comparant les coûts des deux types de DOT au WOT et utilisant des données provenant des sources publiques de traitement, les coûts en personnel, les dépenses du patient et les réponses aux interviews. Le modèle a pris en considération le coût du traitement pour le service de santé publique et le coût encouru par le patient pour être traité. On a identifié les facteurs de coût pour le suivi du traitement pour *M. tuberculosis* et on a mené quatre analyses univariées de sensibilité pour des variables sélectionnées.

**RÉSULTATS :** On a estimé que le coût du WOT représentait 36% du DOT de 7 jours et 71% du DOT de 3 jours dans les coûts de traitement pour les services de santé publique. Le coût-patient pour être traité par le WOT a été estimé représenter 4% du DOT de 7 jours et 8% du DOT de 3 jours. Les analyses de sensibilité ont montré que le WOT était susceptible d’obtenir des réductions immédiates du coût pour une marge de coûts WOT, de réduire le temps passé à suivre le WOT, ainsi que les taux d’échec du traitement liés au WOT et les compensations pour le clinicien.

**CONCLUSION :** Parmi différents scénarios potentiels de coût, le coût immédiat du traitement de *M. tuberculosis* par le WOT s’avère substantiellement inférieur à celui du DOT. Un développement ultérieur du WOT semble justifié pour le traitement de la tuberculose.