RCTs for TB diagnosis with novel molecular assays

Dr J Peter

UCT Lung Infection and Immunity unit

Cape Town, South Africa

jonnyp@mweb.co.za

GenXpert MTB/Rif assay – automated RT-PCR results ready in 90 minutes
Multicentre evaluation study - excellent performance characteristics

Overall sensitivity: 92% (90-94); S+C+: 98% (97-99); S-C+: 73%(65-79)
Cape Town TB NEAT: S+C+: 96 %(90-100); S-C+ 47%(37-53)
(Theron G, Peter J & Dheda K)
Overall specificity: 99% (98-100)

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Rapid Molecular Detection of Tuberculosis and Rifampin Resistance

Catharina C. Boehme, M.D., Pamela Nabeta, M.D., Doris Hillemann, Ph.D., Mark P. Nicol, Ph.D., Shubhada Shenai, Ph.D., Fiorella Krapp, M.D., Jenny Allen, B.Tech., Rasim Tahirli, M.D., Robert Blakemore, B.S., Roxana Rustomjee, M.D., Ph.D., Ana Milovic, M.S., Martin Jones, Ph.D., Sean M. O'Brien, Ph.D., David H. Persing, M.D., Ph.D., Sabine Ruesch-Gerdes, M.D., Eduardo Gotuzzo, M.D., Camilla Rodrigues, M.D., David Alland, M.D., and Mark D. Perkins, M.D.

- Diagnostic test alone has no clinical impact as an intervention

BUT

- Diagnostic test plus treatment has measurable clinical impact

Study Design Options

Observational cohort impact study

Open to multiple confounders

(F-up of results poor at clinic; Pts do not return for results)

Randomised control trial

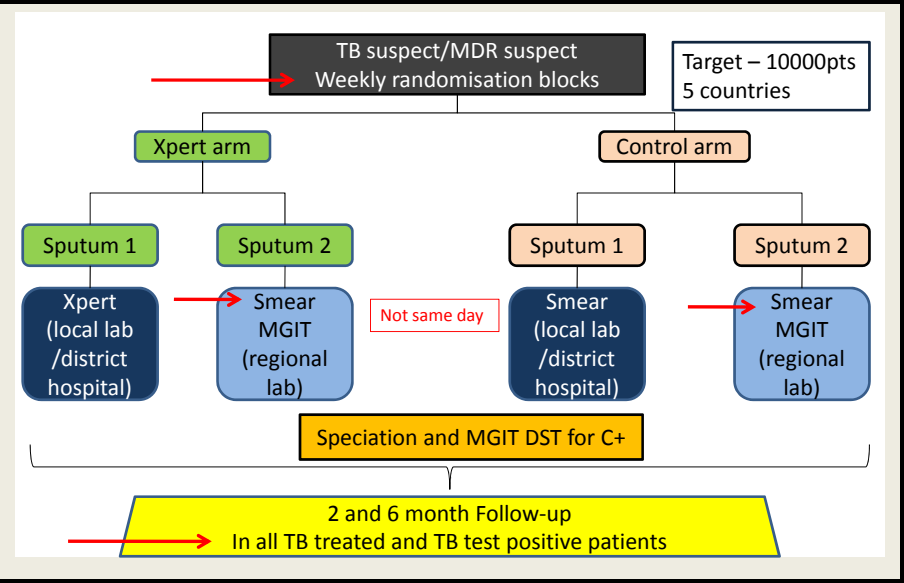
Less open to confounders

Requires narrow research question

Hypothesis – demonstration study

One sputum GeneXpert MTB/RIF assay performed at the district level of care will improve TB diagnosis and the time-to-treatment for patients presenting to primary TB clinics

FIND Xpert demonstration study design



Study design

Strengths

- Direct comparison of Xpert vs smear in programmatic setting
- Quality sub-study of smear performance
- Feasible design
- Controls for important confounders

Weaknesses

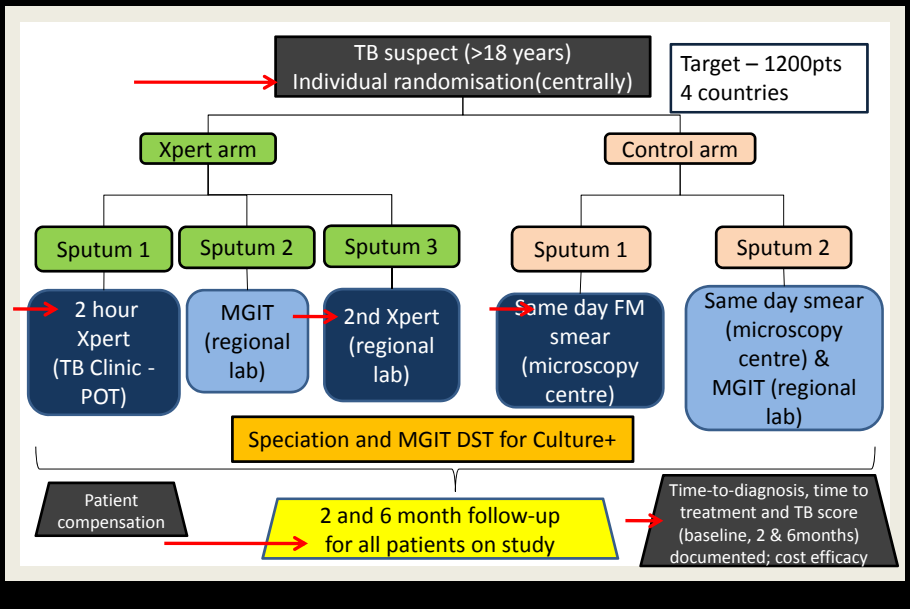
- Randomisation strategy
- No smear "best practice"
- Limited follow-up
- Missing important patient-outcomes e.g. Morbidity

Hypothesis – Xpert POT

One sputum GeneXpert MTB/RIF assay performed at point-of-treatment (POT) will improve TB diagnosis, time-to-treatment and

TB related patient morbidity for HIV-positive and patients with TB presenting to primary level TB clinics in high HIV prevalent settings

Xpert point-of-treatment (POT) study



Study design

Strengths

- Randomisation strategy
- Xpert vs. "best practice" smear microscopy
- Internal validity of POT Xpert
- Controls for important confounders
- Patient morbidity assessment

Weaknesses

- Potential for post-randomisation bias; inability to blind
- Xpert evidence limited raising ethic issues e.g. MDR treatment initiation & treatment monitoring
- Site disparity may impact morbidity statistical power

Sputum Induction(SI)

Tututester mobile SI unit

- Safe, durable method for enhanced sputum collection
- Applicable/feasible in resource-limited settings

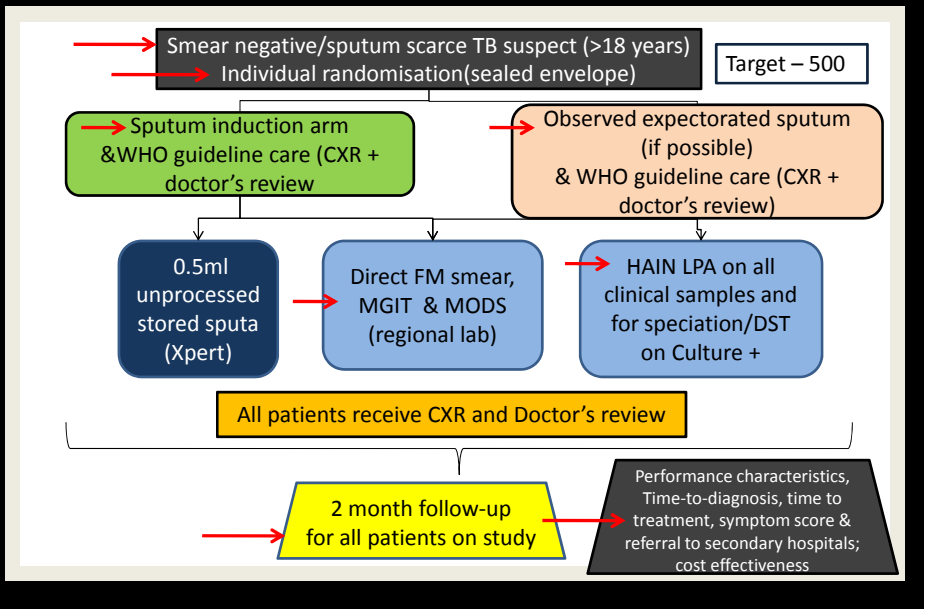
Battery powered-SI in Tanzania

Sputum Induction background

Author(s)	Study Location(s)	n	HIV Prev.	Inclusion criteria/diagnostic algorithm	Smear pos no (n)(%)	Culture pos no. (n)(%)
Bell D Et al.	Malawi (hospitalised in pt Balantyre)	150	75/111 (79%)	In pt clinician referral or registering for smear neg. Empiric TB treatment	39/150(26) – ExpSputumObs 4/111(3.6) – IS*	48/150(34) – ExpSputumObs 13/111(11.7) - IS
Morse M Et al.	Gabarone, Bots (hospitalised in pt)	140	111/140 (79%)	Symptoms & CXR suggestive of PTB#, no response to antibiotics (72/140)	18/57 (32)*	48/57 (84)
Brown et al.	Middlesex, UK(pts referred to IDU at hospital)	140			/107 (12)	42/107(39)
Li LM et al.	Hunan province China (district TB clinics)	1648 (978)	Not done	symptoms reported) (previous TB Rx & Sx)	1648 (33.9) (13/978 – 1.3)	Not done
Conde MB et al.	Rio de Janiero (outpt referral to resp hospital)	251	44/251 (17%)	Respiratory symptoms and CXR suggestive of TB	49/251 (19.5)	94/251 (37.4)
Al Zahrani K et al.	Montreal chest insitute	500	?	Symptoms of PTB (unclear if clinic-radiographic or only clinical, likely both)	10/497 (5)	44/497 (9)
Parry et al.	Blantyre hospital Malawi	82	?	Clinical suspicion of active TB	18/82 (22)	30/82 (37)

NO IMPACT STUDIES

Sputum induction RCT



Study design

Strengths

- Feasible/practical position for 'add-on' test
- SI vs. "best practice" observed exp. sputum
- Controls for important confounders
- Patient relevant outcomes studied

Weaknesses

- Randomisation strategy
- Underpowered for assessing morbidity & mortality
- 2 month follow-up maybe too short for diagnostic categorisation

Conclusions

- RCT is optimal design for impact studies of molecular TB diagnostics

Important considerations for RCT study design:

1) Is there sufficient evidence to conduct an RCT?
2) What is the optimal randomisation strategy?
3) What is the currently available "best diagnostic practice" for control arm?
4) What is the follow-up strategy required to measure patient-related outcomes such as morbidity?