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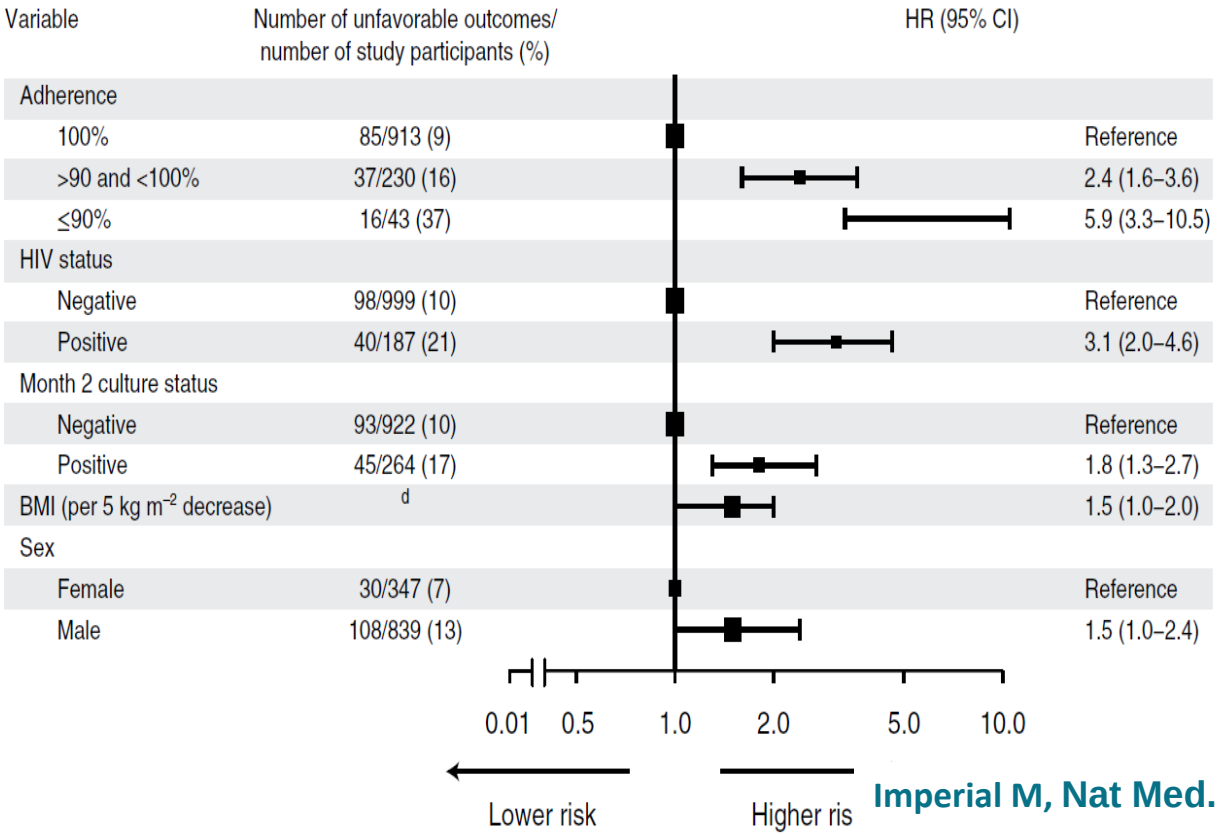
Creating a healthier world for future generations.
Overview and experience of digital adherence technologies (DATs) in DS-TB regimens to improve patient outcomes

Evidence of adherence related to treatment outcomes

Baseline characteristics, on-treatment culture status and adherence



Imperial M, Nat Med. 2018 Nov;24(11):1708-17

Effectiveness of MERM in DS-TB

1st China RCT Showed 45% Improvement In Adherence Over Standard of Care

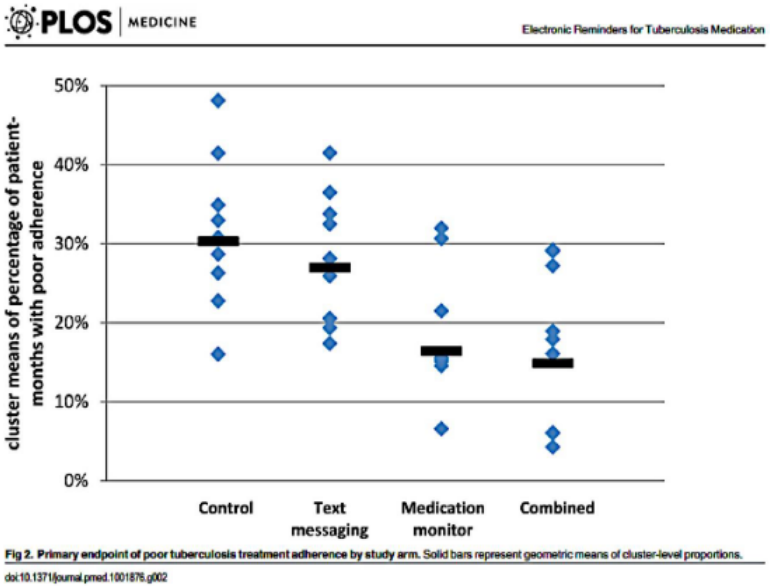


Fig 2. Primary endpoint of poor tuberculosis treatment adherence by study arm. Solid bars represent geometric means of cluster-level proportions.

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RESEARCH ARTICLE

Effectiveness of Electronic Reminders to Improve Medication Adherence in Tuberculosis Patients: A Cluster-Randomised Trial

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- 4500 patients
- Rural and urban settings
- Well accepted by both patients (satisfaction 82%) and providers
- Use of a medication monitor reduced poor medication adherence by 40%–50% compared to the standard of care in China's National Tuberculosis Control Program. This reduction was seen for all TB treatment adherence measures in this study."

Liu, Plos Medicine 2015; 12(9): e1001876,

Effectiveness of MERM in DS-TB

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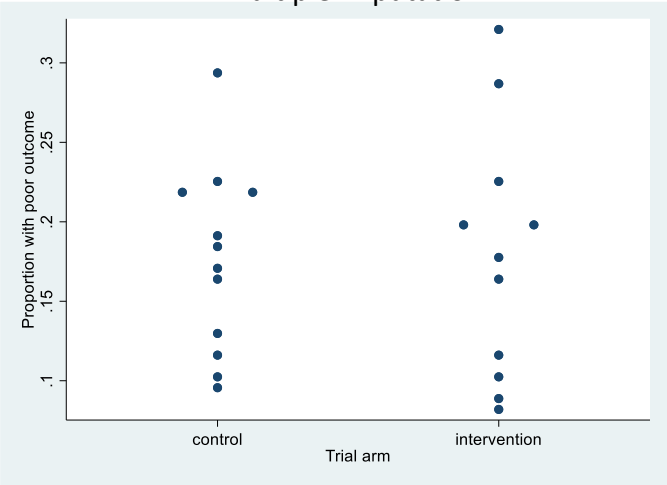
2nd China trial: Primary outcome – Treatment outcomes

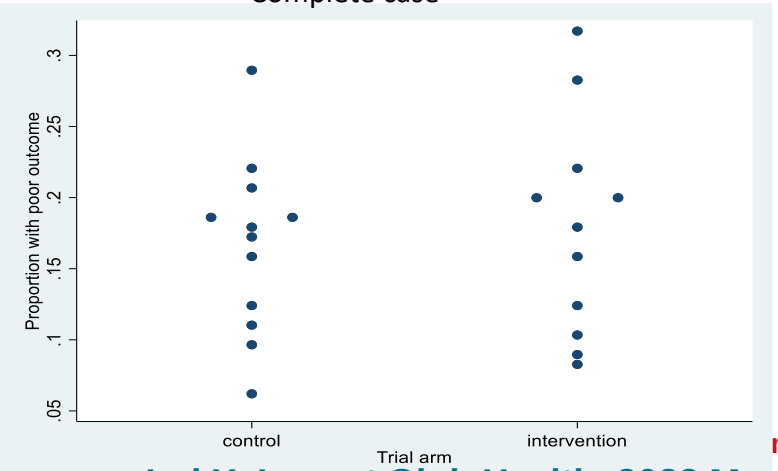
	SoC arm n/N[1] (GM)	Intervention arm n/N[1] (GM)	Unadjusted Risk Ratio (95% CI)	P value	Adjusted risk ratio (95% CI)	P value
Multiple imputation	239/1388 (16%)	224/1298 (16%)	0.99 (0.66, 1.48)	0.96	1.01 (0.73, 1.40)	0.95
Complete case	217/1300 (16%)	216/1238 (16%)	1.03 (0.71, 1.51)	0.85	1.05 (0.78, 1.41)	0.72

[1] for multiple imputation analysis n=imputation-mean of total number of events; GM geometric mean of cluster-level proportions
Adjusted for age, sex, occupation, local resident, distance to clinic, education level, household expenditure, and smear result at treatment initiation

Multiple imputation



Complete case



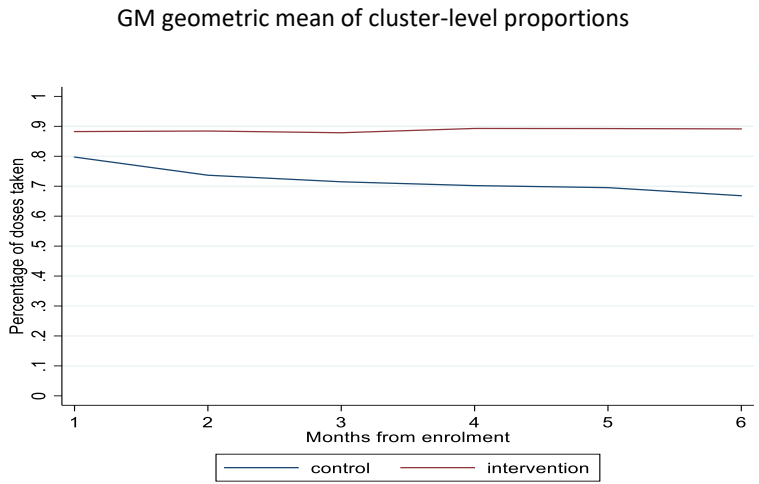
minstitute.org

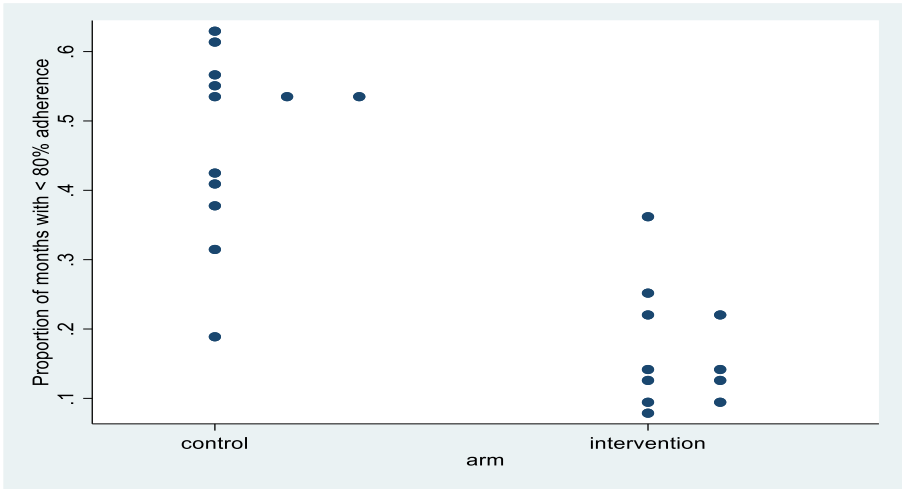
Lui X, Lancet Glob Health. 2023 May;11(5):e693-e

Effectiveness of MERM in DS-TB

2nd China trial: Secondary outcome: Adherence

	SoC arm (GM)	Intervention arm (GM)	Unadjusted Risk Ratio (95% CI)	P value	Adjusted risk ratio (95% CI)	P value
Months in which patients missed >20% of doses	2.7/6.0 (46%)	0.9/6.0 (16%)	0.34 (0.24,0.49)	<0.001	0.36 (0.27, 0.50)	<0.001
Doses missed/ doses expected per person	42/160 (27%)	16/160 (11%)	0.40 (0.31, 0.53)	<0.001	0.43 (0.34, 0.53)	<0.001





Lui X, Lancet Glob Health. 2023 May;11(5):e693-e

Effectiveness of MERM in DS-TB (Vietnam)

Table 1 Effectiveness of intervention on TB treatment adherence using different treatment outcome definitions

Endpoint (study group)	Patients *n*	Geometric mean % (95% CI)	Mean ratio (95% CI)
Proportion of patient months with at least 6/30 doses missed*			
Control	126	35.8 (29.8–41.2)	1.00
Intervention	124	25.8 (19.2–31.8)	0.72 (0.67–0.77)
Proportion of patient months with at least 14/30 doses missed			
Control	126	20.2 (15.1–25.0)	1.00
Intervention	124	12.4 (7.6–17.0)	0.61 (0.54–0.68)
Proportion of total doses missed			
Control	126	21.2 (18.3–23.9)	1.00
Intervention	124	15.8 (12.9–18.7)	0.75 (0.68–0.80)

* Primary endpoint.
CI = confidence interval.

Velen K, Int J Tuberc Lung Dis. 2023 Apr 1;27(4):322-328.

TB Monitoring Adherence and Treatment Endpoints

Study design: Pragmatic cluster randomised control trial

Study setting: 18 primary health clinics (PHC) in 3 **South African** provinces with high number of identified TB cases and with varying prevalence of HIV infection

Target population: Approximately 2610 adults and children with DS-TB receiving TB treatment from a local PHC

Study Objectives

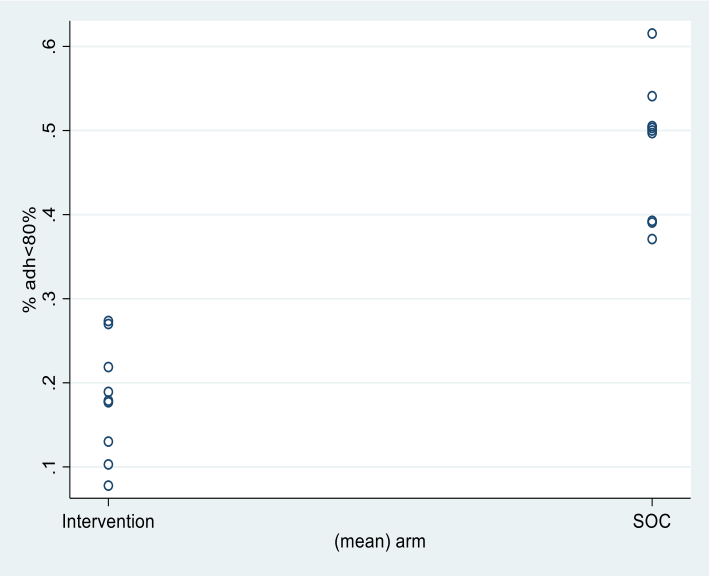
Primary objective

- To evaluate whether implementation of the Wisepill evriMED device with real-time monitoring and differentiated care was able to **increase the proportion of patients with >80% adherence** to DS-TB treatment

Secondary objectives

- To evaluate patients who successfully complete DS-TB treatment
- To measure unfavourable outcomes 18 months post-enrolment
- To explore the feasibility, acceptability and fidelity
- To evaluate cost-effectiveness

Primary: Proportion with <80% Adherence

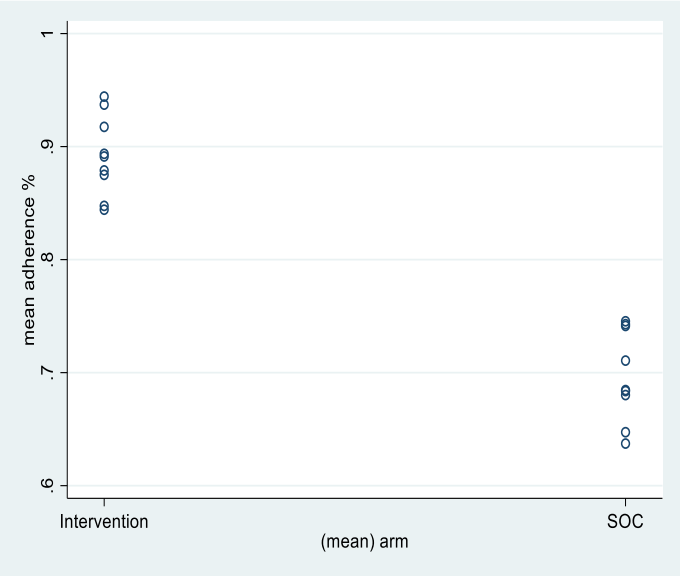


% of patients with <80% adherence

- log transformation, giving geometric means, and risk ratio (Intervention vs SoC)

Intervention	SoC	Risk ratio (95% CI)	P-value
18.8	48.7	0.37 (0.28-0.49)	<0.0001

Secondary: Overall Percentage Adherence



Risk difference:

- Unlogged, arithmetic mean for each cluster, compared by arm
- Effect estimate is difference in means (Intervention – SoC)

Intervention	SoC	Mean difference (95% CI)	P-value
88.5%	69.7%	18.8% (15.2%-22.3%)	<0.0001

Geometric mean ratio:

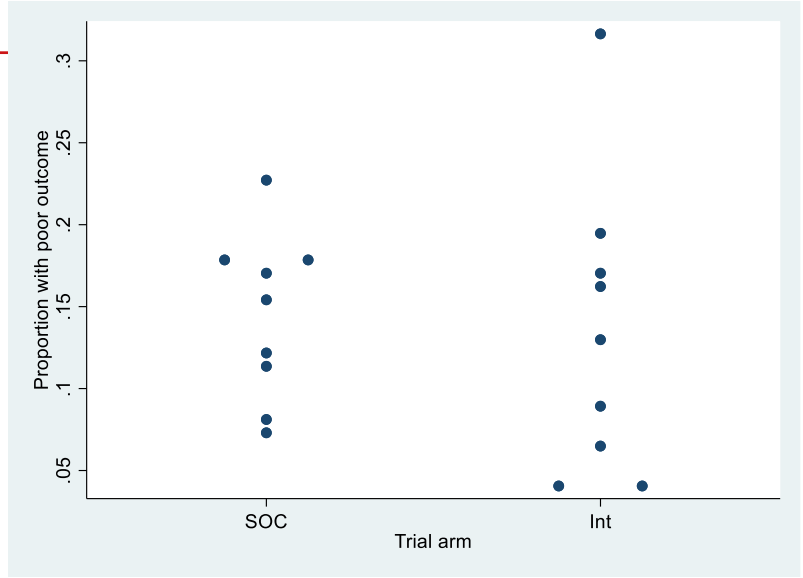
- Log-transformed, geometric mean for each cluster, compared by arm
- Effect estimate is geometric mean ratio (Intervention vs Soc)

Intervention	SoC	Geometric mean ratio (95% CI)	P-value
88.5%	69.7%	1.27 (1.22-1.35)	<0.0001

Poor End of Treatment Outcome

	SoC		Intervention	
		% outcome		% outcome
N	1259		1279	
n, %	172	13.7%	176	13.8%
Mean (cluster %s)		14.3%		13.5%
Geometric mean (cluster %)		13.4%		11.0%

	Risk difference	lower	upper	P-value
Unadjusted (95% CI)	-0.74%	-8.00%	6.49%	0.83
Adjusted (95% CI)*	-0.49%	-6.00%	5.02%	0.85
	Risk ratio	lower	upper	P-value
Unadjusted (95% CI)	0.82	0.46	1.45	0.47
Adjusted (95% CI)*	0.82	0.56	1.22	0.31

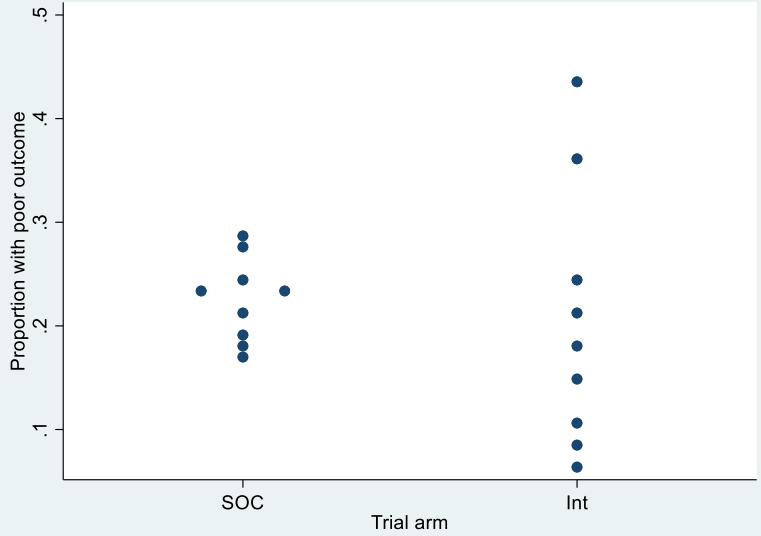


* Adjusted for age, sex, TB diagnosis, ethnic group, marital status, HIV/ART status and province

Composite Unfavourable Outcome

	SoC		Intervention	
N	974		1,096	
n, %	216	22.2%	216	19.7%
Mean (cluster %s)		22.6%	20.4%	
Geometric mean (cluster %)		22.3%	17.1%	

	Risk difference	lower	upper	P-value
Unadjusted (95% CI)	-2.22%	-11.59%	7.16%	0.62
Adjusted RD (95% CI)*	-1.73%	-9.74%	6.28%	0.65
	Risk ratio	lower	upper	P-value
Unadjusted RR (95% CI)	0.77	0.48	1.23	0.25
Adjusted RR (95% CI)*	0.78	0.53	1.16	0.21



* Adjusted for age, sex, TB diagnosis, ethnic group, marital status, HIV/ART status and province

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Adherence Support Coalition to End TB

To implement and evaluate DAT systems using

- medication sleeve/label and smart pill box,
- linked to a web-based adherence platform to create a differentiated response to patient adherence (DAT engagement)

among adults with drug-sensitive TB in South Africa, Tanzania, the Philippines, Ukraine and Ethiopia

Degu Jerene, Kristian van Kalmthout, Jason Alacapa, Natasha Deyanova, Tanyaradzwa Dube, Andrew Mganga, Bianca Tasca, Alexsey Bogdanov, Egwuma Efo, Katya Gamazina, Anna Marie Celine Garfin, Adrian Leung, Jens Levy, Norma Madden, Noriah Maraba, Christopher Finn McQuaid, Liberate Mleoh, Baraka Onjare, Rachel Powers, Yana Terleiva, Job van Rest, Agnes Gebhard, Katherine Fielding, Salome Charalambous

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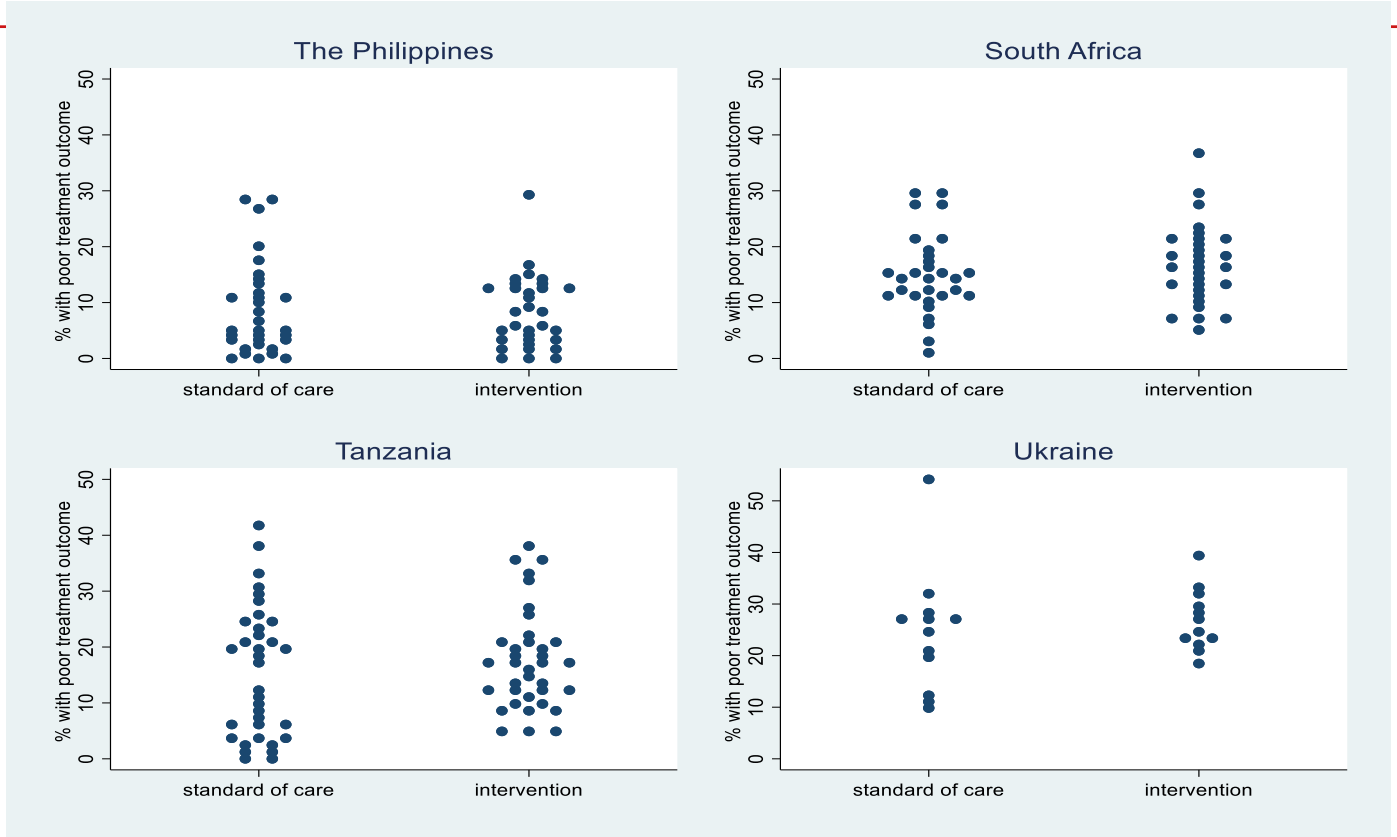
Effectiveness of MERM in DSTB

4 Cluster randomised trials, 220 clusters, 4 countries, 23 804 individuals



OTHER CONSIDERATIONS

Acceptability and Feasibility

- Very high levels of acceptability among PWTB
- Very high levels of acceptability among Health care workers
- Very large scale roll-out achieved in Ascent
- Evidence of sustainability: one district in SA implementing despite no mandate from government

Costs

- Related to standard of Care
- Replacement for DOT – very high cost
- Affordability – different scenario to TB Preventive therapy or Case finding

OVERALL CONCLUSIONS

Mismatch between adherence and end of treatment outcomes – Possible reasons

- Inaccurate adherence measures particularly in control arms
- Poor end of treatment outcome: non-specific outcome
- Special population enrolled – less likely to have poor outcomes
- Poor sensitivity of uptake of relapse
- Treatment regimen is very forgiving

What is the way forward?

- Drug resistance TB work
- More important in Bedaquilline or the four-month DSTB regimen
- Further work to understand the mismatch – possibly using adherence measures
- Improve intervention using more patient-centered designs

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District health authorities: City of Cape Town, eThekwini and Ekurhuleni

ACKNOWLEDGEMENTS

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We are thankful to them all.