Tuberculosis (TB) has long been the leading killer of infectious disease globally. TB treatment is lengthy, usually six months or longer, and is often difficult to complete. Medication non-adherence poses a serious challenge to TB management efforts as it fuels the development of drug resistance, reduces treatment success, and contributes to disease transmission.

- Conditions in Tibet, China
  - Sparse population
  - Severe weather conditions
  - Long travel distances
  - Shortage of human resources

Challenges
- Low level of directly observed treatment (DOT)
- Patients either self-administer their treatment or receive inadequate supervision from a health worker
- Consequences
  - Treatment non-adherence
  - Poor treatment outcomes and high default rates
  - Emergence of TB drug resistance

Study design
Pragmatic, multi-centre, individually-randomised, parallel-arm, controlled trial

Intervention mode
In the intervention group:
- Deactivated e-monitors without automated voice reminders (only collect medication history)
- Will not select family treatment supporters
- Treatment supervisors will contact patients through traditional means, such as physical visits or phone calls
- Will not invite patients to connect with their TB physician or treatment supervisors through the WeChat app

Routine care in both groups:
- All patients are treated according to the standard WHO DOTS programme and the China NTP guidelines.
- Patients refill their medications in their e-monitor boxes every 2 months at TB dispensary (county hospital).
- Treatment supervisors through the WeChat app (only collect medication history)

Intervention effects on main outcomes:

<table>
<thead>
<tr>
<th>Main outcomes</th>
<th>Intervention arm</th>
<th>Control arm</th>
<th>Adjusted risk difference (95% CI); p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of recruited patients</td>
<td>142</td>
<td>115</td>
<td>28.7 (-4.5, 52.2); 0.061</td>
</tr>
<tr>
<td>Monthly poor treatment adherence (missing ≥20% of planned doses in the treatment month)</td>
<td>9.0% (64/714)</td>
<td>5.7% (65/114)</td>
<td>3.3 (-4.0, 10.6); 0.317</td>
</tr>
<tr>
<td>Overall poor treatment adherence (missing ≥10% of all planned doses)</td>
<td>22.5% (32/142)</td>
<td>19.7% (27/134)</td>
<td>2.8 (-0.9, 6.5); 0.149</td>
</tr>
<tr>
<td>Treatment success (cured, completed treatment or missing ≤10% of planned doses in the entire treatment period)</td>
<td>60% (86/142)</td>
<td>72.8% (97/134)</td>
<td>-12.8 (-20.6, -4.9); &lt;0.001</td>
</tr>
<tr>
<td>Lost to follow-up (never started treatment after diagnosis or missed ≥2 consecutive months of treatment)</td>
<td>4.5% (5/142)</td>
<td>5.7% (7/134)</td>
<td>-1.2 (-6.1, 3.7); 0.653</td>
</tr>
</tbody>
</table>

Proportion of patients missing 20% or more planned doses per treatment month:

<table>
<thead>
<tr>
<th>Proportion of patients</th>
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<th>Control arm</th>
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</tr>
</tbody>
</table>

Incremental cost-effectiveness analysis:
- Total per patient cost will be calculated as the sum of below:
  - Cost of clinic consultation estimated with doctor
  - Cost of patient follow-up
  - Medication cost including inpatient and outpatient service charge and indirect cost
  - Unit implementation cost per district will be calculated as the sum of below:
    - Cost of staff time of both trainers and trainees
    - Preparation of intervention materials and devices

World Health Organisation recommends that electronic medication monitors (EMMs), a form of digital adherence technology, complement directly observed treatment for TB.

This trial has provided evidence that a comprehensive package of interventions based on EMMs can improve treatment adherence and treatment outcomes among drug-susceptible TB patients in Tibet. Based on our results and continuous engagement with policy makers, our intervention package, including the EMM and associated app, has been included in the national TB program with the Tibetan Autonomous Government providing funding to ensure every TB patient in Tibet can access a monitor and other interventions of our package.

In settings where mobile connectivity functions, EMMs that are adapted to the local context can be a key tool towards reaching the ambitious goals of the global END-TB Strategy by 2035.

The study was funded by TB REACH, administrated from the STOP TB Partnership at the United Nations.

We thank colleagues from the Chinese Centre for Disease Control and Prevention (CDC) for their technical and administrative support, and Shigatse CDC, county CDCs and county hospitals of Samzhubze, Sa’gya, Gyantse, Nangmring, Tingri and Bainang for their efforts in implementing the study, and Tibetan provincial CDC and Shigatse Health Commission for their policy support.

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