DIGITAL TECHNOLOGY

# The role of wirelessly observed therapy in improving treatment adherence

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ABSTRACT

**Wirelessly observed therapy (WOT) offers a novel way of monitoring treatment adherence. In this article, we provide an overview of how this technology works and discuss the evidence for its clinical effectiveness in tuberculosis, hepatitis C virus infection, mental health and cardiovascular disease. We consider the acceptability of WOT to patients as well as potential issues relating to patient autonomy and data protection. We highlight the current limited data on its economic impact and reflect on its future role in patient care.**

**KEYWORDS:** wirelessly observed therapy, ingestible sensors, digital health, health policy, tuberculosis

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## Introduction

Maintaining treatment adherence may be challenging due to the burden associated with taking complex drug regimens, medication side effects, the sense of stigma that individuals may experience and a potential lack of awareness among some patients about the course of a disease if left untreated. Variable adherence increases the risk of treatment failure and, in the case of antimicrobial use, the emergence of drug resistance. This, in turn, results in poorer clinical outcomes. There is also a significant economic impact to consider, with one systematic review identifying that non-adherence results in an annual adjusted disease-specific cost of between $1,000 – $44,000 per person.[1] There is, therefore, not only a clinical but also an economic imperative to develop effective strategies to improve treatment adherence.

Digital technologies have been utilised to complement or replace traditional directly observed therapy (DOT) schemes that have been used to support adherence, including in the management of tuberculosis (TB).[2] Examples of such technologies include short message service (text messages) to send medication reminders to patients; video-observed therapy, in which patients are observed taking medications by video in real-time or after submitting videos for review; and medication monitors, whereby microelectronic chips register each time a bottle or blister pack is opened and transmit a signal to healthcare providers. In recent years, there has been burgeoning interest in using wirelessly observed therapy (WOT) in conjunction with ingestible sensors to promote treatment adherence, both for TB and beyond. Herein, we describe the premise of WOT; consider its potential utility by drawing upon evidence from studies in TB, hepatitis C virus (HCV) infection, mental health and cardiovascular disease; and reflect on the current barriers to its widespread uptake.

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## What is WOT?

In WOT, an ingestible sensor is tagged onto tablets. Upon ingestion, the sensor undergoes a biochemical reaction, producing an electrical field that is detected by a wearable sensor on the patient. Data including the date and time of ingestion are transmitted wirelessly to the patient's mobile device, from there, the data are then transmitted to healthcare providers, enabling real-time, continuous monitoring of adherence.[3] Such a system was developed by Proteus Digital Health.[4] Protocols for co-encapsulating medications with ingestible sensors have been described.[5] Extensive testing has demonstrated that such technologies appear to be safe, with no reports of associated mechanical injury, electrical injury or toxicity; although in one study, <1% of patients reported nausea or vomiting possibly attributable to their ingestion and 12% reported self-limiting skin rashes at the site of the wearable sensor patch.[6] Notably, manufacturers advise against use of ingestible sensors in certain situations, such as when undergoing magnetic resonance imaging or external defibrillation.[6]

## Clinical utility

### TB

Adherence is of paramount importance in TB to increase the likelihood of treatment success and reduce the risk of drug-resistant TB developing. An early feasibility study in patients on various TB regimens demonstrated that WOT had a high positive detection accuracy (95.0%; 95% confidence interval

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(CI) 93.5–96.2) and high specificity (99.7%; 95% CI 99.2–99.9). The system was safe: out of 1,080 ingestion events, there were 11 adverse events, of which, four were potentially attributable to the sensor (three mild skin rashes and one case of nausea).[7] The first randomised controlled trial involving use of WOT in patients with TB recently demonstrated that it has a positive detection accuracy of 99.3% and found that 92.9% of prescribed doses were confirmed as being taken in the WOT arm compared with 63.1% of doses in the DOT arm ($p<0.001$).[8] Notably, however, DOT was only recorded on working days and not on weekends or public holidays, whereas WOT could be used 7 days per week. It is possible that patients in the DOT arm were still taking their doses on weekends or public holidays, but that these were self-administered and not observed. In a secondary analysis in which adherence was assessed only on working days, no significant difference in confirmed doses was found between the WOT and DOT arms (95.6% vs 92.7%, respectively; $p=0.31$).[8] All participants expressed a preference for WOT over DOT.[8]

### HCV infection

In a study of patients with HCV, adherence to ledipasvir (an HCV inhibitor) / sofosbuvir (a nucleotide analogue inhibitor) tagged with an ingestible sensor was found to be 97%.[9] The main adverse reaction was contact dermatitis. Limitations, however, included the open-label nature of the study, lack of comparator group and small sample size.[9] In another study, in patients with a history of HCV infection and drug use, there was no significant difference in ledipasvir/sofosbuvir adherence between participants using WOT or video DOT, although the odds of missing a dose were lower with the latter (odds ratio (OR) 0.43; 95% CI 0.21–0.87; $p=0.02$).[10]

### Mental health

In an observational study in patients with bipolar disorder or schizophrenia, patients' mean adherence rate when co-ingesting a sensor with their regular psychiatric medications was 74%, but no comparator group was reported.[11] Mild dermatological irritation was the most common adverse event (18% of participants).[11] In another open-label, single-arm study in patients with bipolar disorder, major depressive disorder or schizophrenia, the mean adherence to the atypical antipsychotic aripiprazole tagged with an ingestible marker was 88.6%.[12] A key limitation in these studies is the lack of an enrolled control group to allow for a comparative judgement to be made. The first drug with an ingestible sensor to be approved by the US Food and Drug Administration (FDA) was a formulation of aripiprazole called the Abilify MyCite that was jointly produced by Proteus Digital Health and Otsuka Pharmaceutical Co.[13] The results of a phase III clinical trial evaluating its effect on hospitalisation rates in patients with schizophrenia are awaited.[14]

### Cardiovascular disease

In a small cluster-randomised pilot study of patients with poorly controlled hypertension and type 2 diabetes mellitus, ingestible sensors were co-encapsulated with antihypertensives, antidiabetic medications and statins using Proteus Digital Health technology to evaluate the effect on blood pressure, glycaemic control and lipid profile. Relative to patients receiving standard care, patients taking the co-encapsulated medications exhibited a greater mean reduction in systolic blood pressure at 4 weeks and this was maintained at 12 weeks; and they exhibited greater reductions in glycated haemoglobin and low-density lipoprotein cholesterol.[15] The most common adverse events were mild skin reactions and mild to moderate gastrointestinal side effects.[15] Notably, however, no comparison was made of the actual adherence rates between the two treatment groups. In a separate feasibility study investigating the effect of co-encapsulating valsartan with an ingestible sensor, the mean rate of adherence for taking the medication was 90%, although there was no control group or data provided on the clinical effect on blood pressure control.[16]

## Acceptability

For any digital health technology to be successfully implemented in practice, it is vital for it to be considered *acceptable* to various stakeholders, including patients, clinicians, healthcare institutions and health policymakers.[17] In a pilot study in which antiretroviral therapy was co-encapsulated with a pill sensor system for patients living with human immunodeficiency virus (HIV) infection, 2/14 participants were unable to tolerate the co-encapsulated formulation, although at least three-quarters of participants felt that the patch was tolerable.[18] In a study of patients with bipolar disorder or schizophrenia, 70% of participants found the concept of the ingestible sensor easy to understand.[11] In a separate study evaluating the perceived usability of such systems in patients with schizophrenia, 78% of participants reported at least some level of satisfaction with the concept.[19] However, on the basis of these very limited data, it is difficult to generalise whether patients deem WOT to be acceptable and this may vary depending on the patient population or disease being assessed.

Proponents of DOT would argue that it provides a valuable form of treatment support by virtue of the personal relationship that patients may develop with observers from the care-giving team.[20] This sense of a connection with healthcare providers could be seen as lacking in WOT, which by its very nature is a remote means of monitoring treatment adherence without the need for direct human interaction.

For clinicians and healthcare providers, WOT may provide a vast quantity of data to inform and tailor clinical decision making to meet individual patient needs, but there are important ethical considerations to take into account. While it may be argued that attempts to promote treatment adherence should be lauded and encouraged, this must be balanced by ensuring that patients do not find such interventions to be excessively intrusive and that their autonomy is respected. There is an undoubted need to ensure that any approach that is utilised is not perceived by patients as being coercive in nature or impinging on their personal liberties, as this could give rise to resentment and a negative perception of care, with detrimental consequences on treatment adherence. From a data protection and regulatory perspective, it is important for appropriate safeguards to be instituted to prevent security breaches that may compromise confidentiality when data are transmitted to healthcare providers and for the generated data to be stored securely in compliance with local policies and legal frameworks.[21]

## Economic impact

Economic evaluations on WOT use are sparse and formal cost-effectiveness studies are still lacking. An early modelling study


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suggested that WOT for TB therapy incurs 36% of the costs associated with 7-day DOT under specific modelling conditions.[22] DOT remains far more widely used than WOT. From a health policy perspective, widespread uptake of WOT will be contingent not only upon its clinical effectiveness but also on there being demonstrable cost savings associated with its use relative to DOT and other existing adherence support strategies. The cost effectiveness of implementing WOT will be influenced by various factors, including the disease for which it is used, the type of drug with which the digital sensors are co-encapsulated, the length of treatment and the need to train healthcare professionals in its use.

The appropriate infrastructure to support rollout of WOT needs to be available and this may be particularly challenging in resource-limited settings. In low- and middle-income countries, it is already known that healthcare services may be understaffed and securing personnel to deliver traditional in-person DOT can be difficult.[23] In such settings, it may simply be unfeasible or unrealistic to meet the inevitable costs that are associated with implementing WOT, which will include purchasing medications tagged with ingestible sensors, acquiring the necessary monitoring equipment, storing the data securely and training staff. The current paucity of cost-effectiveness data is likely to be a reflection that WOT use is highly limited to a small number of research studies at select institutions. The feasibility from a financial standpoint of implementing WOT, therefore, remains essentially unknown.

## Outlook

Supporting adherence to treatment is an important aspect of clinical care across all medical disciplines. The use of ingestible sensors and WOT may represent an emerging way of promoting adherence to oral medications in a safe, relatively non-intrusive manner. There remain, however, limited data in the published literature on its clinical effectiveness, with only one randomised controlled trial on its use published to date in TB. Studies are also limited to a finite number of conditions and there is insufficient information available on the cost effectiveness of its use. The dearth of research studies may possibly reflect a lack of awareness or confidence in the concept among clinicians or clinical researchers; a perception that existing adherence support methods are sufficiently effective from a clinical and economic standpoint; or local resource or monetary constraints.

If WOT is to be brought into routine clinical practice, convincing evidence from robust studies with defined clinical endpoints, sufficient power and appropriate comparator groups will be needed. This will vary according to the disease and treatment under consideration. Establishing the most relevant outcome measures for such studies will require a consensus to be reached among researchers and policymakers. Similarly, economic evaluations that report standardised primary outcomes (such as quality-adjusted life years or disability-adjusted life years) and that utilise appropriate economic evaluation models will be required by policymakers to reach informed decisions about whether WOT warrants funding. Studies that directly explore patient and clinician perceptions of WOT compared with DOT will also be crucial for determining whether WOT is likely to attain sufficient traction among potential users and prescribers.

From a financial perspective, a strong economic incentive needs to exist to convince pharmaceutical companies to invest in co-encapsulating their drugs with ingestible sensors; this may, for example, be enhanced if co-encapsulation were associated with extending a drug's patent protection.[24] Furthermore, consideration could be given to targeting ingestible sensors and WOT at patient populations that are more likely to be receptive to their use in the first place. Challenges in achieving the latter have been mooted as potentially contributing to Proteus Digital Health ultimately filing for bankruptcy in 2020.[25]

Despite this, health technology companies have continued to bloom in the ingestible sensor market space. The ID-Cap System (etectRx, Gainesville, USA) utilises a gelatine capsule containing an ingestible sensor that, following dissolution in the stomach, transmits a signal to a wearable lanyard on the patient, with the data subsequently transmitted to an application on the patient's smartphone and, from there, the data are then relayed to a cloud-based clinician dashboard.[26] The lanyard circumvents the need for adhesives that have direct contact with skin and offers a way of bypassing the potential dermatological irritation that may sometimes arise. The system has received clearance from the FDA and results from a clinical trial on its utility in supporting adherence to HIV pre-exposure prophylaxis are awaited.[27] Examples of ingestible sensors that have been developed for purposes other than supporting treatment adherence include the CorTemp ingestible sensor (HQ, Palmetto, USA) for monitoring core body temperature; and the CapsoCam Plus (CapsoVision, Saratoga, USA) and PillCam (Medtronic, Minneapolis, USA) for performing capsule endoscopy of the bowel.

It should also be acknowledged that remote digital adherence monitoring can take place without the need for ingestible sensors. 'Intelligent' nebulisers capable of recording and transmitting data on adherence have been used in clinical trials; for example, the I-neb adaptive aerosol delivery device (Philips Respironics, Chichester, UK) has been used to measure per protocol adherence to nebulised colistin versus placebo among patients with bronchiectasis with chronic *Pseudomonas aeruginosa* infection, helping to develop insights into the relationship between adherence and outcomes in this patient group.[28]

Thus, while WOT using ingestible sensors may hold promise, it remains difficult to discern just how efficacious this intervention is in supporting treatment adherence. Further comprehensive studies are required to evaluate not only its clinical effectiveness but also its cost effectiveness, safety and acceptability to stakeholders. There will also be merit in evaluating its utility in other acute and chronic conditions where adherence poses a challenge. Whether further data will ultimately be sufficient to confer confidence in the system among patients, clinicians and health policymakers remains to be seen. ■

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## Conflicts of interest

Kartik Kumar is a member of the editorial board for FHJ. Michael R Loebinger has received consultancy and/or lecture fees from Insmed, Savara and Meiji. Saira Ghafur is a co-founder of Prova

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Health and a co-founder of Psyma. The views expressed herein are those of the authors alone and not necessarily those of the NIHR or the Department of Health and Social Care.

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