Institution: University College London
Unit of Assessment: 2 - Public Health, Health Services and Primary Care
Title of case study: Use of virtual observed therapy to transform global tuberculosis control and treatment adherence in vulnerable TB patients.
Period when the underpinning research was undertaken: Between 2007 and 2020.
Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Professor Andrew Hayward	Professor of Infectious Disease Epidemiology and Inclusion Health	Between 2000 and present
Professor Robert Aldridge	Professor of Public Health Data Science	Between 2010 and present
Professor Ibrahim Abubaker	Professor of Infectious Disease Epidemiology	Between 2005 and present
Dr Alistair Story	Honorary Associate Professor in Inclusion Health	n/a (honorary since 2010)

Period when the claimed impact occurred: Between 2014 and 2020
Is this case study continued from a case study submitted in 2014? N

1. Summary of the impact

Led by UCL, an NIHR-funded, randomised controlled trial of Video Observed Therapy (VOT) for tuberculosis (TB) demonstrated that VOT was more effective, cheaper and preferable to patients compared to the previous international standard of care – face-to-face Directly Observed Therapy (DOT). This contributed to the World Health Organisation (WHO) now recommending VOT as an alternative to DOT, and its subsequent widespread adoption throughout North America, Eastern Europe and China and the commissioning of a national VOT service for TB in England. VOT is now recommended by NHS England and used as the standard of care for multidrug-resistant TB (MDRTB) patients and socially complex patients who require support in adhering to their treatment.

2. Underpinning research

UCL researchers based at UCLH (University College London Hospital) and the Collaborative Centre for Inclusion Health, led by Dr Alistair Story and Professor Andrew Hayward, conducted the world's first randomised controlled trial of Video Observational Treatment (VOT) to improve tuberculosis (TB) treatment and patient adherence to medication. Story subsequently collaborated with researchers at University of California at San Diego to evaluate, refine and improve SureAdhere, a secure and effective app for managing and administering VOT sessions.

TB remains the world's biggest bacillary killer, with about 1.4 million deaths per year (compared with 1.8 million deaths from COVID-19 globally in 2020). For most forms of TB, patients receive combined treatment lasting a minimum of six months, which they are directed to take regularly to ensure cure, reduce transmission of disease and prevent the emergence of drug-resistant disease. TB infections that are resistant to rifampicin, the most effective drug against TB, require different, longer-lasting treatment, generally involving more drugs. However, side effects, pill burden, and improving symptoms over the course of treatment make it very challenging for patients to adhere to their treatment. The WHO has recommended Directly Observed Therapy (DOT) to support patients with adherence to their treatment. This involves patients attending clinic or a healthcare worker going out to the patient to observe each dose being taken by the patient. In some places, the schedule has been altered to a three times weekly dose to facilitate observation, even though daily treatment is more effective.

In 2007, Story, Hayward and other UCL colleagues published a cohort study of 1,941 TB patients in London. The findings revealed high disease prevalence, poor outcomes, high levels of drug

resistance and poor adherence to treatment in socially complex TB patients including homeless people, drug users, prisoners and those with mental health problems **[R1].** This led to the National Institute for Health and Care Excellence (NICE) recommending that DOT should be targeted to socially complex groups.

As DOT became more prevalent, it also became clear that some patients struggled to engage consistently with treatment. Patients with MDRTB require daily dosing, making DOT highly challenging to deliver, especially among socially complex patients. Despite this, in the UK, DOT was recommended for patients who have a history of poor adherence; those with previous TB, MDRTB, or HIV; and socially complex patients including homeless people, drug users, prisoners, and those with alcohol and mental health problems. This DOT strategy has been criticised because of its high delivery cost, its inconvenience to patients, the lower rates of adherence to DOT in socially complex patients, the stigma involved in attending a clinic regularly or health workers visiting the home, and the variable evidence of DOT's effectiveness **[R2].**

VOT presents some important advantages over in-person DOT. Instead of attending a healthcare site daily, or three times a week, patients on VOT record themselves whilst taking their medication and the app shares the footage with health workers remotely, who check it against a timestamp to ensure the correct dosage has been taken at the right time. Where internet connection permits, and the patient and healthcare worker can be available at the same time, synchronous (real-time) VOT is possible. This emulates the face-to-face visit and allows a more interactive encounter. Researchers at the University of California San Diego developed an app to mediate VOT in mobile TB patients. Story and Hayward led a randomised control trial (from 2014 to 2017) using this app to assess its suitability and effectiveness for treating socially complex TB patients **[R3]**. Several observational studies demonstrated the in-principle feasibility of using VOT as an alternative to face-to-face DOT. However, prior to the UCL work, there were no studies of VOT usage in socially complex patients (who can be difficult to engage in care) and no randomised controlled trials comparing VOT to DOT.

The UCL VOT trial recruited patients eligible for DOT from 22 clinics in London, Leicester and Birmingham. A total of 112 patients were randomised to VOT and 114 to DOT. Of those randomised, 58% had a history of homelessness, drug use, imprisonment, alcohol problems or mental health issues. The trial provided free smartphones and data plans for participants to submit daily videoclips of themselves taking their medication throughout treatment. Of the VOT patients, 70% successfully completed over 80% of their scheduled treatment observations, compared to 31% of DOT patients. A large part of the effect was due to patients not engaging in DOT from early on in the course of their treatment. Conversely, high levels of adherence to VOT were maintained over six months of treatment. VOT was cheaper to deliver than DOT, even though smartphones and data plans were provided free to patients. VOT costs were estimated at GBP1,645 per patient over six months compared to GBP3,420 to GBP5,700 for DOT **[R4]**.

3. References to the research

[R1] Story A., Murad S., Roberts S., Verheyen M., Hayward A.C., London Tuberculosis Nurses Network. (2007). 'Tuberculosis in London: the importance of homelessness, problem drug use and prison'. *Thorax.* **62** (8),667-71. DOI: 10.1136/thx.2006.065409.

[R2] Story A., Garfein R.S., Hayward A., Rusovich V., Dadu A., Soltan V. et al. (2016). 'Monitoring therapy compliance of tuberculosis patients by using video-enabled electronic devices'. *Emerg Infect Dis*. **22**(3), 538–40. DOI: 10.3201/eid2203.151620

[R3] Story A., Aldridge R.W., Smith C.M., Garber E., Hall J., Ferenando G., Possas L, Hemming S., Wurie F., Luchenski S., Abubakar I., McHugh T., White J., Watson J., Lipman M., Garfein R., Hayward A.C. (2019). 'Smartphone-enabled video-observed versus directly observed treatment for tuberculosis: a multicentre, analyst-blinded, randomised, controlled superiority trial'. *Lancet*. **393**(10177), 1216-1224. DOI: 10.1016/S0140-6736(18)32993-3.

[R4] Story A., Garber E., Aldridge R.W., Smith C.M., Hall J., Ferenado G., et al. (2020). 'Management and control of tuberculosis control in socially complex groups: a research programme including three RCTs'. *Programme Grants Appl Res.* **8**(9) DOI: https://doi.org/10.3310/pgfar08090

4. Details of the impact

By leading the first randomised, controlled trial showing the superiority of VOT over DOT in terms of user engagement, retention, outcomes and reduced costs, UCL research has driven the rapid translation of this work into service provision, both nationally and internationally. Through UCL's engagement with the WHO and national health commissioners, VOT is now in widespread use in the US and England and is increasingly being used around the world to improve management of TB.

Evidence of VOT's effectiveness to change NHS England and WHO policy and guidelines:
VOT is recommended by NHS England as a key tool to reduce health inequalities, particularly for TB patients with complex social needs and those with MDRTB. The guidance specifically recommends the UCLH 'Find&Treat' model, citing Story and colleagues' UCL initial 2007 clinical trial and subsequent papers on the effectiveness of the SureAdhere app used in the trial, along with multiple studies applying the UCLH VOT in several other countries and with Inclusion Health groups. It concludes by assessing and recommending SureAdhere specifically, citing its high standards of governance as well as its clinical effectiveness **[S1]**. In 2019, NIHR created an 'NIHR Signal' based on the UCL SureAdhere clinical trial which highlights impactful studies for decision makers in the NHS, public health and social care **[S2]**.

By engaging key decision-makers and thematic leads with emerging findings from UCL VOT clinical trials, UCL researchers have had a major influence on WHO strategy and recommendations around TB, and in particular treating vulnerable or marginalised TB patients or those with MDRTB, who require lengthy treatment plans. In 2014, the WHO developed the 'End TB Strategy' with the aim of ending the global TB epidemic by 2035 and in the following year it launched the Global Taskforce for Digital Health and TB, of which Story was a member. Hayward and Story contributed research insights and evidence to both areas of WHO activity.

The UCL VOT studies contributed to the 2015 WHO report 'Digital Health for the End TB Strategy: An agenda for action' **[S3]**. Hayward, Story and colleagues presented the preliminary results of the UK studies at a series of WHO meetings, including the technical consultation on the role of e/mHealth in tuberculosis and tobacco control from 25 to 27 February 2015; the launch of the Global Taskforce on Digital Health for TB in April 2015; and a subsequent International collaborative group on VOT for TB on 14 July 2015.

The invitations to the UCL team were issued by the WHO because this work was one of the few health interventions whose effectiveness was backed by field studies, and eventually the first RCT that was completed, in this domain. The Digital Lead for the WHO Global TB Programme says: *"At that time there was no evidence from randomised controlled trials and no evidence of effectiveness within socially complex groups. It was therefore extremely helpful to have trial-based evidence, showing the higher degree of acceptability, increased levels of observation and lower costs compared to traditional DOT. [...] The UCL research was a very important part of the evidence that led to the development of a series of [WHO] policy and guideline documents promoting increased use of VOT and wider promotion of Digital Adherence Technologies"* **[S4]**.

In the subsequent 2015 WHO report titled 'Digital Health for the End TB Strategy: An agenda for action', VOT is identified as a key emerging technology and clinical tool to tackle TB health inclusion challenges and health inequalities within and between countries more broadly, noting the increasing availability of internet-enabled smartphones in higher and lower income health settings, and the flexibility of the intervention compared to DOT. It also notes the broad applicability of VOT to other sorts of social-determined health inequalities, for example smoking cessation. It emphasises the patient-centred principles underpinning VOT, and its relationship to UN Sustainability Goals: specifically, that the often lengthy treatment process for TB should

accommodate the patient's needs and commitments, and that it should place as little burden and stigma upon them as possible **[S3]**.

Following this, in 2017 the WHO published a *'Handbook for the use of digital technologies to support tuberculosis medication adherence'*, including technical specifications for commissioning VOT platforms and guidance on establishing national digital health strategies **[S5]**. The WHO quotes Story's 2019 paper **[R3]** in support of the specifications for VOT, as one of three digital technologies identified in the handbook. In 2020, in the WHO/EUR 'Quick guide to video-supported treatment of tuberculosis', SureAdhere is listed as one of the products employed in the field to deliver VOT (in Ukraine). UCL research is also cited in the Stop TB 'Partnership guidance on Technologies for Improving TB Medication Adherence and Treatment Outcomes', as evidence for the WHO 2017 recommendations on the use of VOT for improving adherence in TB medication **[S6]**. Stop TB is an INGO (international NGO) with over 1,700 partners dedicated to the eradication of TB by influencing international policy and treatment guidelines.

Improved outcomes for TB service users in the UK and other countries:
In 2017, Hayward presented the results of the clinical trial of SureAdhere (prior to final publication) to the London TB board and other commissioners of TB services across England **[S7]**. The Chair of the London TB Board at the time said: "*The trial was already supporting a high proportion of the most socially complex cases and most of the multidrug resistant cases in London, so we saw a clear need to urgently translate this NIHR research investment into a commissioned service based on the strong evidence of acceptability, effectiveness and cost effectiveness provided by the study […] I can say with confidence that the VOT service only exists because of the research conducted in partnership between UCL, UCLH and TB clinics across the country*" **[S7]**.

TB services differ considerably in their structure across England, as do concentrations of need. By engaging with key decision-makers during the conclusion of the clinical trial, the UCL team facilitated the rapid scale-up and expansion of the service nationally as appropriate evidence-based action could now be taken, and secured a seamless transition from trial to real-world adoption. VOT is now commissioned as an England-wide TB treatment service delivered from UCLH through the 'Find&Treat' service. 'Find&Treat' is led by Story, and the national VOT service within it is now led by one of the UCL research team. Most of the MDRTB patients in England are now treated with VOT along with a high proportion of socially complex patients. On average, around 75 to 80% of MDRTB London patients are referred to VOT (in some London TB Services it could be as many as 90% of MDRTB patients). Around 55 to 60% of patients on VOT have at least one social risk factor and around 60% will have had previous treatment episodes or experience previous non-adherence **[S8]**.

The use of VOT increased substantially during the 2020 COVID-19 pandemic, as face-to-face DOT became unfeasible. The service is commissioned across London and also provides VOT on an ad hoc basis outside of London. Including clinical trials, since 2014 'Find&Treat' VOT services have treated a total of 531 TB patients, including a high proportion of the most vulnerable eligible TB patients in England **[S8]**.

UCL worked with the University of California (San Diego) to evaluate and refine the SureAdhere app. Both UCL and UCSD have gone on to work with health services in the UK, US and other countries to implement VOT TB treatment using SureAdhere, which is now a commercially available platform. VOT is now being used to treat TB widely across the US and increasingly in a wide range of other countries. In addition to TB, it is also being used for HIV and Hepatitis C treatment and Opioid Substitution Therapy. SureAdhere is now used across several US State TB control programmes (Arkansas, California, Colorado, New York, Texas, Vermont, Washington) and is being used in some high incidence countries, including Mexico, Vietnam and Uganda **[S9]**.

UCL researchers including Hayward and Story advised the UK Behavioural Insights Team on the setup of a trial of VOT in Moldova, which showed similar effectiveness to the original UK

study. VOT is now part of the national programme **[S10]**. UCL VOT research has also influenced TB treatment in Belarus. In 2015, the Ministry of Health of Belarus, with support from the WHO Global TB Programme Medical Officer (who had also led on the TB Digital Strategy work developed with Story), implemented its first VOT intervention at Minsk Tuberculosis Dispensary number 2, a major TB clinic in the capital city with around 26,000 outpatient consultations per year and approximately 85 TB patients attending for observed treatment every day. Staff at the dispensary volunteered to introduce VOT as an additional option to support their patients. This pilot showed that VOT was well accepted by patients and underpinned the roll-out of a larger programme by the Belarus Red Cross across 450 treatment centres in 2018, with the support of the Global Fund to Fight AIDS, Malaria and TB **[S11].**

5. Sources to corroborate the impact

[S1] NHS England (2020): 'Commission use of the Find and Treat Video Observed Therapy on the SureAdhere platform to support tuberculosis treatment completion'. Menu of evidence based interventions to reduce health inequalities. https://www.england.nhs.uk/ltphimenu/better-care-tuberculosis/find-and-treat-video-observed-therapy

[S2] NIHR Signal: 'Smartphones instead of direct supervision can improve adherence rates for TB treatment'. 11 June 2019. DOI: 10.3310/signal-000777

[S3] WHO DIGITAL HEALTH FOR THE END TB STRATEGY: AN AGENDA FOR ACTION. (2015) World Health Organisation. WHO Press: Geneva, Switzerland. [PDF]

[S4] Testimonial letter, Digital Lead, WHO Global TB Programme

[S5] Handbook for the Uses of Digital Technologies to Improve TB Medication Adherence (2017) World Health Organisation. WHO Press: Geneva Switzerland.

[S6] Technologies for Improving TB Medication Adherence and Treatment Outcomes. (2017) Stop TB Partnership [PDF]

[S7] Testimonial Letter, Former Chair of the London TB Board and Medical Director, Public Health England

[S8] 'Find&Treat' supplied data on patient numbers/ patient profiles [PDF]

[S9] 'Where we work'. SureAdhere company website. http://www.sureadhere.com/our-story/where-we-work

[S10] Story A., Garfein R.S., Hayward A., et al. (2016). 'Monitoring Therapy Compliance of Tuberculosis Patients by using Video-Enabled Electronic Devices'. Emerging Infectious Diseases. **22**(3), 538-540. DOI: 10.3201/eid2203.151620

[S11] Sinkou, H., Hurevich, H., Rusovich, V., Zhylevich, L., Falzon, D., de Colombani, P., Dadu, A., Dara, M., Story, A., & Skrahina, A. (2017). 'Video-observed treatment for tuberculosis patients in Belarus: findings from the first programmatic experience'. *The European respiratory Journal*, **49**(3), 1602049. DOI: https://doi.org/10.1183/13993003.02049-2016