The impact of digital health technologies on tuberculosis treatment:
A systematic review

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Supplementary material

Table S1: Search strategy

Terms to denote "TB disease

Tuberculosis OR pulmonary tuberculosis OR Kochs disease OR Phthisis OR TB OR MTB OR drug resistant tuberculosis OR MDR TB OR XDR TB OR drug resistance TB OR DR TB OR latent TB OR LTBI OR DOTS OR directly observed treatment short course OR TB-DOTS OR anti-TB treatment OR Kochs disease

Terms to denote "digital technologies"

Digital health OR telehealth OR eHealth OR mhealth OR telemedicine OR video health OR video recordings OR virtually observed treatment OR SMS OR reminders OR short message service OR text messages OR MMS OR multimedia messages OR MEMS OR medical electronic monitoring OR monitoring sensors OR monitoring devices OR video monitoring OR video conferencing OR Webcam OR videophone OR message reminders OR technology OR web based strategies OR health IT OR health ICT

Terms to denote "TB treatment outcomes"

Adherence OR treatment adherence OR compliance OR TB treatment adherence OR TB treatment compliance OR medication adherence OR doses OR cure OR completion OR default OR costs OR death OR lost to follow up OR side effects OR adverse events OR mortality OR morbidity

Table S2: Studies Excluded and Included After Review (n = 33 total)

Ref	Stage and reason	Author, Year		Title	Intervention
	EXCLUDED STUDIES: Stage of exclusion and reason				
[1]	Abstract – protocol	Green 2015	Protocol	Do clinical decision-support reminders for medical providers improve isoniazid preventative therapy prescription rates among HIV-positive adults?: Study protocol for a randomized controlled trial.	SMS
[2]	Abstract – protocol	Bediang 2014	Protocol	SMS reminders to improve the tuberculosis cure rate in developing countries (TB-SMS Cameroon): a protocol of a randomised control study	SMS
[3]	Abstract - systematic review	Nglazi 2013	systematic review	Mobile phone text messaging for promoting adherence to anti-tuberculosis treatment: a systematic review	SMS
[4]	Abstract - systematic review	Chen 2015	systematic review	Mobile phone based interventions for promoting adherence to tuberculosis treatment: a systematic review and meta-analysis	Mobile phones
[5]	Abstract - systematic review	Liu 2014	systematic review	Reminder systems to improve patient adherence to tuberculosis clinic appointments for diagnosis and treatment	Telephone call reminders and letters
[6]	Abstract - study not complete	Browne 2016	Protocol	Wireless Observed Therapy in Comparison to Directly Observed Therapy for the Treatment of Tuberculosis	MM
[7]	Abstract - study not complete	Garfein 2016	Protocol	VDOT for monitoring adherence to LTBI treatment (VMALT)	VOT
[8]	Abstract – other endpoints	Belknap 2010	Conference abstract	Feasibility of a microchip-based system for electronically observed tuberculosis therapy	MM
[9]	Abstract - other endpoints	Narasimhan 2014	Original article	A customized m-Health system for improving Tuberculosis treatment adherence and follow-up in south India.	Voice call based
[10]	Full text - other endpoints	Lei 2013	Original article	Is the short messaging service feasible to improve adherence to tuberculosis care? A cross-sectional study	SMS
[11]	Full text - other endpoints	Windish 2015	Original article	Video observed therapy for multidrug-resistant tuberculosis: a qualitative study of patient perspectives	VDOT
[12]	Full text - other endpoints	Chaiyachati 2013	Original article	A Pilot Study of an mHealth Application for Healthcare Workers: Poor Uptake Despite High Reported Acceptability at a Rural South African Community-Based MDR-TB Treatment Program.	Mixed

Ref	Stage and reason	Author, Year		Title	Intervention
[13]	Full text - other endpoints	Li 2011	Original article	A feasibility study on short messaging service (SMS) as a strategy to improve adherence to TB services.	SMS
[14]	Full text - other endpoints	Mohammed 2012	Original article	User engagement with and attitudes towards an interactive SMS reminder system for patients with tuberculosis.	SMS
[15]	Full text - other endpoints	Hoffman 2010	Original article	Mobile direct observation treatment for tuberculosis patients: a technical feasibility pilot using mobile phones in Nairobi, Kenya.	VDOT
[16]	Full text - other endpoints	Owiti 2012	Conference abstract	Mobile phone text messaging reminders to aid adherence to tuberculosis care in Eldoret, Kenya	SMS
[17]	Full text – Qualitative	Albino 2014	Original article	Perceptions and acceptability of short message services technology to improve treatment adherence amongst tuberculosis patients in Peru: a Focus Group Study.	SMS
[18]	Full text - Qualitative	Belknap 2013	Original article	Feasibility of an Ingestible Sensor-Based System for Monitoring Adherence to Tuberculosis Therapy.	MM
[19]	Full text - Qualitative	Person 2011	Original article	Text messaging for enhancement of testing and treatment for tuberculosis, human immunodeficiency virus, and syphilis: a survey of attitudes toward cellular phones and healthcare.	SMS
[20]	Full text - Qualitative	Iribarren 2015	Original article	Qualitative Evaluation of a Text Messaging Intervention to Support Patients With Active Tuberculosis: Implementation Considerations	SMS
[21]	Full text – Costing	Krueger 2010	Original article	Videophone utilisation as an alternative to DOTS for tuberculosis	VOT
[22]	Full text - Costing	Mirsaeidi 2015	Original article	Video directly observed therapy for treatment of tuberculosis is patient oriented and cost-effective	VOT
[23]	Full text – latent TB study	Lester 2015	Protocol	TB mHealth study - use of cell phones to improve compliance in patients on LTBI treatment	SMS
[24]	Full text - no control group	Garfein 2015	Original article	Feasibility of tuberculosis treatment monitoring by video directly observed therapy: A binational pilot study.	VOT
[25]	Full text - no control group	Husler 2005	Unpublished report	Evaluation of the On Cue Compliance Service Pilot. Testing the Use of SMS Reminders in the Treatment of Tuberculosis in Cape Town, South Africa	SMS
[26]	Full text - no control group	DeMaio 2001	Original article	The application of telemedicine technology to a directly observed therapy program for tuberculosis: A pilot project	VOT

				INCLUDED STUDIES	
[27] Full text - included	Wade 2012	Original article	Home Videophones Improve Direct Observation in Tuberculosis Treatment: A Mixed Methods Evaluation.	VOT
[28] Full text - included	Chuck 2016	Original article	Enhancing management of tuberculosis treatment with video directly observed therapy in New York City	VOT
[29] Full text - included	Broomhead 2012	Original article	Retrospective return on investment analysis of an electronic treatment adherence device piloted in the Northern Cape Province	MM
[30] Full text - included	Mohammed 2016	Original article	Impact of a daily SMS medication reminder system on tuberculosis treatment outcomes: a randomized controlled trial	SMS
[31] Full text - included	Liu 2015	Original article	Effectiveness of Electronic Reminders to Improve Medication Adherence in Tuberculosis Patients: A Cluster-Randomised Trial	MM & SMS
[32] Full text - included	Bediang (Submitted for publication in 2017)	Original article	SMS Reminders to Improve Tuberculosis Cure in Developing Countries (TB-SMS Cameroon): A Randomised Controlled Trial [Unpublished]	SMS
[33] Full text - included	Iribarren 2013	Original article	Text TB: A parallel design randomized control study to evaluate acceptance and feasibility of a patient driven mobile phone based intervention to support adherence to TB treatment	SMS

Table S3: Assessment of bias of randomized trials included in the review

Bias	Reviewers' judgment	Reasons for judgment
Bediang (Submitted for publication in 2017) [32]		
Random sequence generation (selection bias)	Low risk	This is a blinded, randomised controlled multicentre study carried out in Cameroon. Randomisation was carried out using a computer program by the main investigator.
Allocation concealment (selection bias)	Low risk	The health personnel in the hospitals were not involved in the allocation of participants into groups
Blinding of participants and personnel (performance bias)	High risk	Both participants and personnel were aware of the intervention
Blinding of outcome assessment (detection bias)	High risk	Assessors were aware of the intervention received by study participants
Incomplete outcome data (attrition bias)	Low risk	There was a low rate of attrition
Selective reporting (reporting bias)	Low risk	The authors reported results in the way they had originally proposed in the protocols.
Iribarren 2013 [33]		
Random sequence generation	Low risk	Patients newly diagnosed with TB who were 18 or older, and had mobile phone access were recruited and randomized to usual care plus either medication calendar or text messaging intervention for the first two months of treatment.
Allocation concealment	Low risk	Eligible participants were randomized in a 1:1 allocation ratio in blocks of 10. Physicians were not made aware of the group allocation of their patient unless the patient informed them.
Performance bias	High risk	Both participants and personnel were aware of the intervention
Detection bias	Unclear risk	Not documented in the original paper
Attrition bias	High risk	47% of calendars were not returned for analysis
Reporting bias	Unclear risk	We did not have access to the protocol
Liu 2015 [31]		
Random sequence generation	Low risk	36 clusters were randomised to the four arms by rural/urban stratum and restricted such that each province had at least two clusters in each arm. From 5,000 randomly generated acceptable allocations, one was chosen at random as the final allocation
Allocation concealment	Low risk	
Performance bias	High risk	Both participants and personnel were aware of the intervention
Detection bias	Unclear risk	Not documented in the original paper
Attrition bias	Low risk	Five patients transferred to another clinic and one patient had missing outcomes
Reporting bias	Low risk	The primary endpoint was a quantitative measure of the proportion of months on TB treatment where at least 3 doses were missed in a month
Mohammed 2016 [30]		
Random sequence generation	Low risk	Patients were randomized through an electronic randomization process at the time of enrolment, to prevent personal bias from contaminating the randomization process. Patients were randomized into either the control arm or the Zindagi SMS arm of the study using programs on the clinic representatives' mobile phones.
Allocation concealment	Low risk	Participants were informed of their randomization status but it was not shared with their treating clinics by the study representatives.
Performance bias	High risk	Both participants and personnel were aware of the intervention
Detection bias	Unclear risk	Not documented in the original paper
Attrition bias	Low risk	
Reporting bias	Low risk	Treatment outcomes for TB patients included cure, treatment complete, treatment failure, died, transfer out, or default.

Figure S1: Risk of bias graph: review authors' assessments of each risk of bias item presented as percentages across all included randomized trials
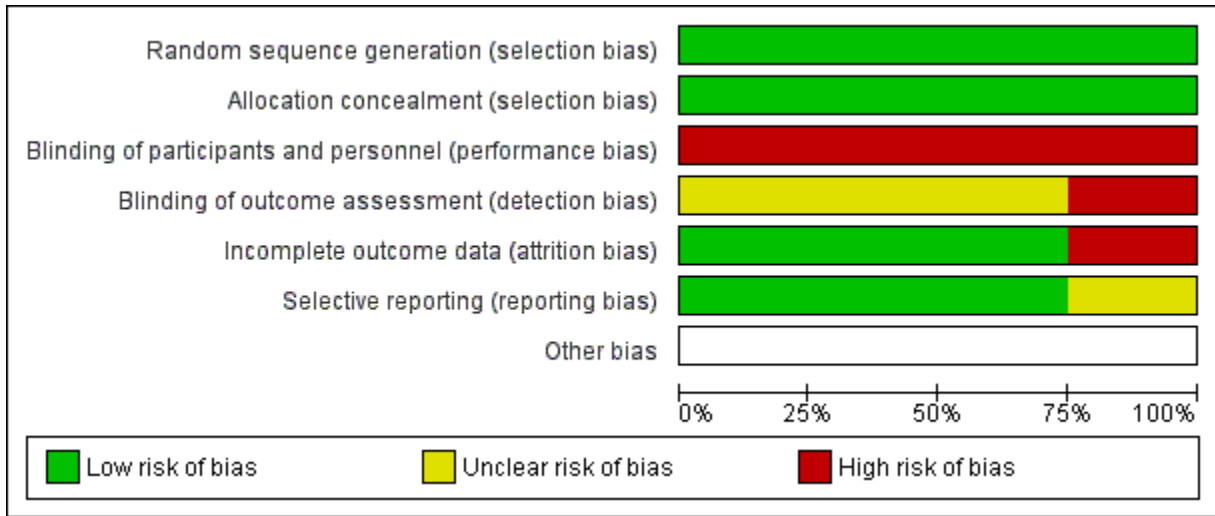

Figure S2: Risk of bias summary: review authors' assessments of each risk of bias item for each included randomized trial

References

1. Green EP, Catalani C, Diero L, Carter EJ, Gardner A, Ndwiga C, Keny A, Owiti P, Israelski D, Biondich P. Do clinical decision-support reminders for medical providers improve isoniazid preventative therapy prescription rates among HIV-positive adults?: study protocol for a randomized controlled trial. Trials. 2015;16(1):141
2. Bediang G, Stoll B, Elia N, Abena J-L, Nolna D, Chastonay P, Geissbuhler A. SMS reminders to improve the tuberculosis cure rate in developing countries (TB-SMS Cameroon): a protocol of a randomised control study. Trials. 2014;15(1):35
3. Nglazi MD, Bekker L-G, Wood R, Hussey GD, Wiysonge CS. Mobile phone text messaging for promoting adherence to anti-tuberculosis treatment: a systematic review. BMC infectious diseases. 2013;13(1):566
4. Chen S, Pan Y, Qu Y, Liu Z, Yao L, Xiang L. Mobile phone based interventions for promoting adherence to tuberculosis treatment: a systematic review and meta-analysis. The Lancet. 2015;386:S29
5. Liu Q, Abba K, Alejandria MM, Sinclair D, Balanag VM, Lansang MAD. Reminder systems to improve patient adherence to tuberculosis clinic appointments for diagnosis and treatment. Cochrane Database of Systematic Reviews. 2014;10.1002/14651858.CD006594.pub3(11).http://dx.doi.org/10.1002/14651858.CD006594.pub3
6. Browne S, Haubrich R, Moser K, Tucker A, Vaida F, Peloquin C, Benson C. Wirelessly observed therapy in comparison to directly observed therapy for the treatment of tuberculosis. ClinicalTrialsgov [database] Bethesda (MD): National Library of Medicine (US). 2016(https://clinicaltrials.gov/ct2/show/study/NCT01960257#contacts).http://clinicaltrials.gov/ct2/show/NCT01960257
7. Garfein R. VDOT for Monitoring Adherence to LTBI Treatment (VMALT). ClinicalTrialsgov [database] Bethesda (MD): National Library of Medicine (US). 2016(https://clinicaltrials.gov/ct2/show/NCT02641106).https://clinicaltrials.gov/ct2/show/NCT02641106
8. Belknap R, Luna L, Reves R, Turk L, Weiss S, Au-Yeung K, Moon G, Karplus E, editors. Feasibility of a microchip-based system for electronically observed tuberculosis therapy. Proceedings of the American Thoracic Society International Conference; 2010 https://doi.org/10.1164/ajrccm-conference.2010.181.1_MeetingAbstracts.A5462.
9. Narasimhan P, Bakshi A, Kittusami S, Prashant S, Mathai D, Bakshi K, MacIntyre CR, Ray P. A customized m-Health system for improving Tuberculosis treatment adherence and follow-up in south India. Health and Technology. 2014;4(1):1-10
10. Lei X, Liu Q, Wang H, Tang X, Li L, Wang Y. Is the short messaging service feasible to improve adherence to tuberculosis care? A cross-sectional study. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2013;107(10):666-8
11. Windish P, Luchenski S, Hall J, Appleby Y, Possas L, Hemming S, Story A. Video observed therapy for multidrug-resistant tuberculosis: a qualitative study of patient perspectives. The Lancet. 2015;386:S78
12. Chaiyachati KH, Loveday M, Lorenz S, Lesh N, Larkan L-M, Cinti S, Friedland GH, Haberer JE. A pilot study of an mHealth application for healthcare workers: poor uptake despite high reported acceptability at a rural South African community-based MDR-TB treatment program. PLoS One. 2013;8(5):e64662
13. Li L, Lei X, Liu Q, Wang H, Tang X, Wang Y. A feasibility study on short messaging service (SMS) as a strategy to improve adherence to TB services. Chinese Journal of Evidence-Based Medicine. 2011:631-5.http://caod.oriprobe.com/articles/27472030/A_Feasibility_Study_on_Short_Messaging_Service__SMS__as_a_Strategy_to_.htm
14. Mohammed S, Siddiqi O, Ali O, Habib A, Haqqi F, Kausar M, Khan AJ. User engagement with and attitudes towards an interactive SMS reminder system for patients with tuberculosis. Journal of telemedicine and telecare. 2012;18(7):404-8
15. Hoffman JA, Cunningham JR, Suleh AJ, Sundsmo A, Dekker D, Vago F, Munly K, Igonya EK, Hunt-Glassman J. Mobile direct observation treatment for tuberculosis patients: a technical feasibility pilot using mobile phones in Nairobi, Kenya. American journal of preventive medicine. 2010;39(1):78-80
16. Owiti P, Gardner A, Szkwarko D, Diero L, Carter E, editors. Mobile phone text messaging reminders to aid adherence to tuberculosis care in Eldoret, Kenya. 43rd World Conference on Lung Health of The Union, Kuala Lumpur, Malaysia; 2012
17. Albino S, Tabb KM, Requena D, Egoavil M, Pineros-Leano MF, Zunt JR, García PJ. Perceptions and acceptability of short message services technology to improve treatment adherence amongst tuberculosis patients in Peru: a focus group study. PloS one. 2014;9(5):e95770

18. Belknap R, Weis S, Brookens A, Au-Yeung KY, Moon G, DiCarlo L, Reves R. Feasibility of an ingestible sensor-based system for monitoring adherence to tuberculosis therapy. PloS one. 2013;8(1):e53373.https://doi.org/10.1164/ajrccm-conference.2010.181.1_MeetingAbstracts.A5462

19. Person AK, Blain ML, Jiang H, Rasmussen PW, Stout JE. Text messaging for enhancement of testing and treatment for tuberculosis, human immunodeficiency virus, and syphilis: a survey of attitudes toward cellular phones and healthcare. Telemedicine and e-Health. 2011;17(3):189-95

20. Iribarren SJ, Sward KA, Beck SL, Pearce PF, Thurston D, Chirico C. Qualitative Evaluation of a Text Messaging Intervention to Support Patients With Active Tuberculosis: Implementation Considerations. JMIR mHealth and uHealth. 2015;3(1)

21. Krueger K, Ruby D, Cooley P, Montoya B, Exarchos A, Djojonegoro B, Field K. Videophone utilization as an alternative to directly observed therapy for tuberculosis. The International Journal of Tuberculosis and Lung Disease. 2010;14(6):779-81

22. Mirsaeidi M, Farshidpour M, Banks-Tripp D, Hashmi S, Kujoth C, Schraufnagel D. Video directly observed therapy for treatment of tuberculosis is patient-oriented and cost-effective. European Respiratory Journal. 2015:ERJ-00110-2015

23. Lester R. TB mHealth Study - Use of Cell Phones to Improve Compliance in Patients on LTBI Treatment. ClinicalTrialsgov [database] Bethesda (MD): National Library of Medicine (US). 2015(https://clinicaltrials.gov/ct2/show/NCT01549457).https://clinicaltrials.gov/ct2/show/NCT01549457

24. Garfein R, Collins K, Munoz F, Moser K, Cerecer-Callu P, Raab F, Rios P, Flick A, Zuniga M, Cuevas-Mota J. Feasibility of tuberculosis treatment monitoring by video directly observed therapy: a binational pilot study. The International Journal of Tuberculosis and Lung Disease. 2015;19(9):1057-64

25. Hüsler J. Evaluation of the On Cue Compliance Service Pilot: Testing the use of SMS reminders in the treatment of tuberculosis in Cape Town, South Africa. Bridges org report 2005, 1-41. http://www.kiwanja.net/database/document/report_tb_compliance.pdf

26. DeMaio J, Schwartz L, Cooley P, Tice A. The application of telemedicine technology to a directly observed therapy program for tuberculosis: a pilot project. Clinical infectious diseases. 2001;33(12):2082-4

27. Wade VA, Karnon J, Eliott JA, Hiller JE. Home videophones improve direct observation in tuberculosis treatment: a mixed methods evaluation. PLoS One. 2012;7(11):e50155

28. Chuck C, Robinson E, Macaraig M, Alexander M, Burzynski J. Enhancing management of tuberculosis treatment with video directly observed therapy in New York City. The International Journal of Tuberculosis and Lung Disease. 2016;20(5):588-93

29. Broomhead S, Mars M. Retrospective return on investment analysis of an electronic treatment adherence device piloted in the Northern Cape Province. Telemedicine and e-Health. 2012;18(1):24-31.http://online.liebertpub.com/doi/pdfplus/10.1089/tmj.2011.0143

30. Mohammed S, Glennerster R, Khan AJ. Impact of a Daily SMS Medication Reminder System on Tuberculosis Treatment Outcomes: A Randomized Controlled Trial. PloS one. 2016;11(11):e0162944.https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5089745/pdf/pone.0162944.pdf

31. Liu X, Lewis JJ, Zhang H, Lu W, Zhang S, Zheng G, Bai L, Li J, Li X, Chen H. Effectiveness of Electronic Reminders to Improve Medication Adherence in Tuberculosis Patients: A Cluster-Randomised Trial. PLoS Med. 2015;12(9):e1001876.https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4570796/pdf/pmed.1001876.pdf

32. Bediang G, Stoll B, Elia N, Abena J-L, Nolna D, Chastonay P, Geissbuhler A. SMS Reminders to Improve Tuberculosis Cure in Developing Countries (TB-SMS Cameroon): A Randomised Control Trial. Trials. 2014;BioMed Central.http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3902069/

33. Iribarren S, Beck S, Pearce PF, Chirico C, Etchevarria M, Cardinale D, Rubinstein F. TextTB: A Mixed Method Pilot Study Evaluating Acceptance, Feasibility, and Exploring Initial Efficacy of a Text Messaging Intervention to Support TB Treatment Adherence. Tuberculosis Research and Treatment. 2013;2013:12.http://dx.doi.org/10.1155/2013/349394