INTRO TO DIAGNOSTIC RCTS

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VERY FEW DIAGNOSTIC RCTS IN TB

- Whatever little we have, is all new!!
  - A few on active case detection
  - A trial on same-day smear diagnosis (TDR)
  - A trial on Xpert MTB/RIF in South Africa
  - Ongoing trials on Xpert MTB/RIF
  - Cluster-randomized stepped wedge designs for phased implementation

Comparison of two active case-finding strategies for community-based diagnosis of symptomatic smear-positive tuberculosis and control of infectious tuberculosis in Harare, Zimbabwe (DETECTB): a cluster-randomised trial

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See Comment page 1205

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Summary

Background Control of tuberculosis in settings with high HIV prevalence is a pressing public health priority. We tested two active case-finding strategies to target long periods of infectiousness before diagnosis, which is typical of HIV-negative tuberculosis and is a key driver of transmission.

Methods Clusters of neighbourhoods in the high-density residential suburbs of Harare, Zimbabwe, were randomised to receive six rounds of active case finding at 6-monthly intervals by either mobile van or door-to-door visits. Randomisation was done by selection of discs of two colours from an opaque bag, with one disc to represent every cluster, and one colour allocated to each intervention group before selection began. In both groups, adult (≥16 years) residents volunteering chronic cough (≥2 weeks) had two sputum specimens collected for fluorescence microscopy. Community health workers and cluster residents were not masked to intervention allocation, but investigators and laboratory staff were masked to allocation until final analysis. The primary outcome was the cumulative yield of smear-positive tuberculosis per 1000 adult residents, compared between intervention groups; analysis was by intention to treat. The secondary outcome was change in prevalence of culture-positive tuberculosis from before intervention to before round six of intervention in 12% of randomly selected households from the two intervention groups combined; analysis was based on participants who provided sputum in the two prevalence surveys. This trial is registered, number ISRCTN84352452.

Findings 46 study clusters were identified and randomly allocated equally between intervention groups, with 55 741 adults in the mobile van group and 54 691 in the door-to-door group at baseline. HIV prevalence was 21% (1916/9060) and in the 6 months before intervention the smear-positive case notification rate was 2·8 per 1000 adults per year. The trial was completed as planned with no adverse events. The mobile van detected 255 smear-positive patients from 5466 participants submitting sputum compared with 137 of 4711 participants identified through door-to-door visits (adjusted risk ratio 1·48, 95% CI 1·11–1·96, p=0·0087). The overall prevalence of culture-positive tuberculosis declined from 6·5 per 1000 adults (95% CI 5·1–8·3) to 3·7 per 1000 adults (2·6–5·0; adjusted risk ratio 0·59, 95% CI 0·40–0·89, p=0·0112).

Interpretation Wide implementation of active case finding, particularly with a mobile van approach, could have rapid effects on tuberculosis transmission and disease.

Lancet 2010

Twelve-monthly versus six-monthly radiological screening for active case-finding of tuberculosis: a randomised controlled trial

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ABSTRACT

Background The incidence of tuberculosis has increased among South African gold miners despite comprehensive control programmes, including a radiological screening programme. No data are available as to the optimal frequency of screening. The aim of this study was to compare 6-monthly and 12-monthly radiological screening for active tuberculosis case-finding.

Methods Employees of a gold mining company were randomly assigned to the control arm (screening at baseline, 12 and 24 months) or the intervention arm (additional 'intervention' radiographs at 6 and 18 months after baseline). Study outcomes included proportion of tuberculosis cases detected by screening, proportion smear-positive, extent of disease and mortality.

Results 22 634 miners were randomised. Compared with 12-monthly screening, 6-monthly screening detected more tuberculosis suspects but not more cases, partly due to greater attrition between screening and further investigation after 'intervention' compared with routine radiographs. Tuberculosis cases detected in the 6-monthly versus the 12-monthly screening arm had less extensive disease (p=0.05) and a lower tuberculosis-specific mortality (death on tuberculosis treatment) (2.1 and 2.8 per 1000 person-years respectively, HR 0.73, 95% CI 0.50 to 1.08, p=0.1), which was most marked in the first 2 months of treatment (HR 0.48, 95% CI 0.23 to 0.98, p=0.04) when death from tuberculosis is most likely.

Discussion In settings with a high prevalence of HIV and tuberculosis despite standard tuberculosis control measures, more frequent case-finding may reduce the extent of disease, tuberculosis mortality and tuberculosis transmission through earlier detection of active tuberculosis cases. To be effective, however, all tuberculosis suspects identified through screening must be investigated for tuberculosis.

programmes[6–9] that include active case-finding using radiological screening as well as passive case-finding and treatment with fixed-dose combination tables taken under direct observation for the entire treatment period, tuberculosis rates among miners rose during the 1990s to over 3000 per 100 000 per year by 1999.[8] Silica dust exposure and silicosis are both risk factors for tuberculosis.[10–17] Silicosis occurs commonly among gold miners, so that miners now have a high prevalence of two of the most powerful risk factors for developing tuberculosis disease following infection (silicosis and HIV), and their combined effect is multiplicative.[16]

Radiological screening has been used in the gold mining industry for decades[18]; both 6- and 12-monthly radiological screening were used in different companies, with no data concerning the most effective screening frequency, particularly in the context of high HIV prevalence. Earlier detection of tuberculosis could reduce tuberculosis-specific morbidity, particularly chronic lung sequelae, mortality and the duration of infectiousness. In support of this, observational studies have demonstrated significantly less extensive radiological disease[19] and lower case fatality rates among tuberculosis cases detected by the radiological screening programme compared with those who self-presented with symptoms.[7] However, no trial has previously investigated the optimal frequency of active tuberculosis case-finding using radiological screening.

The aim of this trial was to compare the individual level effect of 6-monthly versus 12-monthly radiological screening on the proportion of tuberculosis cases detected by screening, the proportion who were smear-positive, the extent of the disease and mortality.

Thorax 2010

OPEN ACCESS Freely available online PLoS MEDICINE

A Multi-Country Non-Inferiority Cluster Randomized Trial of Frontloaded Smear Microscopy for the Diagnosis of Pulmonary Tuberculosis

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Abstract

Background: More than 50 million people around the world are investigated for tuberculosis using sputum smear microscopy annually. This process requires repeated visits and patients often drop out.

Methods and Findings: This clinical trial of adults with cough ≥2 wk duration (in Ethiopia, Nepal, Nigeria, and Yemen) compared the sensitivity/specificity of two sputum samples collected "on the spot" during the first visit plus one sputum sample collected the following morning (spot-spot-morning [SSM]) versus the standard spot-morning-spot (SMS) scheme. Analyses were per protocol analysis (PPA) and intention to treat (ITT). A sub-analysis compared just the first two smears of each scheme, spot-spot and spot-morning. In total, 6,627 patients (3,052 SSM/3,575 SMS) were enrolled; 6,466 had culture and 1,526 were culture-positive. The sensitivity of SSM (ITT, 70.2%, 95% CI 66.5%–73.9%) was non-inferior to the sensitivity of SMS (PPA, 65.9%, 95% CI 62.3%–69.5%). Similarly, the specificity of SSM (ITT, 96.9%, 95% CI 93.2%–99.9%) was non-inferior to the specificity of SMS (ITT, 97.6%, 95% CI 94.0%–99.9%). The sensitivity of spot-spot (ITT, 63.6%, 95% CI 59.7%–67.5%) was also non-inferior to spot-morning (ITT, 64.8%, 95% CI 61.3%–68.3%), as the difference was within the selected −5% non-inferiority limit (difference ITT = 1.4%, 95% CI −3.7% to 6.6%). Patients screened using the SSM scheme were more likely to provide the first two specimens than patients screened with the SMS scheme (98% versus 94.2%, $p<0.01$). The PPA and ITT analysis resulted in similar results.

Conclusions: The sensitivity and specificity of SSM are non-inferior to those of SMS, with a higher proportion of patients submitting specimens. The scheme identifies most smear-positive patients on the first day of consultation.

Trial Registration: Current Controlled Trials ISRCTN53339491

Please see later in the article for the Editors' Summary.

Cuevas L et al. PLoS Med 2011

Feasibility, diagnostic accuracy, and effectiveness of decentralised use of the Xpert MTB/RIF test for diagnosis of tuberculosis and multidrug resistance: a multicentre implementation study

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Summary

Background The Xpert MTB/RIF test (Cepheid, Sunnyvale, CA, USA) can detect tuberculosis and its multidrug-resistant form with very high sensitivity and specificity in controlled studies, but no performance data exist from district and subdistrict health facilities in tuberculosis-endemic countries. We aimed to assess operational feasibility, accuracy, and effectiveness of implementation in such settings.

Methods We assessed adults (≥18 years) with suspected tuberculosis or multidrug-resistant tuberculosis consecutively presenting with cough lasting at least 2 weeks to urban health centres in South Africa, Peru, and India, drug-resistance screening facilities in Azerbaijan and the Philippines, and an emergency room in Uganda. Patients were excluded from the main analyses if their second sputum sample was collected more than 1 week after the first sample, or if no valid reference standard or MTB/RIF test was available. We compared one-off direct MTB/RIF testing in nine microscopy laboratories adjacent to study sites with 2–3 sputum smears and 1–3 cultures, dependent on site, and drug susceptibility testing. We assessed indicators of robustness including indeterminate rate and between-site performance, and compared time to detection, reporting, and treatment, and patient dropouts for the techniques used.

Findings We enrolled 6648 participants between Aug 11, 2009, and June 26, 2010. One-off MTB/RIF testing detected 933 (90·3%) of 1033 culture-confirmed cases of tuberculosis, compared with 699 (67·1%) of 1041 for microscopy. MTB/RIF test sensitivity was 76·9% in smear-negative, culture-positive patients (296 of 385 samples), and 99·0% specific (2846 of 2876 non-tuberculosis samples). MTB/RIF test sensitivity for rifampicin resistance was 94·4% (236 of 250) and specificity was 98·3% (796 of 810). Unlike microscopy, MTB/RIF test sensitivity was not significantly lower in patients with HIV co-infection. Median time to detection of tuberculosis for the MTB/RIF test was 0 days (IQR 0–1), compared with 1 day (0–1) for microscopy, 30 days (23–43) for solid culture, and 16 days (13–21) for liquid culture. Median time to detection of resistance was 20 days (10–26) for line-probe assay and 106 days (30–124) for conventional drug-susceptibility testing. Use of the MTB/RIF test reduced median time to treatment for smear-negative tuberculosis from 56 days (39–81) to 5 days (2–8). The indeterminate rate of MTB/RIF testing was 2·4% (126 of 5321 samples) compared with 4·6% (443 of 9690) for cultures.

Interpretation The MTB/RIF test can effectively be used in low-resource settings to simplify patients' access to early and accurate diagnosis, thereby potentially decreasing morbidity associated with diagnostic delay, dropout and mistreatment.

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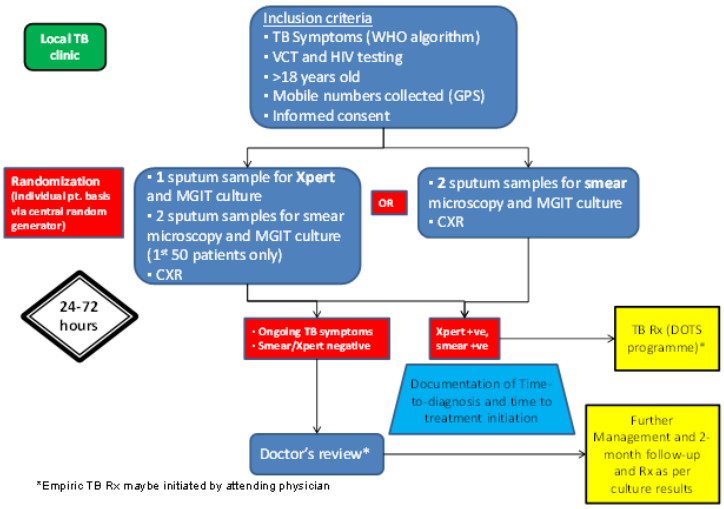
See Online/Comment DOI:10.1016/S0140-6736(11)60513-8

Foundation for Innovative New Diagnostics (FIND), Geneva, Switzerland (C C Boehme MD, P Nabeta MD, C Gray MPH, H Alexander PhD, H Albert PhD, M D Perkins MD); National Health Laboratory Service, Groote Schuur Hospital, Cape Town, South Africa (M P Nicol PhD, A Whitelaw MD); Division of Medical Microbiology and Institute for Infectious Diseases and Molecular Medicine, University of Cape Town, Cape Town, South Africa (Prof M P Nicol, A Whitelaw); Christian Medical College, Vellore, India (Prof J Michael MD); Universidad Peruana Cayetano Heredia, Lima, Peru (J Gotuzzo MD, T Caceres BSc); Special Treatment Institution, Baku, Azerbaijan (R Tahirli MD); Tropical Disease Foundation, Manila, Philippines (M T Gler MD); New Jersey Medical School and Division of Infectious Diseases, University of Medicine and Dentistry of New Jersey, Newark, NJ, USA

In South Africa, the routine use of bleach-pretreatment for fluorescent microscopy meant that MTB/RIF testing on the same sputum sample was not possible. Therefore, in South Africa we used a study design with weekly alternation between a baseline group and implementation group. In the baseline group, routine smear microscopy from a bleach-treated pellet was done, which was replaced by the MTB/RIF test (used for management of patients) in the implementation group. In both groups, a second specimen was obtained for smear microscopy from a sodium hydroxide (NaOH)-treated pellet, culture, and drug-susceptibility testing.

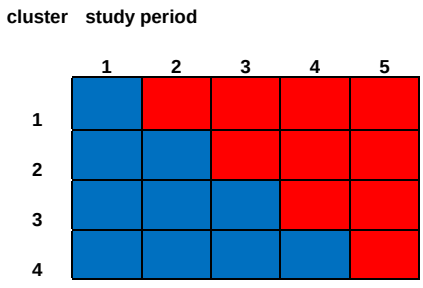
A RANDOMISED CONTROLLED TRIAL OF POINT-OF-TREATMENT GENEXPERT MTB/RIF ASSAY FOR THE DIAGNOSIS OF TB AT PRIMARY CARE CLINICS IN HIGH HIV PREVALENCE RESOURCE LIMITED SETTINGS



TB NEAT consortium. Cape Town, Zimbabwe and Lusaka [Dheda K et al].

STEPPED WEDGE DESIGN

- Unidirectional cross-over
- All transfer from control to intervention, but at different times
- Randomization of order of transfer
  - More than one cluster may transfer at once
  - Restrained in case of small number of clusters
- Need even more time than in regular cross-over design



Van den Hof, S

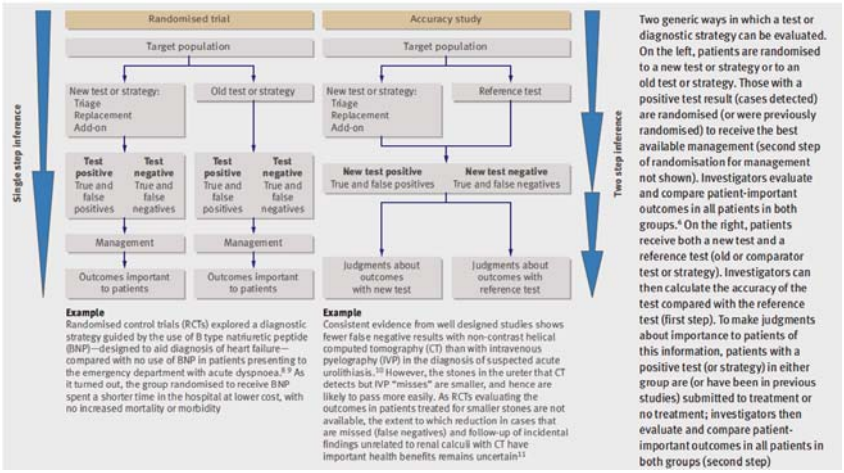
EXAMPLE STEPPED WEDGE DESIGN

- Roll-out of GeneXpert in Brazil
  - Rio de Janeiro and Manaus
- 14 clusters = defined areas in which all health care units send in samples to same laboratory for diagnosis of TB
- GeneXpert used instead of smear microscopy (and culture)
- Transfer from smear to GeneXpert in 7 steps
- Main effects studied:
  - Diagnosis and treatment registration of bacteriologically confirmed pulmonary TB, overall and for HIV+ individuals
  - Proportion of TB patients diagnosed with MDR
  - Time to appropriate treatment after diagnosis for (MDR) TB patients
  - Cost-effectiveness
  - (Treatment outcomes)

Van den Hof, S

METHODOLOGICAL ISSUES IN DX RCTS

GRADE: FOR HIGH QUALITY EVIDENCE, IMPACT ON PATIENT-IMPORTANT OUTCOMES NEEDS TO BE DEMONSTRATED

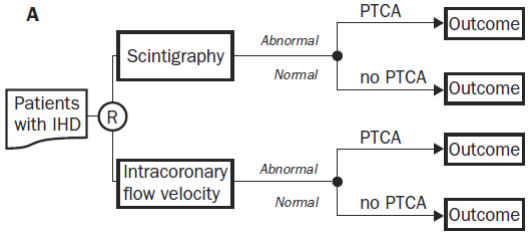


Schunemann H et al. BMJ 2008

Viewpoint

Randomised comparisons of medical tests: sometimes invalid, not always efficient

Patrick M M Bossuyt, Jeroen G Lijmer, Ben W J Mol



- Not just the test, but test-treatment combination that is evaluated
- There must be a clear, pre-specified link between test results and subsequent interventions

> Running trials without a protocol for translating the test results to clinical management decisions is like putting pharmaceuticals to trial without prespecifying the preferred dosage, optimum route of administration, the need for monitoring, or the way to deal with side-effects. Designing such a drug trial would be hardly acceptable these days. Why then should we not apply the same stringent criteria to trials of test-treatment combinations?

Lancet 2000

Distraction From Randomization in Diagnostic Research

CORNELIS J. BIESHEUVEL, PHD, DIEDERICK E. GROBBEE, MD, PHD, AND KAREL G.M. MOONS, PHD

The ultimate goal of medical care, including diagnostic testing, is to improve patient outcome. Accordingly, it has been advocated widely that when establishing a test's diagnostic accuracy, the impact of the test on patient outcome subsequently must be quantified. When studying patient outcome in medical research, the use of randomized comparisons comes into perspective. In our view, randomized studies often are not necessary to validly estimate the effect of the diagnostic test on patient outcome. Results of cross-sectional diagnostic studies, combined with results from therapeutic studies, often will suffice.
Ann Epidemiol 2006;16:540–544.

When performing a randomized trial to determine the impact of a diagnostic test or strategy on patient outcome, an initially *diagnostic* research question is transformed into *therapeutic* research question (with the goal of establishing causality) with corresponding consequences for the design of the study. A disadvantage of a randomized approach to directly quantify the contribution of a diagnostic test and treatment on patient outcome is that it often addresses diagnosis and treatment as a single combined strategy, a "package deal." This makes it impossible to determine afterwards whether a positive effect on patient outcome was attributed solely to the improved diagnosis by using the test under study or to the chosen (new) treatment strategies.

Moons KGM. In: Grobbee & Hoes. Clinical Epidemiology. 2009

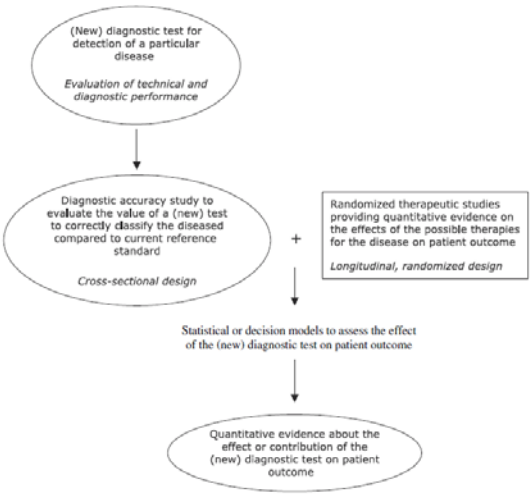


FIGURE 1. In the first phases of evaluating a new test, technical feasibility and diagnostic performance (is the test able to discriminate diseased from nondiseased?) are assessed (1–4). Subsequently, the value of the test to detect a particular disease is obtained by a cross-sectional study in which the diagnostic accuracy of the new test is compared with the current reference test. The information obtained by this study can be combined with information obtained from randomized controlled trials that evaluated the effect of a therapeutic strategy for that disease on patient outcome. By combining results of both studies, one can easily quantify the value of the diagnostic test to improve patient outcome.

Ann Epidemiol 2006;16:540-544.

Annals of Internal Medicine | ACADEMIA AND CLINIC

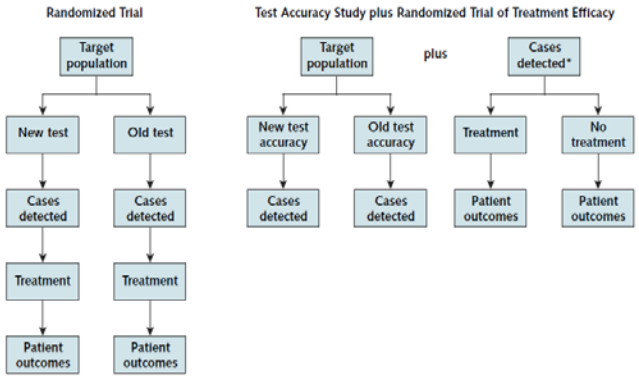
When Is Measuring Sensitivity and Specificity Sufficient To Evaluate a Diagnostic Test, and When Do We Need Randomized Trials?

Sarah J. Lord, MBBS, MS; Les Irwig, MBBCh, PhD; and R. John Simes, MBBS, MS, MD

The clinical value of using a new diagnostic test depends on whether it improves patient outcomes beyond the outcomes achieved using an old diagnostic test. When can studies of diagnostic test accuracy provide sufficient information to infer clinical value, and when do clinicians need to wait for results from randomized trials? The authors argue that accuracy studies suffice if a new diagnostic test is safer or more specific than, but of similar sensitivity to, an old test. However, if a new test is more sensitive than an old test, it leads to the detection of extra cases of disease. Results from treatment trials that enrolled only patients detected by the old test may not apply to these extra cases. Clinicians need to wait for results from randomized trials assessing treatment efficacy in cases detected by the new diagnostic test, unless they can be satisfied that the new test detects the same spectrum and subtype of disease as the old test or that treatment response is similar across the spectrum of disease.

Ann Intern Med. 2006;144:850-855. www.annals.org
For author affiliations, see end of text.

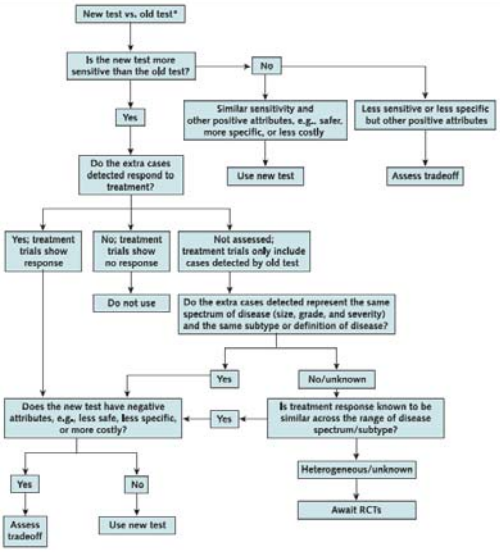
Figure 1. Trial evidence versus linked evidence of test accuracy and treatment efficacy.



*Cases detected by the new and old test may not show similar response to treatment.

Lord, Annals Int Med, 2006

RCT ALWAYS NEEDED?



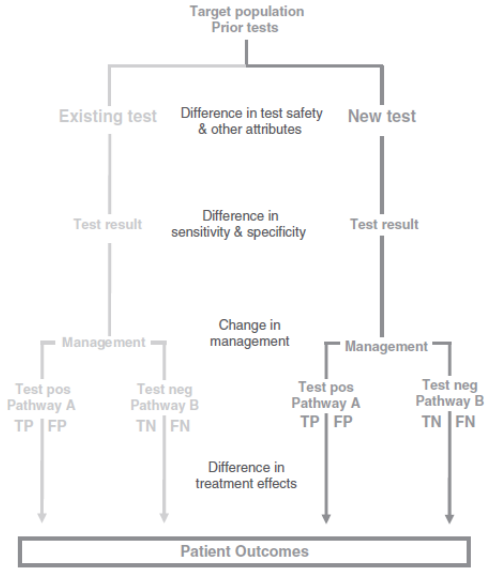
Lord, Annals Int Med, 2006

Using the Principles of Randomized Controlled Trial Design to Guide Test Evaluation

Sarah J. Lord, MBBS, MS, Les Irwig, MBBCh, PhD, Patrick M. M. Bossuyt, PhD

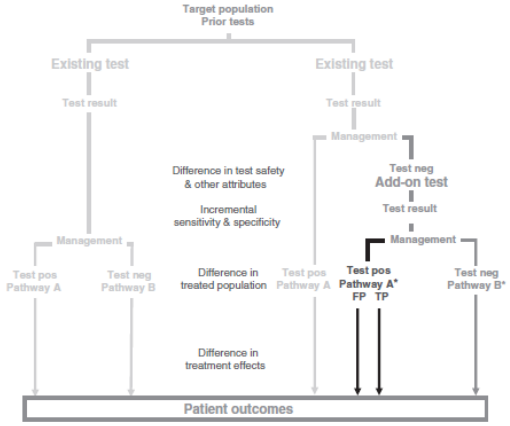
The decision to use a new test should be based on evidence that it will improve patient outcomes or produce other benefits without adversely affecting patients. In principle, long-term randomized controlled trials (RCTs) of test-plus-treatment strategies offer ideal evidence of the benefits of introducing a new test relative to current best practice. However, long-term RCTs may not always be necessary. The authors advocate using the hypothetical RCT as a conceptual framework to identify what types of comparative evidence are needed for test evaluation. Evaluation begins by stating the major claims for the new test and determining whether it will be used as a replacement, add-on, or triage test to achieve these claims. A flow diagram of this hypothetical RCT is constructed to show the essential design elements, including population, prior tests, new test and existing test strategies, and primary and secondary outcomes. Critical steps in the pathway between testing and patient outcomes, such as differences in test accuracy, changes in treatment, or avoidance of other tests, are displayed for each test strategy. All differences between the tests at these critical steps are identified and prioritized to determine the most important questions for evaluation. Long-term RCTs will not be necessary if it is valid to use other sources of evidence to address these questions. Validity will depend on issues such as the spectrum of patients identified by the old and new test strategies. **Key words:** *diagnostic techniques and procedures/standards; sensitivity and specificity; randomized controlled trials as topic; outcome assessment (health care).* **(Med Decis Making 2009;29:E1–E12)**

a. The replacement test

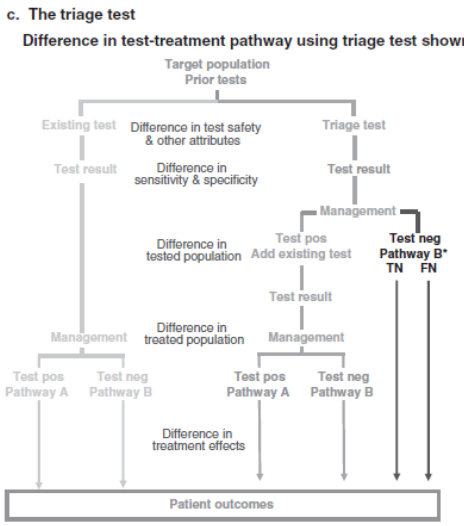


b. The add-on test

Difference in test-treatment pathway using add-on test shown in black



TP = true positive, FP = false positive
Pathway A* includes patients testing positive on the add-on test but negative on the existing test who would not have been assigned to treatment A using the existing test strategy.



SOME ISSUES..

- Actions after each possible test results must follow a clear unambiguous protocol
- Sample sizes may be large
- Diversity and complexity of diagnostic process leads to infinite number of possible trials
- Ethical questions
  - OK to randomize to an experimental test?
    - E.g. Not FDA or WHO approved
  - Once a test is WHO-approved and is shown to be superior to conventional test, OK to deny to half of trial participants?

Mariska Leeflang
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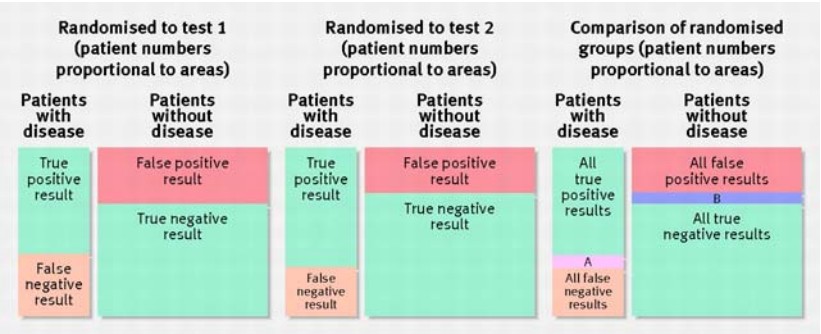
Sample size calculations for test-treatment randomised controlled trials.



Ferrante di Ruffano L et al. BMJ 2012;344:bmj.e686

"The figure identifies those participants who contribute statistical power in a randomised trial comparing two tests (where the difference in outcome originates entirely from a difference in diagnostic accuracy). Test 2 has higher sensitivity than test 1 (difference shown in A). Test 2 also has higher specificity than test 1 (difference shown in B). Different widths of diseased and non-diseased columns indicate the prevalence of disease in the study sample. Only participants in A and B would have different test results if they received test 2 rather than test 1 and therefore the potential for different outcomes (all other participants in the study would have the same test result, irrespective of which test they were allocated to). Statistical power therefore depends on only the numbers of participants in A and B (particularly A)"

BMJ

BIAS IN RCTS

1. Randomization
   a. Valid randomization
   b. Concealment of allocation
2. Blinding
3. Sufficiently long follow-up
4. Analyses