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# The Pragmatic Randomised Trial: A simple research design for real-world evaluation of innovation in Tuberculosis care

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Stockholm 2009

Published by Karolinska Institutet. Printed by Universitetsservice US-AB



**ISBN 978-91-7409-580-7**

## ABSTRACT

Tuberculosis was the first disease in history whose treatment regimens were systematically established using randomised controlled trials (RCTs). As a result TB drug treatment regimens are standardised globally, and have been entirely evidence-based for decades. And yet attempts to establish the same level of evidence for the mode of delivery for these treatment regimens have proved contentious. As a result, WHO and IUATLD disseminate global strategies for promoting adherence by patients, and defining the role of nurses and lay health workers in TB care that are not evidence-based.

This thesis includes four RCTs, each of which helped to establish the effectiveness of an aspect of primary care in South Africa. We studied the delivery of adherence support for TB treatment and the clinical diagnosis and treatment of common adult respiratory illnesses and HIV/AIDS in primary care. The randomised trials in this thesis evaluate the impact on successful treatment completion of compulsory daily nurse observation of treatment at a primary care clinic (Paper I), and of lay health workers as TB treatment supporters (Paper II); of multifaceted educational outreach on syndromic management for improving the sensitivity of nurse diagnosis of TB, and respiratory disease care in primary care clinics (Paper III), and of the effects of a more intensive version of this strategy on a wider range of illnesses, still including TB but adding HIV/AIDS and anti-retroviral treatment (ART) (Paper IV). In the course of conducting these studies I learned how to design randomised trials to evaluate the effects, under real world conditions, of complex interventions. Some of these lessons are captured in a methodological guideline for the conduct of such trials (Paper V).

The individual patient randomised trial of nurse provided Directly Observed Treatment (DOT), in Paper I showed no benefit over self-administered treatment in terms of cure rate or successful treatment completion; and among retreatment patients, reduced the probability of successful treatment completion, suggesting that *nurses make poor treatment supervisors*. This study had a separately published third arm (not included in this thesis) whose results suggested that Lay Health Workers were superior to nurses as DOT providers. To follow this line of thought our next randomised trial on 400 farms in the Western Cape investigated a model of treatment support by peers, volunteer lay health workers, who were trained in a range of primary care skills, including treatment support, and made their support services available on request from newly diagnosed patients. That trial (Paper II) showed that when the decision to use a treatment supporter, and the nature the support that (s)he provides, are left to the patient, lay health workers achieved clinically important and statistically significant increases in successful treatment completion and cure in comparison with usual care controls. In conjunction with Paper I this suggests that *direct support for improvement of TB treatment outcomes is a task best carried out by lay health workers, not by nurses*.

The question remains for human resources planners: if not in the provision of DOT for TB, what is the role of professional nurses in primary care of Tuberculosis? Based on our successful use of educational outreach and leave-behind key point support materials in improving the clinical impact of family doctors on asthma diagnosis and care for children

(not part of this thesis), I proposed we use a similar approach to improve the clinical acumen of nurses to diagnose and treat TB and the range of other respiratory diseases presenting in adult public sector primary care settings (Paper III). This study showed substantial increases in TB diagnosis and appropriate treatment initiation in comparison with usual care control clinics, suggesting that our *outreach approach improves the clinical care of TB by nurses and simultaneously improves their care for other complex conditions, previously treated by doctors only.*

We replicated and strengthened this finding by testing a more intense (but still affordable and sustainable) approach to nurse training on a guideline covering the same conditions plus screening for HIV/AIDS, identifying ART need, and providing ART maintenance treatment and surveillance for side effects and immune status (Paper IV) after physician initiation of ART. This approach was effective in providing superior care across the range of outcomes, confirming that *professional nurses are able to improve the care of TB even as they take on a wider clinical role for other complex conditions*. Paradoxically, our secondary analysis of this data showed that this *clinically focussed multifaceted educational strategy aimed at nurses in clinic teams also has a positive impact on successful treatment completion rates among TB retreatment patients*, formerly thought to be a consequence of DOT.

This series of randomised trials, with several unexpected findings helped to provide a firm evidence base for the organisation of TB diagnosis and treatment supervision, care of other respiratory diseases and HIV/AIDS/ART delivery in primary care in South Africa, with applicability elsewhere. In this process we developed guidelines for reporting pragmatic trials, that is, RCTs in support of real world health care decision-making (Paper V).

Low and middle income countries cannot afford the costs of assuming that interventions based on theory, no matter how plausible, will be effective. We recommend wider use of pragmatic RCTs to provide rigorous evidence in support of decision makers choosing the best among alternative feasible options for health and healthcare.

Key words: randomised controlled trial, pragmatic trial, DOT, nurse, lay health worker, implementation science, tuberculosis, adherence, clinical acumen, health care delivery, management, decision-making, outreach education, evidence-based care.

## LIST OF PUBLICATIONS

**I.** **Zwarenstein M, Schoeman JH, Vundule C, Lombard CJ, Tatley M. Randomised controlled trial of self-supervised and directly observed treatment of tuberculosis. *Lancet.* 1998; 352(9137):1340-3.**

**II.** **Clarke M, Dick J, Zwarenstein M, Lombard CJ, Diwan VK. Lay health worker intervention with choice of DOT superior to standard TB care for farm dwellers in South Africa: a cluster randomised control trial. *International Journal of Tuberculosis and Lung Disease.* 2005; 9(6):673-9.**

**III.** **Fairall LR, Zwarenstein M, Bateman ED, Bachmann M, Lombard C, Majara BP, Joubert G, English RG, Bheekie A, van Rensburg D, Mayers P, Peters AC, Chapman RD. Effect of educational outreach to nurses on tuberculosis case detection and primary care of respiratory illness: pragmatic cluster randomised controlled trial. *British Medical Journal.* 2005; 331(7519):750-4.**

**IV.** **Zwarenstein M, Fairall LR, and Lombard C, for the PALSA PLUS study group: Mayers P, Bheekie A, English RG, Lewin S, Shai-Mhatu P, Bachmann M , Bateman ED. Integration through outreach education and mentoring improves adult HIV/AIDS and tuberculosis primary care: the PALSA PLUS pragmatic cluster randomized trial. *Submitted: New England Journal of Medicine***

**V.** **Zwarenstein M, Treweek S, Altman DG, Gagnier J, Tunis S, Haynes RB, Oxman AD, and Moher D. Improving the reporting of pragmatic trials: an extension of the CONSORT Statement. *British Medical Journal.* 2008; 337:a2390. doi: 10.1136/bmj.a2390.**

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## ABBREVIATIONS AND DEFINITIONS

ART: Antiretroviral treatment

DOTS: WHO approved approach to Tuberculosis treatment programme delivery; formerly acronym for directly observed treatment, short course).

DOT: Directly observed treatment; daily direct observation by another person of a TB patient swallowing their medications.

GTB: Global Programme against Tuberculosis of the World Health Organisation

HSRU: Health Systems Research Unit of the MRC

IMCI: Integrated Management of Childhood Illness, a WHO programme offering syndromic diagnosis and treatment guidelines, and training and organisational approaches, to the main childhood causes of mortality and severe morbidity.

IUATLD: International Union against Tuberculosis and Lung Diseases

KTU: Knowledge Translation Unit of the LI, UCT

KT: Knowledge translation; closing the gap between what is known from research to be effective treatment, and actual practice in the real world.

LHW: Lay Health Worker

LI: Lung Institute of the UCT

NGO: Non-governmental organisation

MRC: Medical Research Council, South Africa

PRCT: Pragmatic RCT, designed for decision-making, in other words, for choosing between alternative interventions.

PHC: Primary Health Care, the WHO strategy embodied in the Alma Ata declaration of 1977.

RCT: Randomised Controlled Trial

SAT: Self administered treatment; treatment autonomously taken by the patient.

TB: Tuberculosis

UCT: University of Cape Town

UKMRC: Medical Research Council of the United Kingdom

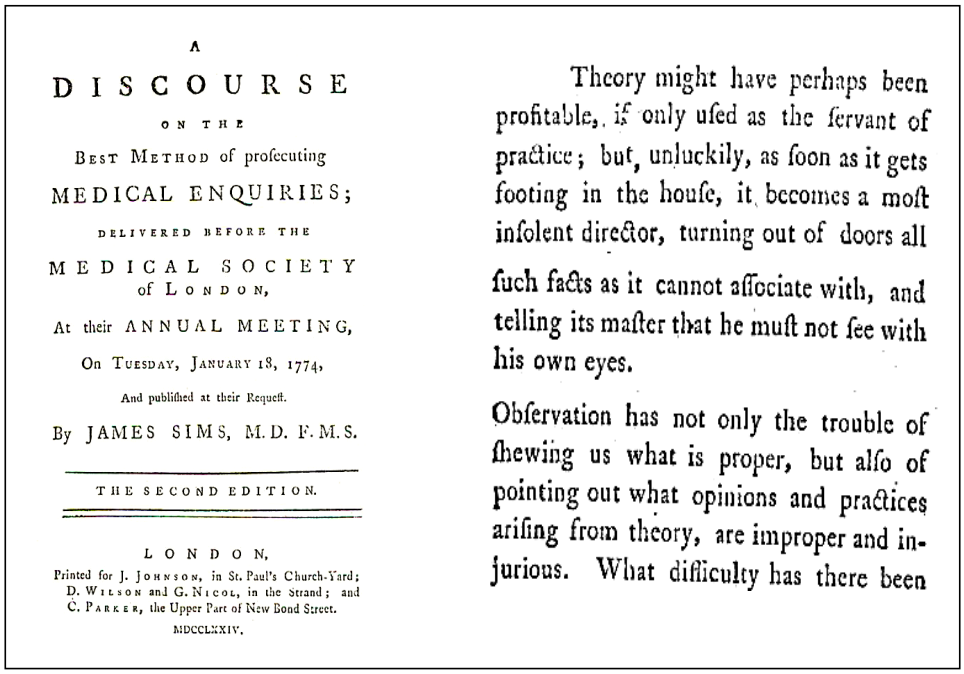
WHO: World Health Organisation

## PREFACE

In a prescient paper, James Sims, an English physician, talked on methods for research in medicine to the Medical Society of London in 1774 (Fig 1). I translate his text into modern speech, unfortunately losing his witty and vivid characterisation of theory as a crotchety servant, struggling to evict research from the house of medicine. Here is its bald meaning, pertinent still: Theory could be useful if the proposed treatments that arise from it are always tested in practice, using observations of facts to evaluate the effectiveness of these treatments. Unfortunately, as soon as a theory gains acceptance, believers reject observed facts which contradict the theory. Observation shows us which treatments work and also indicate which opinions and practices arising from theory fail, or cause harm.

(I would replace "Observation" with "Pragmatic randomised trials").

**Fig. 1: James Sims on evaluating treatments (www.jameslindlibrary.org)**



A

DISCOURSE

ON THE

BEST METHOD of profecuting

MEDICAL ENQUIRIES;

DELIVERED BEFORE THE

MEDICAL SOCIETY of LONDON,

At their ANNUAL MEETING,

On TUESDAY, JANUARY 18, 1774,

And published at their Requeſt.

By JAMES SIMS, M.D. F.M.S.

THE SECOND EDITION.

LONDON,

Printed for J. JOHNSON, in St. Paul's Church-Yard; D. WILSON and G. NICOL, in the Strand; and C. PARKER, the Upper Part of New Bond Street.

MDCCLXXIV.

Theory might have perhaps been profitable, if only uſed as the ſervant of practice; but, unluckily, as ſoon as it gets footing in the houſe, it becomes a moſt inſolent director, turning out of doors all ſuch facts as it cannot aſſociate with, and telling its maſter that he muſt not ſee with his own eyes.

Obſervation has not only the trouble of ſhewing us what is proper, but alſo of pointing out what opinions and practices ariſing from theory, are improper and injurious. What difficulty has there been

# 1. INTRODUCTION

*Chapter 1 describes the contents, chapter by chapter, and ends with a history of the organisations and people with whom I worked on these papers.*

## Outline of the thesis

This thesis has two goals: to contribute to an evidence base of randomised controlled trials (RCTs) for TB, respiratory and HIV/AIDS/ART care delivery at the primary care level in South Africa; and to codify the characteristics of pragmatic randomised controlled trials (PRCTs) that make them more useful in real world decision-making, producing a guideline for the reporting of such trials. The thesis contains four randomised trials (another four randomised trials formed part of this body of work conducted in the research group which I led, but are not included here). The fifth paper in the thesis describes the reporting approach to these pragmatic trials, and is one of several papers produced from a 5th Framework European Union funded project which I initiated, triggered by the experience of conducting the RCTs in this thesis.

## Organisation of the thesis

Chapter 1, this chapter, is the introduction, outlining the thesis, and describing the healthcare research context in which this work took place- the goals, the development and the organisational setting and functioning of the research groups in which I worked during the course of this thesis.

In Chapter 2 I discuss Tuberculosis treatment supervision and support, where the purpose of interventions is to increase adherence to the long drawn out course of tuberculosis treatment (Paper I, through DOT by nurses, and Paper II, through lay health worker support of patients on TB treatment). In this chapter I describe the history and organisation of primary health care in South Africa, the background to the directly observed treatment (DOT) approach, and the role of lay health workers in primary care, showing how these two topics became priorities in the HSRU at the MRC. I also discuss the strategy used in Papers III and IV to transfer skills and abilities to nurses usually only expected of physicians, and describe the development of multi disease comprehensive guidelines, training and upgrading of skills of frontline primary care workers and leave-behind support materials that we used to support this substitution and decentralisation of skills to the periphery, while improving t h e scope and quality of primary care.

Chapter 3 focuses on the design of RCTs aimed at supporting decision-making, known as pragmatic or practical trials (PRCTs). The criteria distinguishing pragmatic trials from the more usual explanatory RCT designs are embodied in a CONSORT Statement on

Pragmatic Trials, where the appropriate format for published pragmatic trials is laid out. This CONSORT statement (Paper V) was deeply influenced by my experiences with the trials in this thesis and so the history and methodology of the pragmatic approach to RCTs is described here. I describe these methodological aspects prior to describing the RCTs themselves in order to give readers the information they will need in the next chapter, where they can assess the degree to which the RCTs in this thesis meet the criteria for pragmatic trial design.

Chapter 4 describes the materials, methods and settings of each of the four randomised trials in this thesis explaining them in terms of the issues raised in Chapter 3 related to real world applicability of the intervention, and design of the trial for decision-making relevance.

Chapter 5 describes the results of the four RCTs.

Chapter 6 contains the main conclusions for Tuberculosis and other primary care delivery, drawn from the four RCTs, in the thesis, and discusses them in the context of other work on these topics conducted by our group, and by others. I draw conclusions about the meaning of these RCTs for future delivery of care for TB and other conditions. The first is direct observation of treatment (DOT) and its disappointing effectiveness, even potential harm when carried out compulsorily, by professional nurses. The second is the substantial success of lay health workers in providing support to patients seeking help with their TB care. The third is the value of syndromic algorithms and focused training in improving nurses' ability to diagnose and initiate treatment for TB, other respiratory diseases, and HIV/AIDS care and ART.

Chapter 7 is a discussion of the results and conclusions, but in contrast with Chapter 6 this chapter is emphasising the relationship between the findings of these RCTs and the choices made in designing them. This is presented in relation to the issues raised in the Consort Statement extension for Pragmatic Trials which forms Paper V of the thesis and to other papers on pragmatic trials to which I have contributed (not included among the papers in this thesis). The main theme in this chapter is the design of summative evaluations of the effects of approaches to care delivery.

Chapter 8 outlines areas of concurrent and future inquiry, both in terms of trials of care for respiratory and other adult disease in nurse led primary care; and in relation to methodology, that is, to the design and promotion of pragmatic randomised trials.

Chapter 9 contains acknowledgements of the many people without whom this thesis and the underlying intellectual developments could not have happened.

Chapter 10 offers a list of references used.

## Research context

From the 1970's the South African Medical Research Council (MRC) conducted research through its Tuberculosis Research Institute (TBRI), focusing mainly on prevalence and biology of the disease. By 1990, the MRC's Centre for Epidemiological Research in Southern Africa (CERSA) had taken over the Tuberculosis health services research of the TBRI, and developed a conscious and planned programme of qualitative and quantitative research to identify barriers to effective TB care in South Africa, and to design, pilot and evaluate real world options for improving the delivery of this care. This work, by Judy Dick, Hennie Schoeman and Hester van der Walt was folded into the Health Systems Research division of CERSA, which I led from its foundation until 2002. The research focus of the division, later expanded as a separate unit (the Health Systems Research Unit, or HSRU), was on "improving the impact of health care on health" across all important diseases. For Tuberculosis, the focus was on the effectiveness of nurse and lay health worker provided TB care, including several attempts to improve the quality and outcomes of care, some evaluated as pilot studies, others as programme changes, and yet others through randomised controlled trials (RCTs). We began to work with the Karolinska Institute in the Sweden/South Africa collaborative project, led by Prof. Diwan. This programme consisted of collaborative research and student exchanges to Sweden.

RCT work on Nurses and their role in care delivery work started off with Paper I. The lay health worker RCT research started off as a separately published arm of the randomised trial reported as Paper I, continued with a Cochrane systematic review on LHWs (neither one included in this thesis) and was extended into new areas in Paper II, led by Marina Clarke, Judy Dick, Hennie Schoeman, Carl Lombard and I. Dr Clarke was then a student at Karolinska under the supervision of Prof. Vinod Diwan. The nurse and lay health worker DOT questions in TB care are thus represented in this thesis by Papers I and II, respectively.

Although my initial work focussed mainly on a single disease, TB and the relations between patients receiving TB treatment, and their carers, it was informed by a philosophy of integrated primary care based on values from the Alma Ata declaration (WHO 1978): comprehensiveness, local appropriateness, respect, effectiveness. My interest widened to quality of care improvement interventions for chronic diseases, including respiratory diseases, diabetes, childhood asthma and HIV/AIDS and anti-retroviral treatment. The HSRU was an intramural MRC unit not affiliated to any hospital, medical school or other source of clinical expertise, and although I am a qualified medical practitioner, the lack of in-house specialist clinical expertise became apparent in a project we conducted on quality improvement for asthma care for children. As a result of the difficulties of obtaining this clinical expertise, I sought out a university medical school base for the wider work I planned to conduct on improving the clinical

diagnosis of TB and respiratory disease. For this reason I approached the Lung Institute of the University of Cape Town, engaging with Eric Bateman, and two newly hired medical doctors in training as respiratory medicine specialist physicians, Lara Fairall and Rene English. Over time, we collaborated increasingly closely.

This collaboration resulted in the adaptation to adult respiratory disease care (in the primary care setting, in the public sector by nurses) of an educational outreach strategy (Soumerai 1990) that Angeni Bheekie, my PhD student, and I had developed (Zwarenstein 2007). We had used an educational outreach strategy to improve private sector family physicians' care of asthma among children. This multifaceted approach consisted of evidence-based guidelines reduced to a small number of key points, educational outreach by a skilled educator, and high quality leave-behind support materials. This set of interventions became the basis of the knowledge translation approach used in the Lung Institute. This field of study is known variously as knowledge translation (a Canadian term), or implementation research (UK and Europe) (Straus 2009). This health care improvement work grew and became the Knowledge Translation Unit (KTU), led by Lara Fairall, and of which I was a founder member. Papers III and IV focus on training of nurse clinicians for delivery of integrated care, and were conducted by the KTU.

Paper V, the Consort Statement extension for Pragmatic Trials, was based on methodological work which began in my collaboration with Carl Lombard, the head statistician and Director of the Institute for Biostatistics at the MRC, as I worked with him on the design and analysis of a number of randomised trials including those in this thesis. I was frustrated with the scarcity of good randomised trials of complex health care interventions, and realised that the lack of clarity on how to design these trials was acting as a barrier to their conduct. I had not found it easy to design and conduct randomised trials on health care delivery interventions, quality improvement interventions, different ways of organizing care and different ways of providing education to clinicians. I thought that guidance could be useful.

The overarching problem I saw was how to maintain a balance between rigour and real world relevance. This tension reduced to the question of how a study could be designed to retain researcher control over allocation of the intervention (essentially, to randomise) while designing an intervention and an evaluation strategy and that could be conducted in a typical, real world health service, under conditions of normal day to day functioning, with few or no extra resources. All four of the randomised trials in this thesis are attempting to maintain this balance between rigour and relevance and their successes and failures in so doing will be discussed.

Papers I and II were developed and completed while I was at the MRC. Papers III to V have been conducted since my move to Sunnybrook Health Sciences Centre, a fully affiliated research hospital of the University of Toronto. With the exception of Paper I, which was completed before registration, all others (Papers II, III, IV and V) as well as related papers not included here, but aimed at related problems, were based on work conducted while I was registered as a student at KI.

# 2. PRIMARY CARE IN SOUTH AFRICA, AND DOT FOR TB

*Chapter 2 introduces readers to the organisation of Primary care in South Africa and describes some of the origins of DOT as a means of Tuberculosis adherence support. I also describe some of the efforts to train Lay Health Workers and nurse clinicians.*

## Primary care in South Africa

An understanding of primary care in South Africa is important, as this thesis embraces four empirical studies all of which took place in primary care settings in South Africa. Within this framework, an understanding of the particular challenges posed by the care of TB in the primary care setting, and the way in which these have been dealt with historically and in South Africa pre and post-apartheid is also important to help contextualise the studies in this thesis (Kautsky 2008).

The Alma Ata declaration on Primary Health Care (WHO 1978) was very influential in South Africa, as a social justice based guide for the organisation of healthcare during the oppressive apartheid period. Because it was not explicitly aligned with any political doctrine, it was legal and could be openly used to promote equity and improvements in health and wellbeing for black South Africans. In the apartheid era anti-apartheid health groups such as the National Medical and Dental Association, student run health groups such as the South African Voluntary Services, and University based community health projects (such as the Tintswalo Project described by Kautsky and Tollman in 2008)) used the Alma Ata declaration as a basis for delivering programmes of community based primary care to disadvantaged black South African communities. These efforts challenged the narrowly technical implementation of first line clinic care preferred by the apartheid government and its surrogates in rural areas. We (for I was involved in all three organisations mentioned above) used a subtly politicised approach in that we promoted health as being dependant on community organisation. Our and other NGO primary health care projects became a site for anti-apartheid activity, mobilising professionals, students and communities around politically "safe" subjects such as health and healthcare, rather than directly around apartheid or democratic representation. This politicisation was carried by many individuals into governmentally funded research organisations such as the MRC and even central and provincial government departments of health. The politicisation of health and healthcare in South Africa ensured that issues of power and justice were prominent in discussions around any aspect of research on healthcare, especially elements that had direct human rights implications, such as compulsory DOT.

Social justice and community participation values of the Alma Ata Declaration resonated with progressive South Africans. There were two specific and very practical aspects of the primary care approach that particularly influenced my thinking on primary care. The first is an integrated, syndromic and simplified approach to delivering basic, essential and effective care for high priority diseases. This developed from a series of separate treatment interventions for children. In final, integrated form this has become the strategy

for Integrated Management of Childhood Illness (IMCI), and is now the standard in nurse run primary care clinics in South Africa and globally (Gove 1997). The second is the engagement of lay members of the community to care for children and adults in their own communities. This cadre of health worker, known as a lay health worker, or sometimes a village health worker is an increasingly vital provider of care for both TB and HIV/AIDS in many countries, including South Africa. Lay workers, often low paid or volunteers, are drawn from communities in which care was to be provided, and trained as basic health workers in variations of the WHO promoted lay health worker programmes of the 1970's (Walt 1988).

Health care organisation under the apartheid regime was extremely complex and contradictory in structure, as well as profoundly inequitable across racial lines, and further, between urban and rural areas. The administrative structure was different for different disease services, and in different administrative jurisdictions. Public health and preventative services (which included immunisations for all illnesses, hygiene, and epidemic control, as well as Tuberculosis prevention, diagnosis and oddly, also TB treatment), were a national responsibility and were organised vertically from Pretoria, the administrative centre. In large urban areas, this work was delegated from the national Department of Health to municipal authorities. Public health and preventive services were separated from ambulatory curative and hospital services, which were provided (somewhat differently) by each of the 4 provinces, directed from one centre in each province. Curative services provided by provinces were run in separate premises from preventive and Tuberculosis services. However, in some rural areas, the apartheid policy decreed that semi (in truth, pseudo) independent "states" be established, for artificially defined African tribes. In these nominally independent "tribal homelands" all primary care delivery, including both TB and curative and preventive care was integrated into a single facility in each locale, serving one or a few communities. It was an abiding irony that only as a consequence of its most extreme distortion of ethnic distinction and physical separation, the homeland policy, was the apartheid government able to establish coherently governed and organisationally integrated health services. This was made somewhat simpler by the extreme poverty of the homelands- with few resources to spend, it was simply impossible to develop duplicate human or physical delivery structures for different kinds of healthcare at one site, as frequently existed in "white" South Africa.

It was this shortage of resources, combined with the relative autonomy that arose from neglect of service delivery by uninterested white politicians in Pretoria that created the context of integrated primary care, and allowed for a number of healthcare delivery innovations, both in the "homelands" and in African urban areas. The innovations that are relevant to this thesis are the implementation of lay health workers as a key provider in the health service and the implementation of advanced clinical roles for nurses in primary care. This integrated pattern of care is increasingly common in post-apartheid South Africa, and is the espoused goal of national health policy: To improve geographic access to care, to avoid duplication, and to address health care needs in the face of a shortage of doctors, most of whom work in the private sector or large urban hospitals, the first post-apartheid government declared its intention to expand drastically and integrate the primary care level of provision. The intent-largely realised over the last 15 years- was to

establish nurse-managed primary care centres as the first point of contact for the diagnosis and care of all illness for which that could be a competent treatment or referral point. Nurses are now the first line providers of primary care to the majority of South Africans dependant on publicly provided free or affordable health care, typically poor, black rural residents, as well as the unemployed, and most women and children in urban areas. The post-apartheid government was more ambivalent in regard to the role of LHWs initially seeing it as a hangover of second class care from apartheid days, but over time, and especially as the onslaught of HIV/AIDS has advanced, and lay people in communities have spontaneously taken on caring roles, the potential value of LHWs as peers with cultural insight and pre-established trust in communities, and therefore with real possibilities for kinds of health work that no professional can achieve, has become clearer. The trials reported in this thesis have in small ways contributed to the confidence of the new government that LHW services have promise and are evidence-based..

For the majority of South Africans, primary care services have taken on responsibility for most adult illness, ranging from minor ailments such as upper respiratory infections, through more serious illness, infectious and non infectious, symptomatic (diabetes, pneumonia, asthma) and asymptomatic (hypertension). The need to provide this care in a systematic way has only increased with AIDS, which is so prevalent and serious that if primary care does not successfully provide the majority of care for most patients, the hospital referral system will be quickly overwhelmed.

Primary care policy in South Africa is committed to provision of integrated care for all common illnesses, near to home, using evidence-based treatment, and in close coordination with referral hospitals on the one hand, and in deep engagement with communities, on the other. While not universally applied, these are valid and likely feasible goals. In this thesis I present four empirical studies, all randomised trials, which are testing interventions aimed at implementing one or more of these policies.

## Tuberculosis regimen development

The modern history of the pharmacotherapy of TB is the story of two sets of innovations, one in clinically applied medical science, and the other in evaluation (Murray 2004). The intertwining of pharmacology and microbiology, on the one hand (to identify chemotherapeutic agents), and biostatistics and clinical studies on the other (to evaluate their effectiveness), is among the most exciting stories of the progress of science against disease. This was the first sustained disease-focused drug development process, the precedent for organised drug discovery through public and industry collaboration that produced the pharmaceutical industry, and the template for the regulatory randomised trials on which licensing of all pharmaceuticals is now based.

In the early 20$^{th}$ century, many attempts were made to identify chemotherapeutic agents against Tuberculosis. The ones tested included gold salts, sulfones, and Vitamin D, with no success. The treatment remained bed rest, thoracotomy and therapeutic pneumothorax until 1944. This story changed dramatically with the discovery of streptomycin by

Schatz and Waxman in the United States, and almost simultaneously in Sweden, the synthesis of para amino salicylic acid (PAS) by Lehmann. Streptomycin was the first therapeutic agent used to successfully treat a patient, in 1944 while PAS came into clinical use more slowly. By 1948 streptomycin was the subject of the very first randomised trial ever completed and by 1949 it had been tested in combination with PAS. This randomised trial established a key principle of Tuberculosis treatment: multi-drug treatment of active TB to prevent resistance (Murray 2004).

These randomised trials were among several conducted by a long term research and evaluation project of the UK Medical Research Council, which continued to test other drugs and then combinations of drugs, and lastly modes of care. In 1951, separately but simultaneously from the corporate laboratories of Bayer, Squibb and Hoffman-La Roche came isoniazid, a safe, effective and inexpensive antituberculous medication. This was followed by thiacetazone and rifampicin, by the 1960s, giving us the main complement of pharmaceuticals we have relied on until now (Mitchison 2005).

The model of drug discovery which led to these important medicines expanded rapidly to become the modern drug industry. But as TB disappeared from the developed countries the size of the paying market and thus the potential profits from new Tuberculosis treatment shrank, and so too did spontaneous corporate interest in the development of new TB treatments. TB drugs were soon replaced by antibiotics and chronic disease treatments, which still are the commercial mainstay of the large pharmaceutical companies (Commission on Health Research for Development 1990). Only recently, as a consequence of a new approach to public and foundation subsidy of private corporate pharmaceutical research activity, the first new anti-tuberculosis drug in forty years (Moxifloxacin) has just now entered phase 3 trials (TB Alliance 2009).

Central to the successful development of TB treatments was the invention of the randomised controlled trial, still used today for evaluating efficacy of treatments. Over 500 studies, many of them randomised trials, emanated from the UK MRC tuberculosis laboratories and its scientists in India, Tanzania, Hong Kong, the UK and elsewhere. In just two decades this extraordinary public and private effort identified, isolated, synthesised at commercial scale and tested the efficacy of the full first and second line armamentarium for TB. This body of work is a singular achievement, the first globally coordinated disease treatment evaluation initiative, still unsurpassed for its' global reach, and the speed and coherence with which it succeeded. Starting at a point where TB was an untreatable illness, it quickly sorted through a rapidly growing pipeline of drugs for the disease, established a series of first and second line regimens appropriate for different economic situations, and ended with, at least in western developed countries, TB as a forgotten plague (Fox 1999).

## TB care: from regimen to programme

In developing countries, unfortunately, TB is a growing plague and progress has been slow, in spite of the brilliant research achievement which led to successful multi-drug regimens, based on a sequence of randomised trials. Some of these RCTs were aimed at evaluating ways of organising TB care. Why did these trials not achieve the same success in informing the organisation of care that they did in designing the drug regimens?

Initially, when injected daily streptomycin was a key therapy, TB treatment was an inpatient process. The number of sanatorium beds rose rapidly to accommodate the treatment, which in the 1950s was as long as 18 months. It was recognised early at the UKMRC TB institute that ambulatory treatment would be massively cheaper than sanatorium based inpatient therapy, and was essential if TB treatment was to be made available on a mass scale in developing countries. In order to test this dramatic reorganisation of care delivery, a randomised trial of domiciliary (home) versus inpatient (sanatorium) treatment was started, in the Madras Tuberculosis Chemotherapy Research Centre, a collaborative enterprise of the UK MRC, the governments of India and its Madras state government, and the World Health Organisation as well as similar trials- with similar results- in Hong Kong and Singapore (Fox 1958; Fox 1983 a, Fox 1983 b; Fox 1999).

The Madras trial, initiated in 1956, demonstrated that bacteriological cure was achieved similarly in both groups, and that the number of family contacts of patients who developed active TB was similar between the two groups, suggesting that ambulatory treatment was as successful as hospital based treatment at terminating spread in the community. In the Madras study, intensive efforts were made in the home treated patient group to maintain very high adherence, through intensive education of both patients and their families, recruitment of a family member or neighbour to directly observe the patient swallowing their medication, regular visits to patients at their homes by staff, and surprise visits with urine tests and pill counts to assess adherence:

> *The usual routine is for the patient to attend the clinic for a week's supply of sachets every week for at least a year. In the first one or two months a weekly visit is also paid to the home. Gradually home visits are paid less frequently but are never less than two a month, one to collect a urine specimen .the other for a sputum specimen. The patients are assessed clinically, radiographically and bacteriologically every month. Before the start of treatment, to obtain and keep the patient's co-operation, much time is spent during several interviews explaining both to the patient and to the family the seriousness of the disease and the necessity for a long course of chemotherapy. The infectious nature of the disease is explained and the radiographic lesion is demonstrated to the whole family, great emphasis being laid on the nature and extent of cavitation. The patient is warned that he will feel much better after a few weeks of treatment and that he may be tempted to think he is cured and therefore to stop taking his medicine, but that to do so might have very serious consequences. Such instruction on the importance of regularity in taking the medicine is repeated at*

> *every monthly examination, and at other visits to the clinic as well as in the patient's home, by the doctors, by the public health nurses, and by the health visitors. Further, an attempt is always made to get another member of the family actually to watch the patient swallow the sachets. On occasion, it has been necessary and possible to arrange for a neighbour to perform this function. Since in the Madras Centre the other family members are always seen at the outset there is an excellent opportunity to involve the whole family group in the treatment and explain to all the importance of regularity for the future of the patient and his family. It should be emphasised that the explanation is always given in simple language, using homely similies of a type which the family understands.*

The need to provide TB care with DOT has never been questioned, largely as a result of the Madras and similar trials of ambulatory TB care in Singapore and Hong Kong. But did these trials test the effectiveness of DOT? They did not, and were never intended to.

The Madras trial is not a trial of DOT, but of a package of multiple interventions in ambulatory care, including a version of family DOT, visits to the patient's home by nurses to test urine for adherence and to obtain sputa for microscopy, and monthly visits to a facility for X-ray with a physician consultation, together comprising an ambulatory care model. These are the elements on which it differs from the control group, and because they are all different, the effect of any individual element cannot be identified. The second confounding problem is that this entire package was compared to continued sanatorium treatment, which itself has a form of DOT consisting of nurses administering drugs to patients, with some observation. Thus, this trial shows only that ambulatory care with DOT plus home visits by nurses and several other interventions is as effective as inpatient care with a form of DOT. It is, as intended, an evaluation of the effects of intensive, ambulatory care and support compared with (usual) sanatorium care.

As will be discussed in Chapter 3, this trial is an explanatory trial, testing the impact under idealised conditions of an intensively supported ambulatory regimen, and it answers the question of efficacy under these ideal circumstances of the ambulatory care model in-toto, but says nothing about the contribution of DOT itself. Also, it evaluates the intensive ambulatory model in comparison with usual sanatorium care, presumably showing the model to its best advantage, as no special efforts were made to raise the quality of sanatorium care. The applicability of its findings to less well organised conditions of ambulatory care, with fewer resources, and less focused leadership is therefore doubtful.

I also want to draw attention to the nature of DOT that was implemented in Madras. In this study DOT was provided by families, or even neighbours who acted as observers. These observers were not accountable to the health service providers. DOT as practiced in Madras is much doubted by US oriented researchers (Frieden 2007), where DOT has been applied via professionals in the employ of the health service (Bayer 1995).

DOT is now a key element of the DOTS strategy, incorporated prominently into the brand-name, but had never been tested in a randomised trial at the time it became global policy promoted by WHO (WHO 1999), the IUALTD (IUATLD 1996) and the World Bank (World Bank 1993). I will not discuss here the non-randomised studies cited in support of DOT (Chen 2004), other than to say that they have methodological weaknesses, and also test a combined model of DOTS, rather than establishing the effectiveness of each of its components individually. Although all elements of DOTS are frequently mentioned in WHO documents, in low or middle income countries like South Africa, it is DOT, rather than well organised programmes, good staff training, careful patient counselling, intensified supervision of facilities or political support which has become the iconic element of an acceptable TB programme (Garner 1998). Branding the complex programme as DOTS (removing its connection to the original meaning of the acronym, which was Directly Observed Treatment, short course regimen) did not help to bring about comprehensive programme implementation in target countries such as South Africa, instead creating substantial conflict over service design, and misdirecting scarce resources (Ogden 2003).

## DOTS: From global policy to South African programme

There was a substantial amount of other work on the design of programmes of TB care for developing countries. Working closely with the UKMRC laboratories was the much older International Union of Tuberculosis and Lung Disease (IUATLD) contributing ideas for programme design under the leadership of Karel Styblo, the Director of Scientific Activities at IUATLD, working in Tanzania (Nkinda 1984). Other studies came from Jan Gryzbowski, working initially in Canada, where he independently developed and implemented direct observation to maintain patient adherence (Enarson 2000).

Initially, the WHO programme was based upon models of TB spread which assumed that high levels of case finding rather than high levels of successful treatment were the key lever in controlling the epidemic. Initial efforts to control the disease in low income countries focused on case-finding, but this strategy led to increases in drug resistance and in numbers of infectious cases. Work by Enarson showed that high levels of successful cure and low levels of case finding would be more effective at the population level. And so the focus of TB control switched to high adherence, rather than high levels of case finding. This raised the importance of cure and successful treatment completion especially among sputum smear positive patients, from which derives both the emphasis of WHO and the IUATLD on bacteriological confirmation of diagnosis and successful treatment, and the very high priority it assigns to DOT, which is presumed to ensure completion of treatment (IUATLD 1996).

Another key factor which became part of the global policy was the assertive promotion at national level of global organisation (WHO, IUATLD) policies. These were implemented through international consultancy tied to subsidised pharmaceutical supplies which gave substantial leverage to the implementers to ensure that national and local policies were consistent with IUATLD and WHO policies. Enarson (2000) recounts the importance of

this advisory role and the consultants who implemented it, in ensuring rigid adherence to internationally defined policies and maintaining local political commitment to standardised global TB policies:

> *[I]n the model programs developed by the IUATLD (the international federation of national voluntary associations dealing with TB and lung diseases), marketed by the WHO as the DOTS strategy, a key element has been the support of technical experts in developing the strategy both locally and nationally. Rigorous implementation — in particular, the direct observation of the swallowing of medications when rifampin is given — has been a struggle in every location where it has been introduced. Technical advisors have been essential in this struggle[…]*

DOT has become part of the TB treatment regime for patients; and through international consultancies, a form of direct observation of countries has arisen to ensure national adherence to standardised programme design. This form of direct influence on policy was designed to obtain what is described in WHO documents as "high level political support" for TB programmes.

From these pilot and research projects derived the elements which were later assembled in the package known as DOTS (Global Tuberculosis Programme 1997). These elements are high level political support for TB programmes, regular drug supply, microbiological diagnosis and monitoring of cure and programme impact using registers of patients, and a short course regimen containing rifampicin, taken under direct supervision. TB care moved globally towards an ambulatory model in a primary care setting, as evidence-based short course rifampicin based treatment regimens and simplified and reliable microscopy or culture based algorithms for the diagnosis of TB were established. This movement of TB care to the ambulatory, and thus to the primary care level was also a result of the developing IUATLD approach to nurse provided daily direct observation of TB treatment. South African programme managers were acutely aware of this movement, and had explored both LHW supervision, and expanded roles for nurses (personal observation).

The global approach was introduced into South Africa early in the 1980s through informal contacts between South African leaders of the TB programme, and the IUATLD (as contact with WHO itself was limited during the apartheid era). Soon after the new government was elected in 1994, contacts between the head of the Global TB programme within WHO, Dr Arata Kochi, and the Director-General of the Health Department in South Africa began, leading to an external review of the South African programme by WHO and the IUATLD. This review was instrumental in obtaining official South African acceptance of the global approach as national policy (Department of Health 1996).

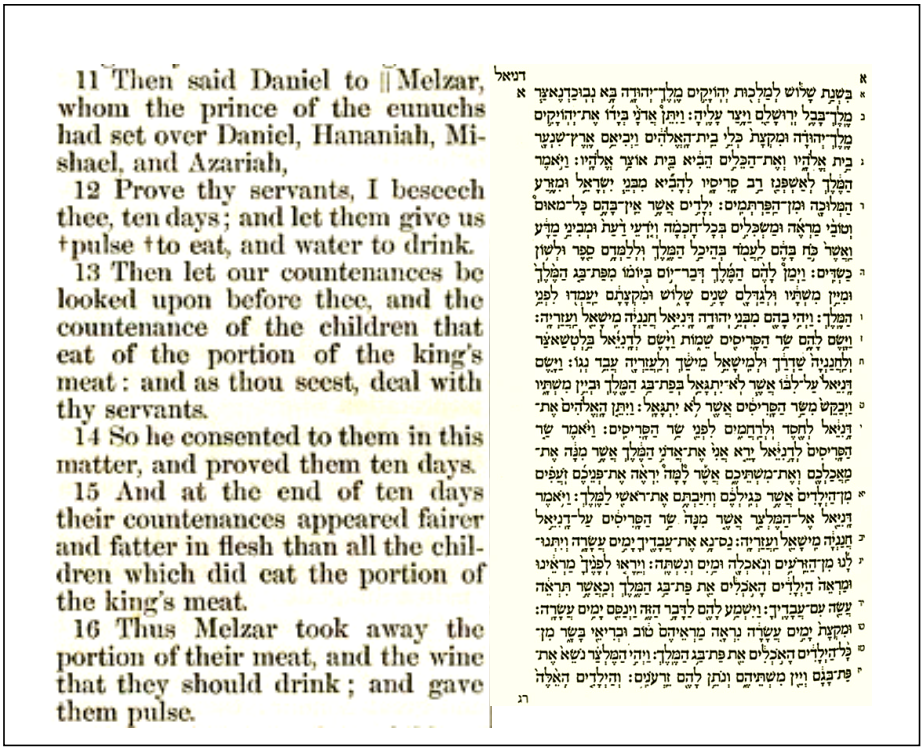
Well before this review, nurse DOT had become the standard of care, starting in better resourced provinces such as the Western Cape. Nurses rather than physicians provided the majority of care for patients with TB in South Africa using national algorithms (based

on IUATLD and WHO models) for diagnosis and treatment of TB, and dispensing from their clinics standardised rifampicin-containing multi-drug TB regimens.

As the number of TB cases diagnosed increased in South Africa, probably due to the then unacknowledged HIV/AIDS epidemic, it increasingly affected urban facilities and populations. By this time, nurse provided DOT based on the IUATLD models were generally used in urban areas; and with the rapid rise in both urban populations, and TB rates, this led to overcrowding, and space and staff shortages in South African primary care clinics treating TB. It was against this background of rigidly enforced nurse DOT, with rising demand and increased crowding that the HSRU was asked by the Western Cape Metropolitan Council, responsible for provision of TB care in Cape Town and surrounds, to help them decide whether to continue nurse DOT, or whether other means could be found which would maintain the same cure rates, but with less resources and overcrowding.

The research leading to Paper I, a randomised trial of nurse DOT versus LHW DOT versus SAT was conceived and recruited its first patient in August 1994, just months after the election which replaced the apartheid government with a democratically elected non racial government. At around the same time, the head of GTB was in South Africa, promoting the implementation of WHO policy as South African national TB policy. Two years later, the GTB/IUATLD review resulted in official acceptance of global policy as South African policy, and attempts at widespread implementation began. These were not rapidly or widely successful, due largely to the still fractured structure of healthcare, and in 1998 the WHO annual report of TB control 'named and shamed' South Africa as a DOTS non-compliant country and a barrier to global TB control (WHO 1998). This was tremendously embarrassing for the South African government, and central enforcement of GTB promoted DOTS approaches intensified.

So, just as our research team was presenting results from our RCT to managers in the health service, national and provincial decision makers were pressured to adhere to global policy. In a poignant moment, following our presentation of the failure of nurse DOT to leadership of the South African TB control programme, the Department of Health participants remained silent, asked no questions, and left without taking the printouts of our results. In retrospect, I now realise they were at that time under enormous pressure to bring South Africa into compliance with GTB policies. There was also pressure from within the MRC to abandon our research: at the meeting of the South African Epidemiological Society in Bellville, 1998, the presenter of our paper, my colleague Hennie Schoeman, was explicitly instructed to withdraw the work, by a senior manager of the MRC, just minutes before his oral presentation. He refused.



11 Then said Daniel to Melzar, whom the prince of the eunuchs had set over Daniel, Hananiah, Mishael, and Azariah,

12 Prove thy servants, I beseech thee, ten days; and let them give us †pulse †to eat, and water to drink.

13 Then let our countenances be looked upon before thee, and the countenance of the children that eat of the portion of the king's meat: and as thou seest, deal with thy servants.

14 So he consented to them in this matter, and proved them ten days.

15 And at the end of ten days their countenances appeared fairer and fatter in flesh than all the children which did eat the portion of the king's meat.

16 Thus Melzar took away the portion of their meat, and the wine that they should drink; and gave them pulse.

דניאל א

א בִּשְׁנַת שָׁלוֹשׁ לְמַלְכוּת יְהוֹיָקִים מֶלֶךְ־יְהוּדָה בָּא נְבוּכַדְנֶאצַּר
ב מֶלֶךְ־בָּבֶל יְרוּשָׁלִַם וַיָּצַר עָלֶיהָ: וַיִּתֵּן אֲדֹנָי בְּיָדוֹ אֶת־יְהוֹיָקִים
מֶלֶךְ־יְהוּדָה וּמִקְצָת כְּלֵי בֵית־הָאֱלֹהִים וַיְבִיאֵם אֶרֶץ־שִׁנְעָר
ג בֵּית אֱלֹהָיו וְאֶת־הַכֵּלִים הֵבִיא בֵּית אוֹצַר אֱלֹהָיו: וַיֹּאמֶר
הַמֶּלֶךְ לְאַשְׁפְּנַז רַב סָרִיסָיו לְהָבִיא מִבְּנֵי יִשְׂרָאֵל וּמִזֶּרַע
ד הַמְּלוּכָה וּמִן־הַפַּרְתְּמִים: יְלָדִים אֲשֶׁר אֵין־בָּהֶם כָּל־מאוּם
וְטוֹבֵי מַרְאֶה וּמַשְׂכִּלִים בְּכָל־חָכְמָה וְיֹדְעֵי דַעַת וּמְבִינֵי מָדָע
וַאֲשֶׁר כֹּחַ בָּהֶם לַעֲמֹד בְּהֵיכַל הַמֶּלֶךְ וּלְלַמְּדָם סֵפֶר וּלְשׁוֹן
ה כַּשְׂדִּים: וַיְמַן לָהֶם הַמֶּלֶךְ דְּבַר־יוֹם בְּיוֹמוֹ מִפַּת־בַּג הַמֶּלֶךְ
וּמִיֵּין מִשְׁתָּיו וְלגַדְּלָם שָׁנִים שָׁלוֹשׁ וּמִקְצָתָם יַעַמְדוּ לִפְנֵי
ו הַמֶּלֶךְ: וַיְהִי בָהֶם מִבְּנֵי יְהוּדָה דָּנִיֵּאל חֲנַנְיָה מִישָׁאֵל וַעֲזַרְיָה:
ז וַיָּשֶׂם לָהֶם שַׂר הַסָּרִיסִים שֵׁמוֹת וַיָּשֶׂם לְדָנִיֵּאל בלְטְשַׁאצַּר
ח וְלַחֲנַנְיָה שַׁדְרַךְ וּלְמִישָׁאֵל מֵישַׁךְ וְלַעֲזַרְיָה עֲבֵד נְגוֹ: וַיָּשֶׂם
דָּנִיֵּאל עַל־לִבּוֹ אֲשֶׁר לֹא־יִתְגָּאַל בְּפַת־בַּג הַמֶּלֶךְ וּבְיֵין מִשְׁתָּיו
ט וַיְבַקֵּשׁ מִשַּׂר הַסָּרִיסִים אֲשֶׁר לֹא יִתְגָּאֵל: וַיִּתֵּן הָאֱלֹהִים אֶת־
י דָּנִיֵּאל לְחֶסֶד וּלְרַחֲמִים לִפְנֵי שַׂר הַסָּרִיסִים: וַיֹּאמֶר שַׂר
הַסָּרִיסִים לְדָנִיֵּאל יָרֵא אֲנִי אֶת־אֲדֹנִי הַמֶּלֶךְ אֲשֶׁר מִנָּה אֶת־
מַאֲכַלְכֶם וְאֶת־מִשְׁתֵּיכֶם אֲשֶׁר לָמָּה יִרְאֶה אֶת־פְּנֵיכֶם זְעֻפִּים
יא מִן־הַיְלָדִים אֲשֶׁר כְּגִילְכֶם וְחַיַּבְתֶּם אֶת־רֹאשִׁי לַמֶּלֶךְ: וַיֹּאמֶר
דָּנִיֵּאל אֶל־הַמֶּלְצַר אֲשֶׁר מִנָּה שַׂר הַסָּרִיסִים עַל־דָּנִיֵּאל
יב חֲנַנְיָה מִישָׁאֵל וַעֲזַרְיָה: נַסֹּ־נָא אֶת־עֲבָדֶיךָ יָמִים עֲשָׂרָה וְיִתְּנוּ־
יג לָנוּ מִן־הַזֵּרעִים וְנֹאכְלָה וּמַיִם וְנִשְׁתֶּה: וְיֵרָאוּ לְפָנֶיךָ מַרְאֵינוּ
וּמַרְאֵה הַיְלָדִים הָאֹכְלִים אֶת פַּת־בַּג הַמֶּלֶךְ וְכַאֲשֶׁר תִּרְאֶה
יד עֲשֵׂה עִם־עֲבָדֶיךָ: וַיִּשְׁמַע לָהֶם לַדָּבָר הַזֶּה וַיְנַסֵּם יָמִים עֲשָׂרָה:
טו וּמִקְצָת יָמִים עֲשָׂרָה נִרְאֶה מַרְאֵיהֶם טוֹב וּבְרִיאֵי בָשָׂר מִן־
כָּל־הַיְלָדִים הָאֹכְלִים אֶת פַּת־בַּג הַמֶּלֶךְ: וַיְהִי הַמַּלְצַר נֹשֵׂא אֶת־
טז פַּת בָּגָם וְיֵין מִשְׁתֵּיהֶם וְנֹתֵן לָהֶם זֵרעֹנִים: וְהַיְלָדִים הָאֵלֶּה
רג

**Fig. 2: Book of Daniel. (www.jameslindlibrary.org)**

# 3. PRAGMATIC RANDOMISED TRIALS

*Chapter 3 focuses on the design of RCTs aimed at supporting decision-making, known as pragmatic or practical trials. The criteria distinguishing pragmatic trials from the more usual explanatory RCT designs are embodied in a CONSORT Statement on Pragmatic Trials, where the appropriate format for reporting this kind of randomised trial is laid out. This CONSORT statement (Paper V) was deeply influenced by my experiences with the trials in this thesis and so the history of the pragmatic approach to RCTs is described here. I describe these methodological aspects prior to describing the RCTs themselves in order to give readers the information they will need in the next chapter, where they can assess the degree to which the RCTs in this thesis meet the criteria for pragmatic trial design.*

## Randomisation for internal validity

The history of knowledge is to a large extent a history of the struggle between theory and empiricism. This struggle between theories generated intellectually, and theories arising from empirical observation was the basis of the struggle between Semmelweis (1861) and the Vienna medical heirarchy. The development of empirical knowledge about causality, the raison d'etre of science, has grown through our increasing ability in an experiment to control each potential influence on outcome not related to the intervention or suspected casue, under study.

An experiment is a test conducted for the purpose of confirming something unknown but speculated, by testing the individual suppositions flowing from the overall theory. There are many kinds of experiments. A controlled trial is one particular kind of experiment in which a supposition about the effects of a treatment is tested by forming groups of subjects, differing only in that one group of subjects does receive, and others do not receive the intervention (treatment) under study, with the observed differences between groups ascribed to the intervention. One design of controlled trial is a randomised controlled trial (RCT) in which the comparability of the groups with and without the intervention is ensured by allocating subjects to groups randomly (Dictionary.com 2009). A pragmatic randomised controlled trial (PRCT) is a RCT aimed at testing a supposition about the effects of a treatment under conditions which greatly resemble those in which the treatment will be used if widely disseminated after being found effective.

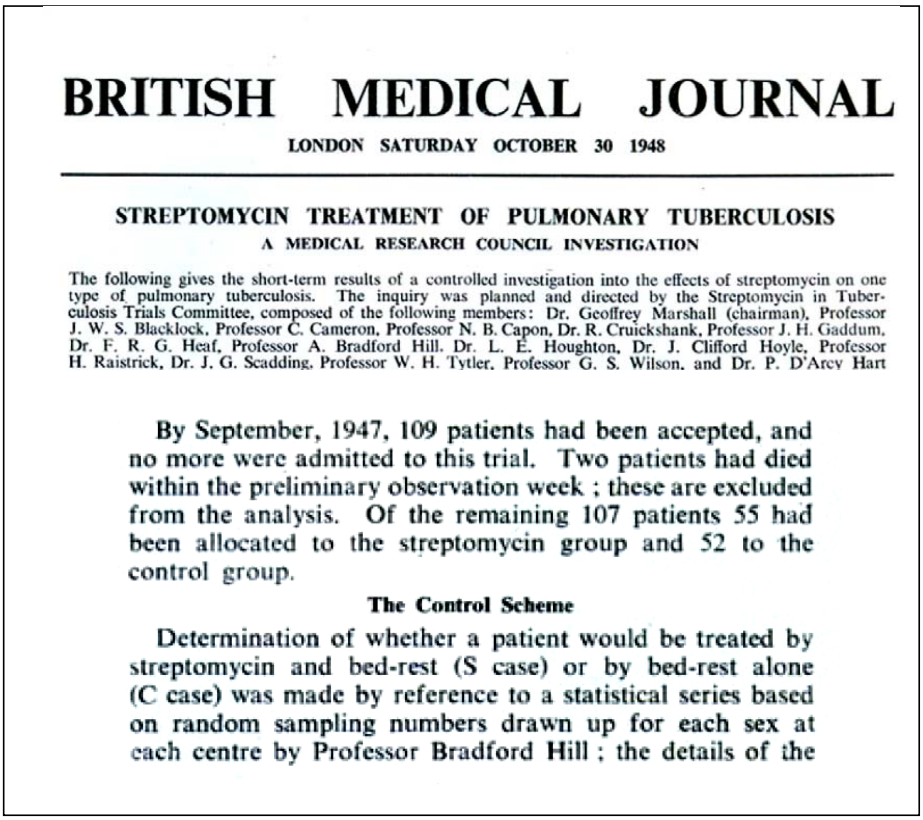
The first recorded controlled trial in humans is found in the book of Daniel, in the Old Testament (fig 2), where a vegetarian and a meat containing diet are compared for their healthfulness. (Some elements of modern trial design are missing- no effort is made to ensure comparability of the groups, co-interventions are not discussed, sample size is small, we are not told how the observations are made or by whom, the follow up period is only ten days, and the outcome measure is rather subjective- 'fairness and fatness of the faces' of the subjects. But the design did at least have a control group, which was studied contemporaneously with the experimental group, and the outcome was evaluated in both groups by a single observer).

By the turn of the 19th century the notion of variability due to chance had been understood, and what was known as "the statistical method" was being used to estimate the probability that a given difference in outcomes could be explained by chance (Heiberg 1897) through replication, that is, repeated conduct of an experiment, often with multiple subjects. By this time, controlled clinical trials were increasingly common in medicine, particularly in therapeutics and public health, addressing important questions with carefully constructed comparable control groups who did, or did not receive the intervention under investigation. All that remained to be added was the method of randomisation for allocation of individual subjects to groups. This followed in 1948 (MRC 1948). The development of the science of clinical trials was relentless and rapid from 1948, but that did not directly or immediately influence clinical practice, which was still characterised by individual practitioners' personal preferences of treatment, influenced by contesting schools of thought. Nor was regulation of therapeutics much affected until some years later. The RCT began to enter these arenas only after long struggles, which proceeded fastest in the United States.

In the early 20th century, as part of its struggle for professionalisation of the medical profession and suppression of others, medical practitioners organised in the American Medical Association (AMA) established a Council on pharmacy and therapeutics, which over the next forty years was increasingly influential in promoting the idea of science based drug regulation. Politically, this assisted in establishing the scientific bona-fides of the allopathic physicians, and eventually led to their exclusive occupation of the realm of medicine, beating back almost all other schools of thought, such as homeopathy and naturopathy. The recommendations and general approach of the AMA Council on therapeutics, and the recommendations it had made to its members on the use or non use of particular medications, was enacted into Federal legislation in 1938, given impetus by an episode of mass poisoning from an untested drug. The law gave the power to the Food and Drug Administration to regulate and license drugs on the basis of its evaluation of their safety, prior to marketing. Safety was defined as a positive balance between good and harm, and thus incorporated a judgement not only on safety but also on efficacy. Higher safety standards were enacted for drugs for minor self limiting illness than for more serious diseases (Marks 1987).

As yet the design of these trials of drugs to demonstrate efficacy and safety was hardly specified in the legislation or the regulations which followed. And so the majority of studies of drugs used for licensing were laboratory studies, animal studies, small clinical case series or non-randomised controlled studies. In 1948 the first reported randomised trial of any healthcare intervention confirmed what many had thought- that Streptomycin was highly effective in treating pulmonary tuberculosis (MRC 1948). Although this was the first randomised trial to be reported, it represents the culmination of a long process of debate and development on the best way to test treatment innovations. Along the way, problems were identified with many designs. For example with, studies that allocated alternative patients to intervention and control groups, it was realised that even if a trial was placebo controlled, clinicians would still develop an opinion on which treatment was

more successful, and could ensure their preferred allocation by managing the order in which patients were recruited to the study (Doll 1995).



BRITISH MEDICAL JOURNAL

LONDON SATURDAY OCTOBER 30 1948

STREPTOMYCIN TREATMENT OF PULMONARY TUBERCULOSIS

A MEDICAL RESEARCH COUNCIL INVESTIGATION

The following gives the short-term results of a controlled investigation into the effects of streptomycin on one type of pulmonary tuberculosis. The inquiry was planned and directed by the Streptomycin in Tuberculosis Trials Committee, composed of the following members: Dr. Geoffrey Marshall (chairman), Professor J. W. S. Blacklock, Professor C. Cameron, Professor N. B. Capon, Dr. R. Cruickshank, Professor J. H. Gaddum, Dr. F. R. G. Heaf, Professor A. Bradford Hill, Dr. L. E. Houghton, Dr. J. Clifford Hoyle, Professor H. Raistrick, Dr. J. G. Scadding, Professor W. H. Tytler, Professor G. S. Wilson, and Dr. P. D'Arcy Hart

By September, 1947, 109 patients had been accepted, and no more were admitted to this trial. Two patients had died within the preliminary observation week ; these are excluded from the analysis. Of the remaining 107 patients 55 had been allocated to the streptomycin group and 52 to the control group.

The Control Scheme

Determination of whether a patient would be treated by streptomycin and bed-rest (S case) or by bed-rest alone (C case) was made by reference to a statistical series based on random sampling numbers drawn up for each sex at each centre by Professor Bradford Hill ; the details of the

**Fig. 3: The first published RCT (www.jameslindlibrary.org)**

Randomisation was only implemented as a requirement for drug registration studies in the 1960s. The caution which led the FDA to prevent the use of thalidomide in the US, resulted in enormous support for expansion of the FDA role. This newfound influence resulted in the 1962 Kefauver Harris Amendment with regulations requiring randomised trials for registration of new pharmaceutical products (USFDA 1997).

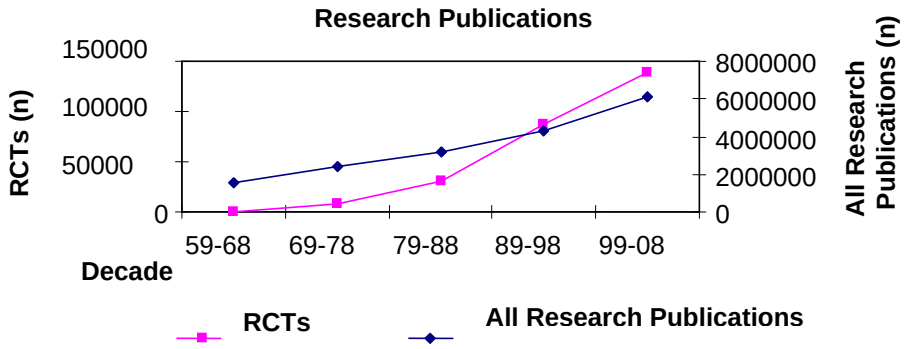



**Fig. 4: RCT publications trends (Data from Medline)**

From just one published randomised trial in 1948, we see on the National Library of Medicine PubMed database a very rapid rise in trials over succeeding decades (figure 4) with an increase in randomised trials as a percentage of all indexed research from 0.05% in the 59-68 decade to 2.2% in 99-2008 (My analysis of data from PubMed, 04/21/09). RCTs have risen in number and proportion and thus influence as an evaluative technique over the last half century, not least because of their critical role in regulation of pharmaceuticals. Because programmes of care delivery have no such licensing requirements, the range of acceptable evaluation approaches is much wider.

## Pragmatism for applicability

Rapid developments in the methodological foundations for the conduct of RCTs accompanied their increased use for regulatory purposes. As the importance of drugs in healthcare increased, so did the importance of the RCT, and, along the way, of the particular form of RCT that had been developed for drug licensing. This form of RCT was quite quickly recognised as limited in applicability to real world situations even for drug trials, and stimulated substantial debate (Schwartz 1967).

In 1967 two French statisticians, argued that there existed two possible attitudes to the design of randomised trials, each aimed at a different purpose (Schwartz 1967). The one attitude, which they named explanatory, they characterised as being interested in using the RCT method because it directly confirms or denies a causal hypothesis about the mechanism of an effect, thus taking science forward. It answers whether a chosen outcome was due to a prescribed intervention; whereas the other attitude, which they named pragmatic obtains information on which to make clinical decisions, in real world conditions as to which of several options for treatment is more desirable. These two attitudes and goals are very different and necessitate different approaches to the design of a randomised trial. For explanatory trials, the ability to sensitively establish the causal connection is improved by designing the trial to maximise adherence, responsiveness, and contrast with the comparator. For a pragmatic trial, the ability to inform

decisionmakers –patients, clinicians and policymakers, both at the trial locale and in many other places after the trial is published, is maximised by making the intervention as realistic and flexible as possible, and to increase the range of healthcare settings, recipients and practitioners of the intervention to closely match the range who will be prescribing and receiving the medication should it be shown to be effective.

A research group which I founded (PRACTIHC) has derived from the work of Schwartz and Lellouch, a list of ten criteria which distinguish these kinds of trial from each other. (Fig.5). Trials at the pragmatic end of the spectrum are widely inclusive of participants- in other words, all patients, and facilities who might get the treatment should it be widely applied are included in the study. The goal is to test the intervention in a group of subjects very like those to whom the intervention may be applied when implemented widely. Pragmatic trials tend to be flexible in the way in which treatment and control group are treated, with few or no restrictions on clinicians, so that they may provide care in whatever fashion they spontaneously would have done so without the trial, under typical conditions of the healthcare system in which they operate. Since this is how they provide care in the real world, (variably over time, between patients and amongst themselves, with little in the way of rigid protocolisation) this improves the applicability of the trial results to the real world. Pragmatic trials seldom monitor and never intervene to support adherence by patients or practitioners to some predesigned detailed trial protocol. Follow up of patient, practitioners or outcomes is kept very unobtrusive in pragmatic trials, to minimise intrusion on the practice or care of subjects that may change their behaviour from their normal, unmonitored practice. The primary outcome in pragmatic trials is usually chosen to be of great importance to the decisionmakers at whom the trial is aimed, and to be as objective as possible in ascertainment- such as mortality data from a reliable registration system. Intention to treat analysis is now universal, irrespective of the pragmatic or explanatory attitude of the trial, but in a pragmatic trial, the per-protocol analysis of patients who adhered to the protocol would not be presented (and could not be, as efforts to monitor adherence are rare in pragmatic trials). The goal is to produce an estimate of the performance of the intervention under conditions of normal “noise”.

By contrast, the goal of trials at the explanatory end of the spectrum is to maximise response to treatment in experimental intervention group, and thus efforts are made both to increase the strength of the signal from the intervention group, and reduce the noise in the overall measurement. Efforts are made to minimise all sources of variation other than the intervention itself. Thus the new intervention is tested under optimum conditions, precisely tailored to patient needs, with highest safe dose in order to increase the effect. Investigators monitor treatment intensely, and remind participants of, or even enforce, protocols, so that the medication is properly prescribed, administered and consumed. Explanatory trials often exclude poorly adherent patients in a pretrial testing period, (so that it is clear that the intervention was actually consumed in the planned dose; and that failure to achieve outcomes could only be explained by failure of the causal relationship, rather than failure to swallow the medication. These kinds of intrusive efforts require that explanatory trials take place in ‘ideal’ settings, where trial staff have ‘control’ (so that adherence by practitioners and patients is knowable). Patients in explanatory trials are

| Domain | Pragmatic trial | Explanatory trial |
|---|---|---|
| **Participants** | | |
| Participant eligibility criteria | All participants who have the condition of interest are enrolled, regardless of their anticipated risk, responsiveness, comorbidities or past compliance. | Stepwise selection criteria are applied that (a) restrict study individuals to those previously shown to be at highest risk of unfavourable outcomes, (b) further restrict these high-risk individuals to those who are thought likely to be highly responsive to the experimental intervention and (c) include just those high-risk, highly responsive study individuals who demonstrate high compliance with pretrial appointment-keeping and mock intervention. |
| **Interventions and expertise** | | |
| Experimental intervention — flexibility | Instructions on how to apply the experimental intervention are highly flexible, offering practitioners considerable leeway in deciding how to formulate and apply it. | Inflexible experimental intervention, with strict instructions for every element. |
| Experimental intervention — practitioner expertise | The experimental intervention typically is applied by the full range of practitioners and in the full range of clinical settings, regardless of their expertise, with only ordinary attention to dose setting and side effects. | The experimental intervention is applied only by seasoned practitioners previously documented to have applied that intervention with high rates of success and low rates of complications, and in practice settings where the care delivery system and providers are highly experienced in managing the types of patients enrolled in the trial. The intervention often is closely monitored so that its "dose" can be optimized and its side effects treated;<br>co-interventions against other disorders often are applied. |
| Comparison intervention — flexibility | "Usual practice" or the best alternative management strategy available, offering practitioners considerable leeway in deciding how to apply it. | Restricted flexibility of the comparison intervention; may use a placebo rather than the best alternative management strategy as the comparator. |
| Comparison intervention — practitioner expertise | The comparison intervention typically is applied by the full range of practitioners and in the full range of clinical settings, regardless of their expertise, with only ordinary attention to their training, experience and performance. | Practitioner expertise in applying the comparison intervention(s) is standardized to maximize the chances of detecting whatever comparative benefits the experimental intervention might have. |
| **Follow-up and outcomes** | | |
| Follow-up intensity | No formal follow-up visits of study individuals. Instead, administrative databases (e.g., mortality registries) are searched for the detection of outcomes. | Study individuals are followed with many more frequent visits and more extensive data collection than would occur in routine practice, regardless of whether patients experienced any events. |
| Primary trial outcome | The primary outcome is an objectively measured, clinically meaningful outcome to the study participants. The outcome does not rely on central adjudication and is one that can be assessed under usual conditions (e.g., special tests or training are not required). | The outcome is known to be a direct and immediate consequence of the intervention. The outcome is often clinically meaningful but may sometimes (e.g., early dose-finding trials) be a surrogate marker of another downstream outcome of interest. It may also require specialized training or testing not normally used to determine outcome status or central adjudication. |
| **Compliance/adherence** | | |
| Participant compliance with "prescribed" intervention | There is unobtrusive (or no) measurement of compliance. No special strategies to maintain or improve compliance are used. | Study participants' compliance with the intervention is monitored closely and may be a prerequisite for study entry. Both prophylactic strategies (to maintain) and "rescue" strategies (to regain) high compliance are used. |
| Practitioner adherence to study protocol | There is unobtrusive (or no) measurement of practitioner adherence. No special strategies to maintain or improve adherence are used. | There is close monitoring of how well the participating clinicians and centres are adhering to even the minute details in the trial protocol and "manual of procedures." |
| **Analysis** | | |
| Analysis of primary outcome | The analysis includes all patients regardless of compliance, eligibility, and others (intention-to-treat analysis). In other words, the analysis attempts to see if the treatment works under the usual conditions, with all the noise inherent therein. | An intention-to-treat analysis is usually performed. However, this may be supplemented by a per-protocol analysis or an analysis restricted to "compliers" or other subgroups in order to estimate maximum achievable treatment effect. Analyses are conducted that attempt to answer the narrowest, "mechanistic" question (whether biological, educational or organizational). |

Note: PRECIS = pragmatic–explanatory continuum indicator summary.

**Fig. 5: PRECIS criteria (Thorpe 2009)**

chosen to be at the severe end of the spectrum of their disease, and to have only that one disease, so that, in the event that the medication causes an improvement, there is

substantial room for it to occur; and so that the changes in the target condition are not masked or diluted by the effects of another disease. Outcomes are chosen to be short term, and physiological (e.g., blood pressure, rather than morbidity or mortality). This is to ensure a short causal chain of consequences between the treatment and the effect, rather than having to wait for downstream consequences of the treatment to unfold and also minimises the sample size (since severe outcomes such as mortality are less common than physiological changes that may lead to these outcomes). Explanatory trials often compare a new treatment to a placebo, or to a low dose of an older drug so that changes in the control group do not reduce the relative impact of the intervention).

In healthcare, the randomised trial is mostly known for it use in evaluating drugs. But in the social sciences, such as psychology, and in the area of educational evaluation, randomised trials were being recommended as the ideal mode of evaluation as early as the 1880's (Campbell 1988).There is thus easier acceptance, due to a longer tradition, of randomised controlled design in evaluation of complex social interventions than there is in the evaluation of complex healthcare delivery interventions. In healthcare, the strong tradition of explanatory drug trials means that RCTs have by and large been viewed as an extension of laboratory studies, with an explanatory approach whose attitude is, as described above, to understand a mechanism of action of an intervention. Fewer than 100 self declared pragmatic trials have been published (Vallve 2003). Even when used in evaluating a complex intervention, health researchers have deployed the RCT with a laboratory model in mind, and so by default have designed their trials so that they test highly protocolised interventions under tightly controlled conditions, with narrowly chosen subjects, and with intense measurement- i.e., in an explanatory fashion. Even in discussions on how to use randomised trials to evaluate complex interventions, the drug discovery model and sequence is directly copied (Campbell 2000), including the need for intensive efforts to understand the mechanism of action. The main adaptation made is to acknowledge the need to study mechanism of action using qualitative methods. While Campbell refers to a pragmatic phase in the cycle of evaluation, and specify that this should be a randomised phase, the specific meaning of pragmatism is not discussed. There is thus no explanation of the design features that could be appropriate for a definitive trial, a missed opportunity to break away from the mechanistic and explanatory approach of drug trials to date.

Nevertheless there is value in the idea of phased progress from intervention design to evaluation of increasing rigour, and we have tried to combine that understanding with the lessons from Schwartz and Lellouch. It is this combined approach, using mixed methods to understand the design of a complex intervention, combined with a pragmatic approach to design of the definitive trial, that we have used in several trials in this thesis, and others, not included here. In succeeding chapters I will try to show how elements of the design of both intervention and evaluation were based upon these lessons.

# 4. SETTING AND METHODS

*Chapter 4 describes the interventions being evaluated, and the research methods and settings of each of the four randomised trials in this thesis explaining them in terms of the issues raised in Chapter 3 on real world applicability and decision-making relevance. For each RCT I will describe the intervention and setting of the trial, with special attention to the degree that it matches real world condition and the design of the trial with special emphasis on the degree to which design choices may limit the applicability of the results. Detailed descriptions of elements that are not related to real world relevance of the intervention, and applicability of the results are described in the appended papers themselves.*

## Setting

All studies took place in South Africa. Study I took place in local authority primary clinics in periurban informal settlements around Cape Town, responsible for TB treatment. Study II took place in a rural, commercial fruit farming district in the Western Cape Province, and was under the auspices of a rural local health authority. The studies for papers III and IV took place in the Free State Province, in primary care clinics run by the Provincial health authority, in urban, periurban and rural areas.

## Paper I

**Intervention:** This three arm trial (two arms of which were reported in Paper I, the third, lay health worker arm being reported in a paper not included in this thesis, made an attempt to have the trial interventions be identical to the interventions as conducted in the real world. This was possible because nurse observation of Tuberculosis treatment was the norm in the high burden districts of the urban Western Cape, where we conducted the trial. This meant that provided we did not disrupt the flow of the clinic's work, we could use entirely "standard" nurse DOT as the one arm, and so we did.

To increase applicability we made sure that the trial included clinics in areas of the city populated by the two main ethnic groups amongst whom poverty creates a high Tuberculosis burden. We thus worked in both Khayelitsha (African) and Elsies River (so called "coloured", in the apartheid terminology of the time, when different residential areas were legislated for occupation by different groups, defined in crude racial terms) community clinics, and in each we randomised patients to different arms of the study. These communities are relatively impoverished within Cape Town, even compared to other ethnically matched neighbourhoods. Khayelitsha is a huge shack and basic housing development, with a population of around 250 000; Elsies River is a much smaller and older established community, but also very poor.

The plan was to compare Nurse DOT with two alternatives. The first was self administered treatment (SAT), in which the patient or a nominated representative simply collected a paper bag of drugs weekly, and returned an adherence card. We were able to

implement this arm in both areas in which our study was conducted, and so it is this comparison, Nurse DOT versus SAT which is reported in Paper I.

A third comparator, Lay Health Worker administered DOT, in which volunteer lay workers, members of a non governmental Tuberculosis control organisation called SANTA (the South African National Tuberculosis Association) acted as community based supervisors, holding drug supplies for each patient on their list (allocated by the clinic) and receiving visits at their homes form their clients, during which supervised treatment administration took place, and an adherence card was filled in. It had been planned that the NGO would be opening a new branch in the Khayelitsha suburb, and that we would have a Lay Health Worker arm in that community as well, to which patients could be randomised. Unfortunately, the process of community organizing is often more complex than expected, and so Khayelitsha was a 2 arm trial, Elsies River a three arm trial, two arms of which were combined with Khayelitsha data at analysis.

In terms of real world trials, all three arms in Elsies River, and both arms in Khayelitsha were very accurate versions of real world care in like communities. There were absolutely no changes made to the Nurse DOT intervention arms for purposes of the trial, and the act of randomisation was separate from the supervision approach, so that it could not affect the way in which the latter was done. SAT was designed for the trial, and so it was a new intervention, but it was designed to be as simple as possible, and to keep patients in clinics for a minimum time period, no more than required to collect there new medication bag. This simplicity made it relatively easy for nurses to explain, and simple for it to be incorporated into the clinic flow. The stage of drug collection was of course unchanged from usual drug collection processes, but the process of presenting the card on adherence to nurses and receiving the prescription for the following month was easy to insert into the clinic flow, and thus, likely to have been implemented in ways which match its real world implementation, had that resulted from the trial.

We had no particular preferences ourselves as to which arm should be superior, and so there is unlikely to have been any bias subtly transmitted to staff conducting the interventions. This was thus a real world intervention, with no research related changes.

**Inclusion criteria:** Paper I did exclude certain patients- those under 15 yrs of age as they would receive their treatment at school, under supervision of teachers in a system whose success was not under examination; working patients who could not attend the clinic and were receiving supervision from workplace nurses or staff, and were thus not using the part of the primary care system we were examining; patients who were severely ill or had multiple drug resistance as managers in the system felt these patients may often be hospitalised and would thus distort the trial, and patients whose treatment was already underway at the start of the trial; in other words only new patients were eligible. This approach was designed to include a group of patients and facilities whose results would be typical of the usual patients attending these primary care clinics.

**Practitioner expertise:** No eligibility, education or performance criteria were imposed on practitioners in any arm of the trial; any nurse may supervise Tuberculosis patients

and the trial did not change this. For the lay health worker arm, any trained and accredited lay health worker could supervise, and this too was left unchanged for the trial. We consciously designed the self administered intervention for simplicity, and imposed no criteria on it at all.

**Adherence:** No efforts were made to change practice, and thus there were no practice changes which had to be monitored or enforced. This allowed for great variation in the way in which nurses, for example, chose to supervise patients with TB, as occurs in usual clinic settings. So once again, our design choice was to match usual care and interfere in its delivery as little as possible.

**Follow up and measurement of the outcome** was extremely unobtrusive, drawing on the clinic files on treatment progress and completion. So again, the trial itself is unlikely to have had any effect at all on the way in which practitioners and patients experienced care; and so the result is likely to be applicable to the usual care experience of patients in this setting.

**Primary outcome** in this study was either bacteriologically proven cure, if that data was available for that patient from routine laboratory information, or documented adherence reflected in completion of more than 80% of the expected doses, with no substantial periods of interruption, within the allocated time. This is a an outcome vulnerable to biased assessments, in the sense that SAT patients may well have falsely completed their record cards while DOT staff supervising patients might be more "truthful". There are two arguments against this- firstly, DOT staff may also be expected to inflate their results to avoid looking like a poor performing clinic; and secondly, we included microbiologically determined cure on its own as a secondary outcome, and this made no difference to the outcome. Both microbiological cure and administratively defined successful treatment completion are not highly pragmatic outcomes, in the sense that neither is of direct relevance to patient well-being, as both are proxies for freedom from disease. Since the target audience for this study was policymakers rather than patients, we justified this choice on the basis of the central concern that these policymakers had with this outcome measure; also, of course, it was easily available, in contrast with long term follow up data on patient wellbeing which would have required primary and expensive data collection. This is a moderate departure from the pure pragmatic approach. The decision to do this arose from the difficulty and cost of following up patients to confirm that clinical or biological cure was followed one or more years later by a healthy life, with no recurrence.

## Paper II

**Intervention:** A community health development team of trainers and a nurse approached farmers (who have great power over their employees) to recruit them and their workers to a lay health worker training and deployment scheme aimed at improving community health awareness , especially of Tuberculosis, and other health conditions amenable to this approach. Of the 409 farms in the district, 107 were not eligible- not in use for

agriculture, too few resident workers, or only temporary workers and 92 refused or proposed a delayed start, leaving 211 participating farms which were randomised to receive a lay health worker training programme immediately (or be delayed by one year). Thus, the setting is typical of fruit and wine districts in this province, and the farms are themselves typical of the district typical, spanning the range of sizes, except for those with fewer than two permanent workers). The refusal rate was large, approaching 25%, and so caution will be needed in applying these results to farms where outside support and engagement is not welcome. Such farms may well be worse managed, and have lower paid workers living in worse conditions. The LHWs for intervention farms were selected by workers on the farm, given 5 weeks of training (in groups of about 10) by the team and deployed with, amongst other responsibilities, TB symptom monitoring and referral for diagnosis. Diagnoses were made in the usual way (clinical and microbiological), and farm LHWs offered support, if wanted, to patients with confirmed TB. This intervention was sustainable by local authority health department financial resources (and indeed, was sustained for years thereafter by the local authority. Although novel for this district, the developer of the intervention (Marina Clarke) had piloted very similar forms elsewhere, and knew both the feasibility and acceptability of the model locally. Marina's engagement with the local authority and its staff was excellent, and allowed for a robust commitment to the LHW by a succession of senior managers and thus sustained support. These factors combined to ensure that, although new to the district, the intervention was nevertheless realistic and could be applied there; implying of course, that the intervention would be feasible elsewhere as well. The only caution on this is that other similar agricultural districts would not have the advantage of the same long relationship with the initiating person.

**Inclusion criteria:** Because of the gatekeeper role of the farmer (who could decide whether or not an intervention was to be admitted, and because of the collective formed by the farm workers on each farm, the nature of the intervention was clustered, and so the units to be viewed as included are farms, rather than patients. This assists with both internal validity- no contamination between individual farms is likely to be less than that between individual workers on the farm, had individual randomisation been used) and it also assists with applicability, as variations between the farm workers on each farm need not be taken explicitly into account, as they are dealt with by randomisation. In this sense then, few inclusion criteria needed to be applied..

**Practitioner Expertise:** On the intervention farms, training was applied, and attendees were evaluated prior to being accredited. While this would normally be viewed as a more explanatory approach to trial design, the training of lay workers is itself the intervention, and since this intervention is deemed feasible, it should no longer be viewed as an explanatory choice of designs- it is simply the intervention. In the control arm, usual care applied, in which no LHWs were involved, as none had been trained on control farms. This is a very pragmatic comparator, allowing the question to be answered to be the very useful one: In comparison with usual approaches to TB and other care on farms, is LHW care superior?

**Adherence:** This was also incorporated into the training and follow up, carefully designed in advance to be sustainable in this setting. In control groups, no change to existing care was implemented, and so no efforts at adherence were required.

**Follow up:** Follow up of TB diagnoses and cure/successful treatment outcome rates were base don local TB registers, and therefore required no specific efforts at data collection, thus resulting in no changes to the intervention, or its outcomes that would make implementation of this intervention difficult in other similar settings. The TB register is standard throughout the country.

**Outcome:** The primary outcome (successful treatment completion) is important to TB programme managers, and for patients allows them to stop taking therapy, so is relevant and pragmatic. It is easy to collect this data as it is routinely collected in the register of TB patients kept in all South African public sector clinics.

**Analysis:** The analysis ignored all withdrawals and late refusals, an intention to treat analysis. Twenty six of the farms that had consented to take part in the programme and had been assigned to the LHW intervention arm, later refused to send candidates for LHW training, but were nevertheless included in the group to which they were randomised, for the entire analysis. A mark of the pragmatism of the outcome data was that it could be collected on patients, irrespective of and independent of decisions by the farm owner or manager to take part in the project.

### Paper III

**Intervention:** Syndromic management of respiratory diseases was introduced to typical primary care clinics in urban and rural areas of one of South Africa's poorer provinces. The intervention consisted of a guideline which integrated the diagnosis of these conditions Tuberculosis, Obstructive Lung Disease including Asthma and Chronic Obstructive Lung disease, Lower and upper respiratory tract infection, and smoking cessation advice, as well as cotrimoxazole preventive therapy for Tuberculosis patient co-infected with HIV), which offered evidence-based recommendations for treatment. The guideline was supplemented, with leave behind materials –posters and desk blotter reminders of key points-for staff that were to use the guideline. These front line nurses received clinical training in use of the guideline and diagnosis and treatment of the conditions during visits to their clinics by specially trained supervisory nurses. Each clinic team received a median of two visits, less than planned.

The guideline was designed to use therapeutic and diagnostic approaches already incorporated into standard policies and practices in the province, with some expanded permission for these standard treatments to be used in decentralised facilities such as clinics, by nurses trained in the PALSA programme. This was deemed feasible and sustainable by managers in the service, as was the training approach in which the (outsider) research team did not provide direct training to front line workers, but trained as front line trainers existing supervisors within the province's health system, repurposing

them in a supportive and educational supervision approach, rather than an inspection and disciplinary or enforcement approach as previously. This meant that no extra personnel were hired to build training capacity for implementation of the syndromic guideline into the provincial health service, a key feature which guaranteed sustainability. This approach was also intensively discussed with managers and selected as feasible and sustainable.

**Evaluation Design:** The intervention was aimed at the level of a clinic team, i.e., the frontline nurses and all other support staff in hat clinic, both administrative and logistic. This meant that training could be conducted in a single group, but also meant that no evaluation of different approaches was possible within facilities, only between facilities. So, realistic implementation strategies necessitated a cluster randomised approach to evaluation, rather than a randomisation of individual patients or staff.

**Inclusion:** In discussion with the Department of Health in the province we decided to implement initially in the largest clinics in the province, which deal with a very large majority of patient visits. Of 236 clinics, 26 were excluded because their staff oversaw more than one facility or because they had already been exposed to the support materials and guideline materials in pilot studies. After this, the 40 largest were thus randomised with no further exclusions. Thus, while the results are clearly directly applicable to large clinics in that province (tested in that very group) , they need to be thoughtfully extrapolated to smaller ones; and a priori, we are doubtful about the extrapolation to very small clinics with no fixed team in full time attendance, hence their exclusion.

**Practitioner Expertise:** The intervention under test was aimed specifically at increasing practitioner expertise, via education, support materials, support visits, team development. In this sense, the trial was highly pragmatic because all of the elements of expertise and training were built into the intervention, and are the only factor distinguishing the intervention from the control arm. There are no other elements of practitioner expertise that need to be considered in making the decision on implementability. However here is one set of considerations that were not evaluated in a randomised fashion, whose applicability in other sites should be carefully considered before attempting to implement this intervention elsewhere, and that element is the training, hiring and deployment of the trainers who visit the clinics to provide support to the frontline nurses. We ensured that this would be an implementable element in the trial setting by keeping the training short, and designing long term strategies for training autonomous trainers who could support the entire system. Thus the practicality of the PALSA intervention was examined before the trial.

**Adherence:** In this case there is no element of patient adherence to the intervention protocol. The staff adherence to the intervention plan is itself the outcome- i.e. evidence-based, guideline compatible diagnosis, and referral and treatment of patients with the target disease was incorporated as the outcome, so adherence (which was a goal of the intervention) is certainly measured. But besides the training and support, no other interventions were applied to improve adherence, and no accidental co-interventions (e.g., as a result of the trial personnel, etc) occurred either.

Adherence of the trainers to the clinics visit schedule was measured only at the end of the study, and no specific efforts were made to encourage or enforce regular visits by the trainers to the clinics; in all levels then, this is a trial on the pragmatic end of the spectrum.

**Follow up:** The follow up of the trial was achieved through a mix of low intensity routine administrative database analysis (the routinely kept and reported register of patients notified to public health authorities as having tuberculosis) and interviews with patients who were selected as part of the evaluation cohort, some 50 patients from each of the 40 clinics in the RCT. For these patients, an initial interview was done by research assistants in the clinics to recruit them to the study, and follow up interviews were conducted three months later, by appointment with patients. Again, this is a pragmatic approach, designed to have low impact on the way the intervention was conducted, that is, to have minimal effects on health care delivery.

**Outcome:** As a multi-facetted intervention with multiple targets there are naturally multiple primary outcomes, one for each target. For tuberculosis, the primary goal (and the one for which the sample size was calculated) was to increase case detection, using as a surrogate positive sputum microscopy, which is recorded by a central laboratory and obtainable for analysis from these databases, thus an objectively measured outcome, but not one which could be described as of immediate importance to patients, thus somewhat less pragmatic. In the final discussion we prominently reported one of the secondary outcomes, for which sputum testing had been the surrogate. This item, the number of patients diagnosed with TB was more pragmatic in that the diagnosis is also objectively measured (the diagnosis is based on the results of sputum microscopy, or culture), but also has direct importance for patients as it triggers a course of treatment. It is also more pragmatic than our chosen primary outcome because it is a better reflection of the totality of the diagnostic process, including clinical acumen in selecting patients for screening for tuberculosis. It is ironic, that in our efforts to develop a pragmatic intervention that would give skills and clinical abilities to front line teams, we did not properly consider the implications of this on the choice of primary outcome. Had we done so, we would have declared “patients on TB treatment” a co-primary outcome. In spite of our pragmatic attitude, we did not break out of the usual explanatory mindset, and were thus caught out by our inability to predict the mechanism by which our intervention improved the situation.

For obstructive lung disease, the primary goal was to improve therapy, indicated by prescriptions for inhaled corticosteroids. This is not recorded in an easily accessible format, and so we used patient reported prescribing of inhalers, which is a relatively salient event and medication delivery system, and thus likely to be a reasonable reflection of our desired outcome.

Receiving counselling for smoking cessation and stopping smoking were indicated by patient report; it would have been more pragmatic to record current and previous smoking history, but smoking cessation is too infrequent for any realistic chance of detecting an effect, and so we focused on the recall of staff telling patients to stop

smoking. For respiratory tract infections, the primary goal was to rationalise prescribing, indicated by antibiotic prescription, measured by recall; and for improved care of HIV/AIDS was indicated by the number of patients receiving voluntary counselling and testing, which was taken from patient history and clinical records. Cotrimoxazole prescription among patients with tuberculosis was also measure dint he same way, and is thus likely to be an objective measure; but none of these three are particularly important, in a direct way to patients. They are, however, very important to managers and nursing clinicians, and were selected for that reason. So in regard to these outcomes, the degree to which t hey are pragmatic is dependant on the perspective of the user of the results. Appropriate referral of patients with severe disease (indicated by any of the following: temperature ≥ 38°C, respiratory rate over 30 breaths per minute, breathlessness at rest, use of accessory muscles) was measured by patient reported referral to a doctor, which is subjective, but of importance to patients, and salient enough to be remembered. Outcomes were assessed one and four months after the intervention began and were deemed present if reported at either interview. This is a fairly short term follow up, and does not say much about the sustainability of the intervention, or sustained impact of the intervention on the chosen outcomes. In this sense then, the degree of pragmatism of the duration of follow up of outcomes was modest.

**Analysis:** Analysis was by intention to treat, and no patients or facilities were excluded. Nor was any adjustment made for the intensity of intervention. In this sense the trial was extremely pragmatic.

## Paper IV

**Intervention:** An extension and intensification of the PALSA project described above, to support the HIV/AIDS/ART clinical service and integrate the functioning of the ART nurses into the general adult care provided at clinics in this province, using the same principle intervention: outreach training by trained trainers, delivered on site in clinics, to entire clinic teams, tailored by the trainer to the circumstances of the clinic, with leave behind support materials, based on evidence-based guidelines, and designed to be compatible with existing approaches to care in the province. The intervention was designed to integrate ART and other HIV/AIDS care, with other services provided at primary care clinics, mainly by sharing knowledge of HIV/AIDS/ART across the whole clinic team, and by reinforcing skills in general illness treatment, mainly adult respiratory disorders with an emphasis on TB, for clinicians who had received specialty training in HIV/AIDS/ART The guidelines and leave behind support materials were also designed to be locally sustainable. The intervention is maximally pragmatic as it was adapted to local conditions, a result of being designed in close collaboration with the Province Department of Health, with trainers from the Department providing all the training to front line clinics and their staff.

**Inclusion:** Enrollment was very pragmatic. All clinics in the first wave of ART Rollout in the province were included, and all patients 16 years and older who enrolled in the HIV/AIDS/ART programme were included.

**Practitioner Expertise:** As with the previous intervention, the goal is to change the knowledge and practice of front line clinical teams in primary care clinics. It is therefore a training intervention, and in this sense, the trial was highly pragmatic because all of the elements of expertise and training were built into the intervention, and are the only factor distinguishing the intervention from the control arm. There are no other elements of practitioner expertise that need to be considered in making the decision on implementability. However, there is one set of considerations that were not evaluated in a randomised fashion, whose applicability in other sites should be carefully considered before attempting to implement this intervention elsewhere, and that element is the training, hiring and deployment of the trainers who visit the clinics to provide support to the frontline nurses. We ensured that this would be an implementable element in the trial setting by keeping the training short, and designing long term strategies for training autonomous trainers who could support the entire system. Thus the practicality of the PALSA Plus intervention was examined before the trial.

**Adherence:** No efforts were made by the study team to ensure adherence, neither for patients, nor for front line clinicians. For trainers of front line staff, a basic five day training programme was offered to selected staff whom the study team and managers thought might do well in this role, and who volunteered. Two follow up training sessions were also offered. It is in the nature of the Public Service that, although not compulsory, attendance was complete. In this sense, in relation to the levels of participants in randomised clinics, this was a very pragmatic trial.

**Follow up:** Follow up of patients was extremely unobtrusive as it was based entirely on data from routinely collected administrative systems (mortality register), electronic medical record systems and an electronic TB register. This is highly pragmatic, being objective and unobtrusive.

**Outcome:** The intervention was intended to improve outcomes by improving collaboration between formally separate parts of the clinic and thus separate clinic teams; and through improved acumen, both among HIV/AIDS/ART focused clinicians and among other staff as well. The outcomes were elements of care for each condition that was expected to be improved: for example, proactive screening (which occurs in the general clinic) should be a larger proportion of cases under care in the programme. To measure quality of HIV/AIDS/ART care we chose the proportion of patients receiving cotrimoxazole prophylaxis prior to referral to physicians for ART prescription. Collaboration between nurses responsible for TB and HIV care was indicated by the rates of TB diagnosis and treatment, assumed to rise with improved coordination. The more patient relevant outcomes, like mortality were chosen as secondary, as we did not have sufficient sample size to detect them, given that both arms of the study are receiving full access to physician ART treatment. One of our other secondary outcomes was viral load suppression, a consequence largely of physician quality of care and regular testing. The likely differences in this outcome were also expected to be small.

The choice of multiple outcomes is a pragmatic response to an intervention aimed at multiple goals; and individually each of the chosen outcomes is either an end in itself- e.g., putting patients with confirmed TB on treatment, and/or an evidence-based practice (e.g. cotrimoxazole prophylaxis in HIV positive patients with low CD4 counts.

It might be argued that the "demotion" of patient relevant outcomes like mortality to the status of secondary outcomes reduces the pragmatic orientation of the trial. But if we view it as decision-making, then the effect of choosing evidence-based process outcomes ameliorates this to some extent.

**Analysis:** For the primary outcomes, the analysis was a simple intention to treat analysis, with no exclusions. In this sense, this was highly pragmatic. Mortality, on the other hand, was analysed in a more explanatory frame of mind, with exclusions of patients who had attended just once, to minimise dilution of effect. Thus, in regard to primary, (but not secondary) outcomes, the trial was at the Pragmatic end of the spectrum.

## 5. RESULTS

*Chapter 5 describes the results of the four RCTs*

### Paper I

Over 1200 patients were eligible in terms of age for our study, but as our question was specifically related to DOT by patients attending the clinic, those patients who were either intending to receive care at schools or their workplaces, or were seeking work and thus were unlikely to be able to attend for care at the clinic were not included in the study. We also excluded from the study patients who could not be traced at a second recruiting visit, or those who transferred out of the clinic or into it. We successfully recruited nearly 300 of the patients attending clinics in our two neighbourhoods. There were no refusals.

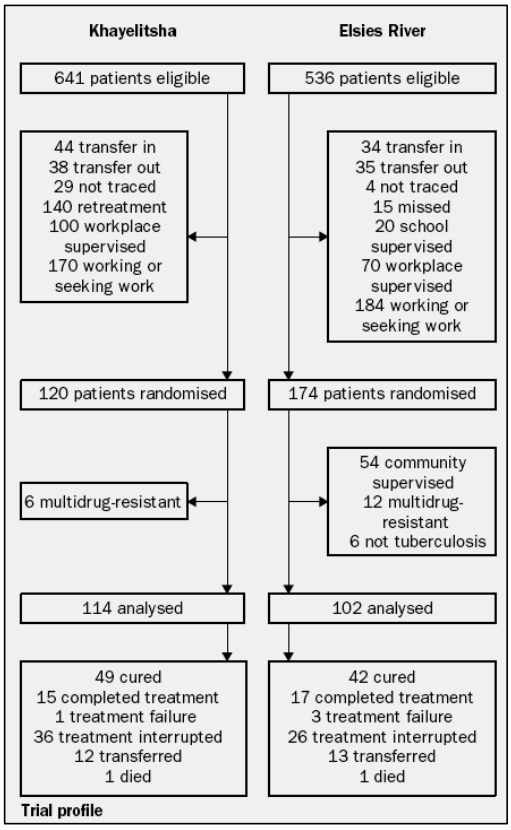


**Fig. 6: Nurse DOT RCT**

| Characteristic | Khayelitsha | | | Elsies River | | |
|---|---|---|---|---|---|---|
| | Clinic DO n=53 (47%) | Self-supervision n=61 (53%) | Total n=114 | Clinic DO n=58 (57%) | Self-supervision n=44 (43%) | Total n=102 |
| **Age (years)** | | | | | | |
| <35 | 36 (68%) | 36 (61%) | 72 (64%) | 28 (48%) | 23 (52%) | 51 (50%) |
| ≥35 | 17 (32%) | 23 (39%) | 40 (36%) | 30 (52%) | 21 (48%) | 51 (50%) |
| No data | 0 | 2 | 2 | | | |
| **Sex** | | | | | | |
| Male | 38 (72%) | 33 (54%) | 71 (62%) | 39 (67%) | 25 (57%) | 64 (63%) |
| Female | 15 (28%) | 28 (46%) | 43 (38%) | 19 (33%) | 19 (43%) | 38 (37%) |
| **Marital status** | | | | | | |
| Single | 39 (74%) | 42 (69%) | 81 (71%) | 39 (67%) | 29 (66%) | 68 (67%) |
| Married | 14 (26%) | 19 (31%) | 33 (29%) | 19 (33%) | 15 (34%) | 34 (33%) |
| **Housing** | | | | | | |
| Formal | 8 (15%) | 7 (12%) | 15 (13%) | 49 (85%) | 41 (93%) | 90 (88%) |
| Informal | 45 (85%) | 54 (88%) | 99 (87%) | 9 (15%) | 3 (7%) | 12 (12%) |
| **Income** | | | | | | |
| Employed | 24 (46%) | 18 (30%) | 42 (38%) | 11 (19%) | 1 (2%) | 12 (12%) |
| Other* | 28 (54%) | 41 (70%) | 69 (62%) | 47 (81%) | 43 (98%) | 90 (88%) |
| No data | 1 | 2 | 3 | | | |
| **Education (years at school)** | | | | | | |
| 0–5 | 19 (36%) | 16 (26%) | 35 (31%) | 16 (28%) | 13 (29%) | 29 (28%) |
| 6–8 | 20 (38%) | 27 (44%) | 47 (41%) | 23 (40%) | 25 (56%) | 48 (47%) |
| ≥9 | 14 (26%) | 18 (30%) | 32 (28%) | 19 (33%) | 6 (14%) | 25 (25%) |
| **Patient** | | | | | | |
| First presentation | 42 (79%) | 55 (90%) | 97 (85%) | 36 (62%) | 27 (61%) | 63 (62%) |
| Retreatment | 11 (21%) | 6 (10%) | 17 (15%) | 22 (38%) | 17 (39%) | 39 (38%) |

DO=direct observation of treatment-drug taking.
*Unemployed, or supported by family, friends, pension, or grant.

**Table 1: Baseline Comparability, DOT vs. SAT RCT**

The process of randomisation resulted in good balance between intervention and treatment arms at baseline. The results for the main outcome (overall cure and successful treatment completion rate show equivalence for the nurse DOT group (control) and the SAT group (intervention) with a non significant benefit in the direction of the intervention; that is SAT may be superior to Nurse DOT . A multiple logistic regression model of successful treatment outcome and supervision method showed that the effect of the supervision method on treatment success was similar across the two sites (p=0·26), for both men and women (p=0·21), and irrespective of employment status (p=0·82). However, the effect of the supervision method differed significantly between patients presenting with a first occurrence of tuberculosis and retreatment patients (p=0·014). The combined data from the two sites (table 3) showed that treatment was successful in 60% of self-supervised patients and in 54% of clinic DO patients. The 6% difference (90% CI –5·1% to 17·0%) was contained entirely within the prespecified equivalence range of –20% to +20%, and included zero rate difference. The two supervision methods showed similar treatment success for male patients (64% self-supervision, 61% DO), for unemployed patients (60%, 58%), and for new patients (56%, 59%, table 4). However, treatment success differed between retreatment patients according to supervision method (74% self-supervision, 42% DO, difference 32% [90% CI 11%–52%]). This difference exceeded the 20% upper bound and excluded zero difference. In these preplanned subgroup analyses patients in the retreatment subgroup (i.e., this was not their first occurrence of TB) the SAT group was substantially and statistically significantly more

likely to complete treatment or be cured. A secondary analysis using cure as the outcome was in agreement with the primary analysis for the principle outcome.

| Treatment outcome | Khayelitsha | | | Elsies River | | |
|---|---|---|---|---|---|---|
| | Clinic DO (n=53) | Self-supervision (n=61) | Total (n=114) | Clinic DO (n=58) | Self-supervision (n=44) | Total (n=102) |
| Cured | 18 (34%) | 31 (51%) | 49 (43%) | 24 (41%) | 18 (41%) | 42 (41%) |
| Completed | 9 (17%) | 6 (10%) | 15 (13%) | 9 (16%) | 8 (18%) | 17 (17%) |
| Failure | 1 (2%) | 0 | 1 (1%) | 1 (2%) | 2 (5%) | 3 (3%) |
| Interrupted | 17 (32%) | 19 (31%) | 36 (32%) | 15 (26%) | 11 (25%) | 26 (25%) |
| Transferred | 7 (13%) | 5 (8%) | 12 (11%) | 9 (16%) | 4 (9%) | 13 (13%) |
| Died | 1 (2%) | 0 | 1 (1%) | 0 | 1 (2%) | 1 (1%) |

DO=direct observation of treatment-drug taking.

**Table 2: Outcomes, DOT vs. SAT RCT**

## Paper II

With over 400 farms in the district, we were able to randomise 211 (Figure 5). These farms (the unit of randomisation) were similar in size and makeup of families (Table 3).

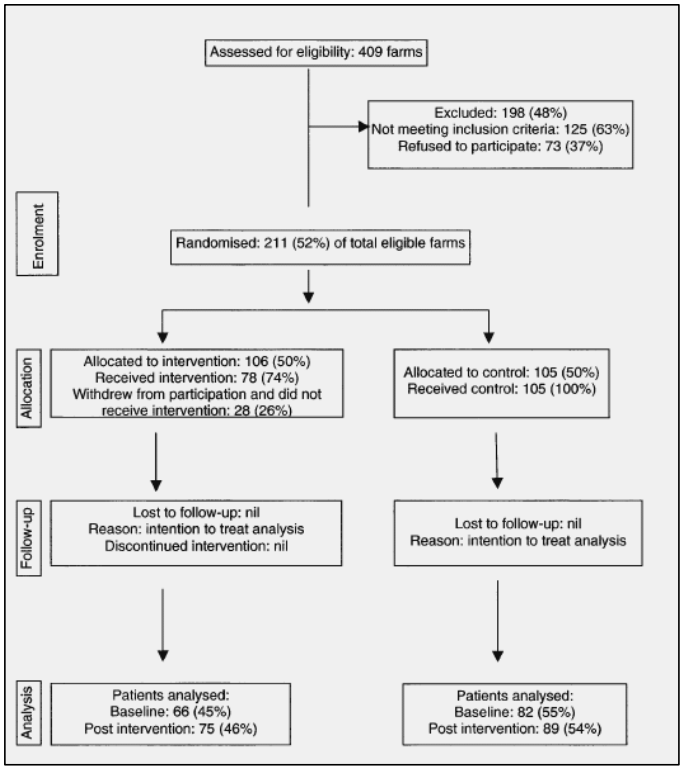


**Fig. 7: LHW RCT**

| Characteristic | Intervention ($n$ = 106) Median (range) | Control ($n$ = 105) Median (range) | Total ($n$ = 211) Median (range) |
|---|---|---|---|
| People living on farm, *n* | 44 (5–267) | 43 (5–462) | 43 (5–462) |
| Families living on farm, *n* | 10 (2–54) | 10 (2–87) | 10 (2–87) |
| Permanent workers, *n* | 18 (2–100) | 18 (3–200) | 18 (2–200) |

**Table 3: Baseline Comparability in LHW RCT**

The results suggest superiority of the intervention. (Table 4). The successful treatment completion rate of adult NSP TB patients in the intervention group of 39/47 (83%), compared to 27/42 (64.3%) in the control group, is significantly different ($P$ = 0.042). The difference amounts to an intervention effect size of 18.7% (95%CI 0.9– 36.4). The intra-cluster correlation for this outcome is 0.023. Successful treatment completion rate on intervention farms increased from 79% at baseline to 83%, while control farms experienced deterioration in the successful treatment completion rate, dropping by 15% from 79% to 64%. The number of NSP TB cases at baseline and post intervention was compared (Table 5). On intervention farms, 26/106 (25%) farms increased their case finding, compared to 18/105 (17%) control farms. This difference is not significant ($P$= 0.267).

| | Baseline | | | Post intervention | | |
|---|---|---|---|---|---|---|
| Variable | Intervention *n* (%) | Control *n* (%) | Total *n* (%) | Intervention *n* (%) | Control *n* (%) | Total *n* (%) |
| Treatment outcome | | | | | | |
| Cure | 22 (67) | 28 (67) | 50 (67) | 31 (66) | 25 (60) | 56 (63) |
| Completed | 4 (12) | 5 (12) | 9 (12) | 8 (17) | 2 (5) | 10 (11) |
| Interrupted | 5 (15) | 5 (12) | 10 (13) | 2 (4) | 11 (26) | 13 (15) |
| Failed | 0 (0) | 3 (7) | 3 (4) | 4 (9) | 2 (5) | 6 (7) |
| Transferred out | 2 (6) | 1 (2) | 3 (4) | 1 (2) | 0 (0) | 1 (1) |
| Died | 0 (0) | 0 (0) | 0 (0) | 1 (2) | 2 (5) | 3 (3) |

TB = tuberculosis.

**Table 4: Outcomes for LHW RCT**

## Paper III

Recruitment was smooth, and no clinics were lost to follow up, as shown in the CONSORT diagram (figure 8).

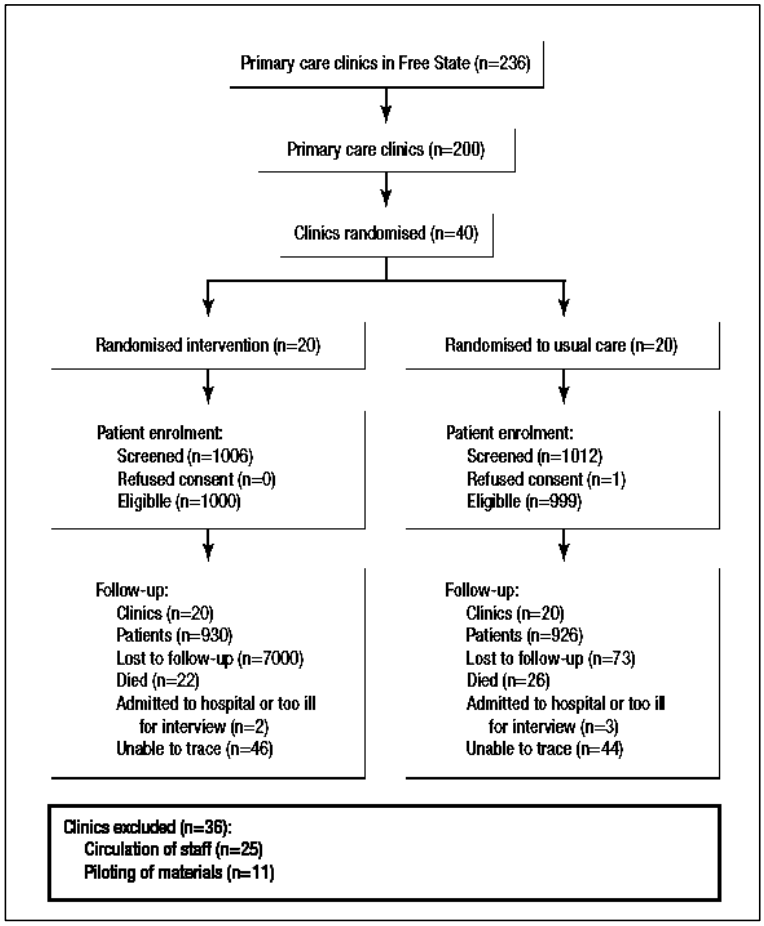



**Fig. 8: CONSORT diagram of flow of Clinics and patients**

Baseline balance was good, both for clinic level variables and for patient level variables. Of the 2000 patients enrolled, 1999 completed the initial interview and one refused consent; 1856 (92.8%) were re-interviewed at four months. Forty eight patients (2.4%) were reported by their families to have died. The groups had similar mortality (intervention, 22/1000; control, 26/999: odds ratio 0.84, 95% confidence interval 0.46 to 1.53). Training intensity fell short of the targets. Nurses in intervention clinics received a median of two educational outreach visits (range 0-4 visits).

*Tuberculosis* Sputum screening for tuberculosis was higher among patients in the intervention arm but not significantly so (odds ratio 1.22, 0.83 to 1.80; table 2). However, during the three months of the study period 57 new cases of tuberculosis were diagnosed in intervention clinics compared with 34 in control clinics (odds ratio 1.72, 1.04 to 2.85) suggesting that the goal was achieved (increased TB detection) but not via the expected route (increased volume of sputum screening).

| Characteristic | Outreach group | Control group |
|---|---|---|
| **Clinics** | | |
| No of clinics | 20 | 20 |
| Median total No of adult attendances a quarter | 12 749 | 12 935 |
| Median No of nurses per clinic | 9 | 8.5 |
| Tuberculosis treatment service available | 19 (95) | 20 (100) |
| 24 hour emergency service available | 4 (20) | 2 (10) |
| Median distance (km) from local referral hospital | 7.0 | 5.5 |
| **Patients** | | |
| No of patients | 1000 | 999 |
| Women | 643 (64.3) | 660 (66.1) |
| Mean age (years) | 44.9 | 44.2 |
| Education: | | |
| Never attended school | 169 (17.0) | 154 (15.4) |
| Attended primary school only | 464 (46.6) | 433 (43.4) |
| Attended secondary school | 363 (36.4) | 410 (41.1) |
| Employment: | | |
| Employed | 155 (15.6) | 209 (21.0) |
| Unemployed without welfare | 569 (57.2) | 557 (56.0) |
| Receiving welfare | 271 (27.2) | 230 (23.1) |
| Smoking history: | | |
| Current | 164 (16.5) | 193 (19.4) |
| Past | 313 (31.4) | 300 (30.1) |
| Never | 519 (52.1) | 504 (50.6) |
| Mean pack year history (smokers only) | 8.9 | 8.3 |

**Table 5: Baseline balance, Farm LHW RCT**

*Obstructive lung disease* Almost twice as many prescriptions were filled out for inhaled corticosteroids in the intervention group than in the control group (13.7%, 137/1000 *v* 7.7%, 77/999; odds ratio 1.90, 1.14 to 3.18). At enrolment 164 patients in the intervention group and 193 patients in the control group reported that they were current smokers. The groups had similar rates for counselling on smoking cessation (68.3%, 112/164 *v* 65.8%, 127/193 in controls) and smoking cessation for the period between interviews (12.2%, 20/164 *v* 10.4%, 20/193).

*Antibiotic prescriptions* The prescription rates of antibiotics commonly used for respiratory indications did not differ between the groups (odds ratio 1.01, 0.74 to 1.38; table 2).

*HIV/AIDS* The groups were similar for voluntary counselling and testing (9.7%, 97/1000 *v* 7.3%, 73/999 in controls) and for prescriptions for co-trimoxazole among patients with a diagnosis of tuberculosis during the study (7.8%, 13/167 *v* 7.5%, 11/147 in controls).

*Referral:* A higher proportion of severely ill patients in the intervention group were referred to a doctor than in the control group (10.5%, 27/257 *v* 4.8%, 8/166; odds ratio 2.59, 1.06 to 6.19). The intervention appeared to achieve the desired effects for TB detection, for improved care for asthma and chronic obstructive airways disease, and for

referral for severe illness, but did not improve (decrease) prescribing of antibiotics, cotrimoxazole among a group of patients who might be expected to have a high prevalence of HIV/AIDS, and nor did it improve the likelihood of receiving counseling for HIV/AIDS, or for smoking cessation. The principal outcomes are shown in Table 6).

| Outcome | No (%) in outreach group | No (%) in control group | Odds ratio (95% CI) | P value |
|---|---|---|---|---|
| Sputum screening for tuberculosis | 226/1000 (22.6) | 193/999 (19.3) | 1.22 (0.83 to 1.80) | 0.33 |
| Tuberculosis case detection | 57/892* (6.4) | 34/890* (3.8) | 1.72 (1.04 to 2.85) | 0.04 |
| Prescriptions for inhaled corticosteroids | 137/1000 (13.7) | 77/999 (7.7) | 1.90 (1.14 to 3.18) | 0.006 |
| Prescriptions for antibiotics | 397/1000 (39.7) | 394/999 (39.4) | 1.01 (0.74 to 1.38) | 0.95 |

*Denominator limited to all patients who had not been diagnosed as having tuberculosis before educational outreach started.

**Table 6: Outcomes PALSA outreach intervention**

## Paper IV

All clinics completed the trial (Figure 10). During the one year study period 5523 HIV infected patients were enrolled in the ART programme through the 8 intervention clinics (median of 724 per clinic, median follow-up 22.7 weeks, interquartile range (IQR) 7-41 weeks), and 4210 through the 7 control clinics (655 per clinic, median follow-up 27.6 weeks, IQR range 9-45 weeks)

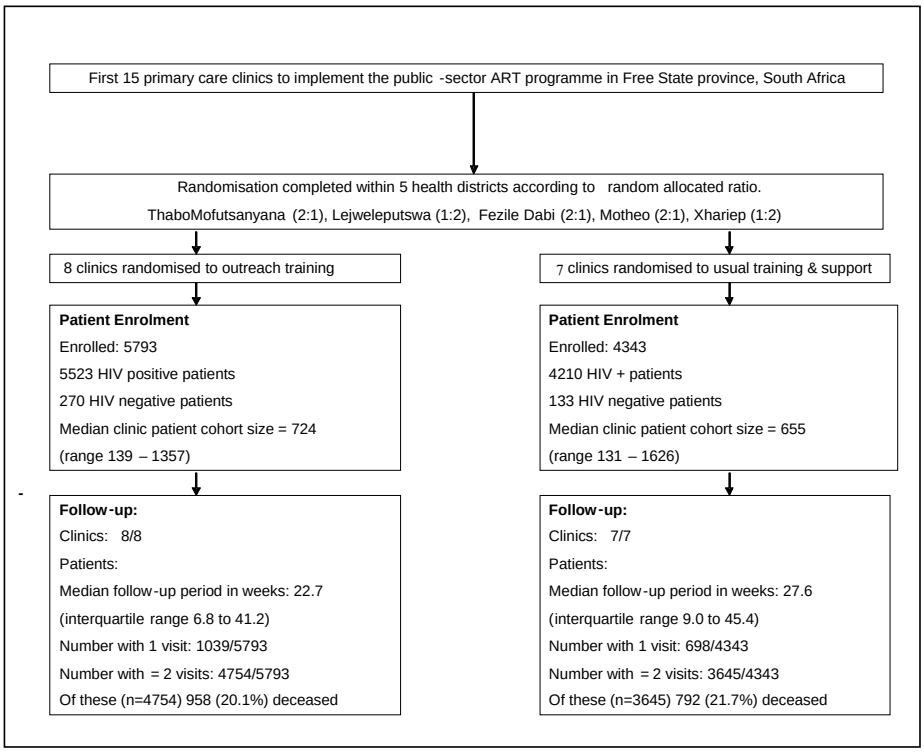



**Figure 10: CONSORT diagram, PALSA Plus clinic and patient flow**

Patient and clinic characteristics were comparable at baseline (Table 7). Intervention clinics were busier (median quarterly attendance 8929 general adult patients versus 7236 patients in control clinics) with more nurses (median 11 versus 9) (Table 1). The median CD4 count at enrolment was slightly higher in the control group (185 vs. 166 cells/mm3) but control patients were more likely to have advanced clinical infection (WHO Stage 3/ 4) recorded at the initial doctor assessment (924/1359 (68.0%) of controls vs.1057/1815 (58.0%) of intervention patients). Trainers delivered a median of 14.5 (range 6-20) educational outreach sessions to each intervention clinic. Nurses attended a median of 5 (range: 0 – 14) sessions each.

| | Outreach | Control |
|---|---|---|
| Clinics (n) | 8 | 7 |
| Median Adult attendances (qtr) | 8929 | 7236 |
| Median nurses per clinic (n) | 11 | 9 |
| Median distance from treatment site (km) | | |
| | | |
| HIV + patients (n) | 5523 | 4210 |
| Female/Total (% female) | 3576/5521 (65) | 2764/4210 (66) |
| Mean age (yrs) | 35.4 | 35.6 |
| Previous antiretroviral therapy- (% yes) | 59 (1.1) | 59 (0.9) |
| Median enrolment CD4 (IQR) | 166 (71-319) | 185 (84-339) |
| Enrolment CD4 count (%) | n/5523 | n/4210 |
| <25 | 388/5523 (7) | 278/4210 (5.2) |
| 25-49 | 344 (6.2) | 219 (5.2) |
| 50-99 | 615 (11.1) | 427 (10.1) |
| 100-199 | 1064 (19.3) | 758 (18.0) |
| 200-349 | 798 (14.4) | 725 (17.2) |
| 350+ | 892 (16.2) | 749 (17.7) |
| Unknown | 1422 (25.7) | 1057 (25.1) |
| Mean enrolment weight (kg) | 56.7 | 57.0 |
| WHO staging at assessment by Doctor | n/1815 | n/1359 |
| Stage 1 or 2 | 761 (42) | 435 (32) |
| Stage 3 or 4 | 1057 (58) | 924 |
| Employed | 127/1014 (12.5) | 102/1044 (9.8) |
| Median persons in household (IQR) | 4 (3.6) | 4 (3.6) |
| Households receiving social welfare payment (%) | 445/1006 (44.2) | 500/1027 (48.7) |

**Table 7. Baseline balance, PALSA plus.**

*Primary outcome (Table 8):*
*Program enrolment through new HIV testing* During the first month of the study, enrolment was more likely in the intervention group to be through new HIV testing than in controls (54.7 % (357/653) vs. 42.9 % (214/499), odds ratio 1.58, 95% CI 1.01 to 1.58). Although not significant, this remained more common in the intervention group for the first year (52.6%, (3048/ 5793) vs. 50.4% (2187/ 4343), odds ratio 1.19, 95% CI 0.51 to 2.77) suggesting a quicker learning curve, with possibly a smaller sustained benefit. )
*Cotrimoxazole prophylaxis prescription* Cotrimoxazole prophylaxis was more commonly prescribed among HIV seropositive patients attending intervention group clinics than among those attending control clinics (40.8% (2253/ 5523) vs. 31.8% (1340/ 4210), odds ratio 1.95, 95% CI 1.11 to 3.40). Provision appeared clinically appropriate as a higher proportion of intervention group patients with CD4≥200 cells/mm3 and no AIDS received cotrimoxazole prophylaxis (72.8% (1762/2419) vs. 65.2% (1025/1572), odds ratio 1.88, 95% CI 1.07 to 3.31).
*Tuberculosis case detection* TB was more likely to be diagnosed among HIV programme patients attending intervention group clinics than among those attending control clinics (7.2% (417/5793) vs. 5.6% (245/4343), odds ratio 1.25, 95% confidence interval 1.01 to 1.55).

| PRIMARY OUTCOMES | PALSA Plus | | Usual care | | Effect size | | P | ICC |
|---|---|---|---|---|---|---|---|---|
| | ***No.*** | ***%, SD or IQR*** | ***No.*** | ***No. SD or IQR*** | ***OR*** | ***95% CI*** | | |
| Enrolment via clinic initated HIV test (1 mo) | 357/653 | 54.7% | 214/499 | 42.9% | 1.58 | 1.01,2.48 | 0.054 | 0.113 |
| Enrollment via clinic initiated HIV test (1 yr) | 3048/5793 | 52.6% | 2187/4343 | 50.4% | 1.19 | 0.51,2.77 | 0.695 | 0.108 |
| Cotrimoxazole provision overall | 2253/5523 | 40.8% | 1340/4210 | 31.8% | 1.95 | 1.11,3.40 | 0.020 | 0.034 |
| Cotrimoxazole prophylaxis for cd4<200, AIDS or TB | 1762/2419 | 72.8% | 1025/1572 | 65.2% | 1.88 | 1.07,3.31 | 0.029 | 0.035 |
| TB case detection | 417/ 5793 | 7.2% | 245/ 4343 | 5.6% | 1.25 | 1.01, .55 | 0.038 | 0.027 |
| Secondary outcomes | | | | | | | | |
| Viral load suppression after 6 mths ART | 332/ 389 | 85.3 | 332/ 389 | 87.6 | 0.96 | 0.74, 1.26 | 0.779 | 0.088 |
| Mortality | 958/ 4754 | 20.1% | 792/ 3645 | 21.7% | Hazard ratio 0.90 | 0.67,1.19 | 0.466 | NA |
| OTHER OUTCOMES | | | | | | | | |
| CD4 follow up among patients with CD4 of 200-500 | 1127/ 1276 | 88.3% | 954/ 1141 | 83.6% | 1.39 | 0.65, 2.96 | 0.40 | 0.022 |
| Weight gain (kg) | 2.3 | S.D.. 5.8 | 1.9 | S.D. 6.1 | Mean difference 0.55 | 0.30, 0.79 | <0001 | 0.10 |
| Clinic visits | 6 | IQR 3.15 | 8 | IQR 4.19 | IRR 0.95 | 0.77, 1.18 | 0.638 | 0.026 |

**Table 8. Outcomes of PALSA Plus RCT.**

*Secondary Outcomes:*
*Viral load suppression* Treatment outcomes for the 2827 patients who received ART were good in both groups, slightly but not significantly superior in the control group (87.6% of control group patients and 85.3% of intervention group patients had suppressed viral loads 6 months after starting treatment).
*Mortality* Mortality was slightly lower in the intervention arm. ((958/4754 (20.1%) vs. 792/3645 21.7%), hazard ratio 0.90, 95% CI 0.67 to 1.19)

*Follow-up CD4 counts among enrolled patients* In the intervention clinics, of HIV seropositive patients not eligible for ART at enrolment (CD4≥200 cells/mm3 and no AIDS), a slightly higher proportion had a second CD4 count measured during the study period than in control clinics (88.3% (1127/12769) vs. 83.6% (954/1141), odds ratio 1.39, 95% CI 0.65 to 2.96).
*Weight gain* Intervention group ART patients gained more weight than patients in the control group (2.3kg vs. 1.9kg, ANCOVA mean difference 0.55kg; 95% CI 0.3-0.8).
*Healthcare utilisation* Utilisation of public-sector healthcare providers was slightly but not statistically significantly lower in the intervention group. Patients attending intervention group clinics completed a median of 6 (IQR 3 to 15) clinic visits during the study period while those in the controls completed a median of 8 (IQR 4 to 19) clinic visits (incidence rate ratio 0.95, 95% CI 0.77 to 1.18).

## 6. DISCUSSION

*Chapter 6 contains the main conclusions for Tuberculosis and other primary care delivery, drawn from the four RCTs, in the thesis, and discusses them in the context of other work on these topics. I draw conclusions about the meaning of these RCTs for future delivery of care for TB and other conditions.*

The randomised trials in this thesis evaluate the impact on successful treatment completion of compulsory daily nurse observation of treatment at a primary care clinic (Paper I), and of lay health workers as treatment supporters (Paper II); of strategies for improving the sensitivity of nurse diagnosis of TB in primary care clinics (Paper III) and the effects of a more intensive version of this strategy on a wider range of illnesses, adding anti-retroviral treatment for AIDS (Paper IV). In the course of conducting these studies I learned how to design randomised trials to evaluate the effects, under real world conditions, of complex interventions. Some of these lessons (inclusiveness of wide range of practitioners and patients for typical healthcare settings, flexibility of intervention and prioritising important primary outcomes) are captured in a methodological guideline for the conduct of such trials (Paper V).

The individual patient randomised trial of nurse provided Directly Observed Treatment (Paper I) showed no benefit over self administered treatment in terms of cure rate or successful treatment completion; and among retreatment patients, substantially and significantly reduced the probability of successful treatment completion. This is potentially serious, as reducing the successful treatment completion rate by 32 % points, is causing more treatment interruption and may be partly responsible for the development and spread of MDR TB. In this sense, then, the unfortunate emphasis on the DOT element (and the view of the overall programme, branded DOTS as a form of easily implementable "vaccine equivalent" (Hopewell 2002)) may have reduced attention to follow up of non-attending patients, and increased social distance between staff and patients, causing retreatment patients in DOT programmes to act as incubators of resistant Tuberculosis. As practiced in typical South African urban clinics, with overextended staff and managers, and poor relations between staff and patients (van der Walt 2002), nurse DOT does no good, and may do harm, in comparison with SAT, suggesting *that professional nurses make poor treatment supervisors and are not able to provide DOT in a fashion which achieves acceptable TB treatment outcomes.*.

The disappointing finding from Paper I on nurse DOT was followed up with a cluster randomised trial in Western Cape TB clinics, evaluating intensive on-site training to improve nurse competencies in patient communication and organisation of care for TB and thereby improve TB treatment outcomes. This intervention had no statistically significant impact on treatment completion rates (Lewin 2005, a) suggesting that within the existing primary care system in South Africa, there is *little prospect for using training on nurse relations with patients and clinic quality improvement skills for improving the outcomes of nurse provided DOT*. This is less surprising when we consider the results of a recent systematic review of all qualitative research on adherence (Munro 2007) which identifies several streams of factors that contribute to adherence, with nurses able to

contribute little to any of these, due to their inability to change structural factors such as patient poverty, physical factors such as distance to the clinics, and their inability, given the existence of rigid managerial hierarchies, to open up space in the running of their clinics to make them more flexible for patients (a function also of their social distance from patients (van der Walt 2002)

Paper I, the Trial of Nurse DOT also had a separately published third arm (Zwarenstein 2000, not included in this thesis) whose results suggested that Lay Health Workers were superior to nurses as DOT providers. To follow this line of thought our next randomised trial on 400 farms in the Western Cape investigated a model of treatment support by peer, volunteer lay health workers, trained in a range of primary care skills, including treatment support, who made their support services available on request from newly diagnosed patients. That trial (Paper II) showed that when the decision to use a treatment supporter, and the nature the support that she will provide, are left to the patient, lay health workers achieved clinically important and statistically significant increases in successful treatment completion and cure in comparison with usual care controls. In conjunction with Paper I this suggests that *direct improvement of TB treatment outcomes is a task best carried out by lay health workers*. The DOT trials indicate that DOT offered via LHWs, whether they are directly known to the recipient, as in Paper III, indeed, live as part of a small community on the same farm, or not, as in the third arm of the Elsies River RCT (Zwarenstein 2000), is an effective form of supervision. Whether offered as a patient choice, accepted by about half of the patients, or whether offered with much less choice, as in Elsies River, the outcome appears to be equivalent, and superior to Nurse administered DOT. This finding is compatible with recent systematic reviews of the effects of LHWs , (Lewin 2005 b) and accords with the successful experiences of large scale LHW programmes with supportive roles for family, friends and others for patients with HIV/AIDS and TB in Haiti (Farmer,1998; Mukherjee 2006) It is likely that LHW supervision is also superior to self administered treatment, but because the LHW programme was never established in Khayelitsha, and the size of the Elsies River trial was small, this finding warrants repeated evaluation. I think unsupported SAT is not superior to LHW supervision, but with remote support using remote electronic pill counts via cell phones, and cell phone based SMS messaging, or telephone call response and advice, supplemented by home visits where needed, it may achieve similar results.

These paired conclusions (inability to provide effective support for TB patients by nurses under compulsory conditions and success of lay worker support for TB care if optional) opened a second line of questioning. After it became clear that nurses were not effective providers of adherence support for patients with tuberculosis, our next study attempted to answer the question: if nurses were not responsible for providing DOT, what could their unique contribution be to improving TB care? This question is key for human resources planners as DOT for Tuberculosis is taking up large amounts of nurse time. Based on our success in improving the clinical diagnostic and therapeutic abilities of family doctors for a multi disease respiratory guideline for children through educational outreach and evidence-based key points materials (Zwarenstein 2007, not included in this thesis), a similar approach to improve the ability of nurses to diagnose tuberculosis and treat both TB and the range of other respiratory diseases which present to nurses providing adult

public sector primary care. In the first of these studies (Paper III) we concluded, after development and testing of a new approach to integrated, syndromic diagnosis of tuberculosis and other respiratory diseases common in primary care among adults (English 2006, Bheekie 2006), that nurses have an extremely valuable role to play as clinicians. The effect of this simple training approach was to double the rate of diagnosis of TB, while simultaneously doubling the proportion of patients with asthma who received a diagnosis and appropriate treatment, in comparison with usual care control clinics, suggesting that our *outreach approach improves the care of TB even as it allows nurses to take on a wider clinical role for other complex conditions*. This is compatible with other studies demonstrating the ability of non-physician providers to take on tasks widely believed to be suitable only for physicians, and to do so at similar levels of quality, with the added advantage of superior retention in post (Pereira 2007).

The success of the PALSA programme, and its acceptability to front line staff emboldened managers in the Free State Province to prepare their antiretroviral treatment programme design based on the PALSA model. We seized this opportunity to test the PALSA approach with even more complex care challenges, and thus requiring more arduous training targets. We developed and implemented a more intense (but still affordable and sustainable) approach to nurse training on a guideline covering a wider range of conditions, including screening for HIV/AIDS, ART treatment need, and ART maintenance treatment and surveillance for side effects and immune status. Primary care clinic teams centred around HIV/AIDS trained nurses became responsible for screening, identifying and recruiting to anti retroviral treatment (ART) all HIV positive patients with CD4 counts below 200, as well as provide ongoing management of ART and a referral channel to doctors. (Paper IV). Once again, this approach was effective in providing superior care across the range of outcomes, confirming that *professional nurses are able to improve the care of TB even as they take on a wider clinical role for other complex conditions*. Paradoxically, our most recent secondary analysis of this data (not yet published and not reported in this thesis) suggests that this *clinically focussed multifaceted educational strategy aimed at nurses in clinic teams may also have a positive impact on successful treatment completion rates among TB retreatment patients*, formerly thought to be amenable only to changes in relating between nurses and patients.

This brings us back full circle to the first DOT trial among nurses, and suggests that nurses are best deployed as clinicians; and empowering them to do their clinical work with excellent supportive education, on-site and in-service, can improve not only their clinical acumen and effectiveness, but also their relations with their patients to the point where patient adherence and engagement with clinical care programmes may benefit.

الكتاب الاول

بسم الله الرحمن الرحيم

الفن الاول من الكتاب الاول في حد الطب وموضوعاته من الامور الطبيعية يشتمل على ستة تعاليم

الفصل الاول من التعليم الاول من الفن الاول من الكتاب الاول من كتاب القانون

في حد الطب

**Fig. 11: Ibn Sina; Kitab Al-Qanun fi al-Tibb.( www.jameslindlibrary.org)**

Translation: “Introduction: Medicine is a science from which one learns the conditions of the human body with regard to health and the absence of health, the aim being to protect health when it exists and restore it when absent. Someone might say to us that medicine is divided into theoretical and practical parts and that, by calling it a science, we have considered it as being all theoretical. To this we respond by saying that some arts and philosophy have theoretical and practical parts, and medicine, too, has its theoretical and practical parts. The division into theoretical and practical parts differs from case to case, but we need not discuss these divisions in disciplines other than medicine. If it is said that some parts of medicine are theoretical and other parts are practical, this does not mean that one part teaches medicine and the other puts it into practice - as many researchers in this subject believe. One should be aware that the intention is something else: it is that both parts of medicine are science, but one part is the science dealing with the principles of medicine, and the other with how to put those principles into practice." (www.jameslindlibrary.org)

# 7. CONCLUSIONS: RCT EVIDENCE INFORMS REAL WORLD DECISIONS

*The main theme in Chapter 7 is the design of summative evaluations of the effects of complex interventions in care delivery and on the design choices we made in the four RCTs in this thesis. This is presented in relation to the Consort Statement extension for Pragmatic Trials which forms Paper V of the thesis and to other papers on pragmatic trials to which I have contributed, but which are not included among the papers in this thesis.*

This series of randomised trials, with many unexpected results, has helped to provide an evidence base for the organisation of TB treatment supervision, and for team outreach training and supportive supervision of front line carers for respiratory diseases and for HIV/AIDS/ART in primary care in South Africa. In the words of Ibn Sina, this is the science of how to put the principles of medicine (in this case, primary care) into practice (Fig 11).

Uptake of our findings into policy has been variable. Papers IV and III had active uptake, in more than one province and with the federal Department of Health. To a lesser extent Paper II was accepted, but has not been implemented as national or provincial policy. Paper I has remained beyond the pale, with very little discussion of adherence and the contribution of nurses through DOT.

The key to the uptake of our findings in the RCTs where there has been uptake has been the real-world nature of both the interventions which we tested, and the comparator group against which its results were contrasted. In all four studies, this recognisability of the interventions and control groups allowed decisionmakers to immediately absorb (and on occasion reject!) the relevance of the results to their own settings. This overcomes a key objection to RCTs by policymakers: “even if your intervention works, that treatment or intervention is not feasible/affordable/acceptable/compatible with our health care delivery system, our clinicians, or our rules and laws; and even if it works and is applicable here, the intervention you tested is simply not familiar to me”. Large amounts of innovation are risky, and rare other than in times of widely acknowledged crisis, and so in ordinary times, an incremental approach, which tests optimised versions of interventions with which managers are already somewhat familiar seems most likely to have the potential to change health services delivery.

By using existing approaches to healthcare delivery or clearly feasible adaptations of existing care delivery from another part of the same health system (self administered treatment is standard for high blood pressure, diabetes and other chronic conditions; PALSA and PALSA Plus approaches are very familiar to decisionmakers because of the widely accepted WHO/UNICEF initiated programme of Integrated management of Childhood illness (IMCI), a guidelines based approach to integrated syndromic management of childhood diseases) we ensured that both interventions and comparators

were easily imaginable for decisionmakers as feasible for the problem under study, in their own settings.

In terms of design of the RCTs themselves, the key element is that we minimised exclusions of facilities and of patients, so that the included subjects (at both levels) were as nearly matched to the overall system view that policymakers have in mind when they think of policy changes. For example, in the DOT trial, we excluded patients currently receiving treatment at school or at work, as this group of patients are not perceived of as a problem by decisionmakers, focusing our trial only on the problem group, those receiving care at primary care facilities. This concept (of focusing the trial on the health care problem which we were aiming to address with the intervention under evaluation proved difficult for global policymakers to grasp. The then leader of the GTB programme of WHO responded to Paper I upon publication with the following (Kochi 1999):

> *The small subset of patients eligible for the study is too small to draw conclusions about the value or otherwise of the two options (self supervision compared with five times weekly supervised swallowing) in relation to all the patients with tuberculosis registered at the two clinics.*
>
> *With a high default rate and unacceptably low cure rate under both reported options, the study shows in this particular setting that supervised swallowing and self-supervision are inadequate to ensure treatment adherence and cure. Therefore the study findings do not justify either the conclusion that "self-supervision ... offers more promise for improved rates of treatment success"*

Of course the point here is not whether a fraction of patients initially detected at this clinic were being supervised by other providers (workplace nurses and physicians, teachers; the point was that we included almost every patient who was going to receive clinic supervision, and randomised this group. Thus Dr Kochi, and several other well known commentators missed the distinction between sample size and recruitment rate. As our study recruited a high fraction of the patients who were to receive care in the primary care setting under clinic nurse DOT, the study is fully applicable to patients who receive DOT from nurses in primary care clinics, in settings like those of the Western Cape. Applicability is a clearly difficult concept which needs much better explanation than we were able to provide. The same correspondent also misunderstood the design of the trial , which was an equivalence trial, that is, one which assesses whether two treatments are broadly equal, within a prespecified range. The very fact that both were equally unacceptable was our entire point, and the reason why we felt the SAT option should be explored for improvement was that we had been commissioned to undertake the study because services were overwhelmed by nurse DOT, and managers were asking us if the different options for supervision were equivalent. Our study suggested they were, and thus SAT warranted further consideration.

By contrast, in Paper III and IV we included the facilities providing all or almost all of the relevant care- in III the largest 40 facilities, and in IV all the facilities providing the relevant care. This made it easy for policymakers to accept the applicability of the results

to other facilities in their own setting. Decision makers are well aware of the variability in results of programme implementation across what might to an outsider seem like similar facilities; and so it becomes important for the RCT to cover the range of facilities to which decisionmakers might wish to apply the intervention. A related issue is that co-interventions, and selection of , say, best performing clinics for the trial, or providing unsustainable training or support to the included facilities or staff is to be avoided. Instead, elements of support for participants should be built into the intervention only, and then only if they are viewed as sustainable, and tested in the context of the trial. An unadmitted co-intervention, such as training may itself be the reason for success of the intervention, and so unless it is counted in with the intervention transparently, the result will not be reproducible elsewhere. The responsibility for ensuring this is for the investigator and the decision maker.

Decision makers are willing to accept proxy outcome measures, based perhaps on an unvalidated belief in the connection between these proxies and outcomes relevant to patients and health systems. Experience, rather than evidence backs up this belief, strengthened by the frequent use of counts of activities in health services performance monitoring. Activity is simply assumed to be of benefit to recipients. This is an instance where researchers must exert great self discipline, and work hard to persuade decision makers that RCTs should try and focus on important outcomes, as it is mainly researchers who are aware that, for example, a change for the better in health services processes may not result in a similar improvement in outcomes such as morbidity reduction, cost reduction or patient satisfaction.

In several of the studies in this thesis, we were unable to use hard outcome measures, often for reasons of sample size. Where this was the case we tried instead to choose proxy measures that had a known relationship to the hard outcomes. For example, in paper I we did not use TB mortality as an outcome, but instead used microbiological proxies (negative sputum culture or microscopy at end of treatment), or documented record of completion of therapy. For both of these proxy outcomes there is previous RCT evidence that they are good indicators of long term cure of the disease and so are decent substitutes for harder to obtain outcomes (long term cure would require long follow up of patients). In papers III and IV we nominated as out primary outcomes a group of proxy health services process measures that were viewed by decision makers as key indicators of programme operational success, but were only able to show “hard” patient outcomes in a small minority of outcomes.

It is also the investigators responsibility to conduct a proper and valid analysis, with a true intention to treat approach that ignores failure of uptake in some facilities, and nevertheless analyses their results in the group to which they were randomised. While decision makers may apply pressure on investigators to remove from the analysis non compliers, it is the scientific honesty of the investigator which will protect against analyses which support overoptimistic estimates of effect.

Low and middle income countries cannot afford the negative consequences of assuming that plausible interventions, like nurse DOT, will be effective; nor can low or middle

income countries afford to miss benefits from seemingly daunting, but potentially feasible interventions, like syndromic algorithms and on site supportive supervision. We recommend the widespread use of pragmatic RCTs to provide rigorous evidence to help make the choice amongst plausible alternative approaches to health care delivery problems.

# 8. CONCURRENT AND FUTURE RESEARCH

*Chapter 8 outlines areas of concurrent and future inquiry, both in terms of trials of care for respiratory and other adult disease in nurse led primary care; and in relation to methodology, that is, to the design and promotion of pragmatic randomised trials.*

## Direct observation for TB

Paper I demonstrated that nurse provision of direct observation of TB treatment during intensive and continuation phases of TB treatment did not contribute to improved adherence. We have pursued this research question further, to attempt to improve the ability of nurses to provide DOT for patients with TB. Pilot data from our team in one facility had suggested that training for nurses around management of clinic flow and communicating with patients could potentially improve the successful treatment outcome rates in TB clinics, and so we expanded the reach of this intervention and tested it in a randomised trial. In spite of extremely thorough training and substantial nurse engagement in the intensive on site training programme, the randomised trial in 20 intervention and 20 control clinics showed no impact. This has led us to the conclusion that training directed at nurses as communicators, or as managers of patient flow and clinic organisation does not contribute to successful treatment outcome. This work was published. This left open the question of the impact of **clinical**, rather than communication skills training on nurses ability to support patients through treatment.

A secondary analysis (not yet finalised) of the data collected in the course of Paper IV, the RCT of PALSA Plus has revealed one exciting finding in relation to the question of support. The primary analysis of PALSA Plus related to patients within the HIV programme at each of the facilities in the trial. However, a secondary analysis, not reported in that paper, and recently conducted suggests that the highly successful training provided to nurses in the clinical care of HIV/AIDS/ART/TB and respiratory diseases had a statistically and clinically significant impact on successful treatment outcome of retreatment patients with tuberculosis in the same clinic, whether or not they were under the care of the ART programme. While it is disappointing that this finding was not present in TB patients with their first diagnosis of TB, it does provide one more small piece of evidence that confident clinicians are also superior TB treatment supporters, and that this support need not, even should not, be offered by nurses through roles in observation of treatment. This warrants new research to confirm that the quality of the interactions between PALSA Plus trained clinicians with tuberculosis patients is different compared with clinicians who do not have that training; as it is conceivable that the impact is not at the level of the individual trained clinician and their direct contact with TB patients, but mediated via more complex changes in the relationships and organisation of work in the entire team of the clinic. This spillover benefit needs further examination: what changes among confident clinicians, and on what does this impact and why?

Paper II in this thesis confirmed the findings of another paper, completed between I and II, which also showed that in the urban clinic setting of Paper I, lay health workers achieved superior outcomes in terms of successful treatment completion, than did nurses or self supervised patients. With the replication of this result in rural areas, and its scale up to an entire district still showing the benefits of lay health workers as treatment supporters, its seems clear that this is an avenue of care provision worth implementing. While the intervention arm in Paper II offered elective support and supervision (patients were not required to get assistance from a lay health worker, and even if they chose to, it was not specified that the assistance should take the form of DOT) the urban lay health worker intervention tested alongside Paper I, did make the DOT relationship between patient and LHW compulsory. It seems likely therefore that the elective approach in which patients and lay health workers jointly choose the mode of support is one point in a spectrum, and other options should be tested with equal rigour- particularly, compulsory LHW DOT needs to be examined in a large pragmatic trial as the initial trial (third arm of trial in Paper I, in one of the two suburbs only) was relatively small in terms of the number of clinics in the study, and may reflect other unique characteristics of that LHW programme, such as its charismatic leadership.

## Supporting knowledge translation

Our approach to simplified, contextualised, evidence-based clinical algorithms, carefully implemented through a locally sustainable multifaceted knowledge strategy has proved able to support nurse clinicians to competently use an ever widening and body of knowledge and successfully acquire clinical acumen for complex care. We are currently expanding this in two directions. The first is a direct expansion of Paper IV. PALSA PLUS clinics in the Free State are responsible for initial screening in, diagnosis and referral for physician ART treatment initiation, and then for maintenance treatment on the patients who are referred back down to clinics when treatment is defined. This leaves a major bottleneck intact- the shortage of doctors is responsible for a very long waiting period for patients who have been diagnosed and are below CD4 of 200, and thus in need of ART. We are currently conducting a randomised trial of nurse initiation in the Free State, where nurses will also prescribe the ART for many-we think up to 70% of patients in need of ART, referring to hospitals and physicians only those patients that have specific complications that make their ART initiation more complex than nurses can currently handle.

We are also currently analyzing data from the Western Cape where we are testing PALSA PLUS in another RCT. We are also applying for funding while preparing to replicate and adapt PALSA PLUS for Malawi's Zomba district, in collaboration with DIGNITAS, a Canadian NGO. The Malawi replication will test the robustness of our approach, with local adaptation, under conditions of much more restricted resources, especially personnel, as well as longer distances for patients to travel for referral.

The third line of expansion for this work lies in the future-we are currently applying for resources from NIH to expand the guideline and leave-behind support materials even

further to include all adult disease presenting in primary care, with special attention to chronic cardiovascular disease and mental health, both extremely common and becoming more prominent in countries in the middle income bracket as they bring infectious diseases under control. This work is well underway, with the new guideline about 70 percent completed.

## The future of pragmatic randomised controlled trials

To date the work on pragmatic trials has been in the nature of opinion pieces and informal consensus development (Thorpe 2009; Zwarenstein 2009; Oxman 2009). This needs to be formalised, so that we get a better sense of what should go into these trials, as so far this is merely based on ad hoc expert opinion. Beyond formally collected expert opinion lies a large agenda of empirical research on the characteristics and their prevalence of this approach to design of trials, as well as on the usefulness of such trials in decision-making, and how this might be influenced by their design characteristics. There is not as yet an empirical basis to confirm that randomised trials designed with pragmatic characteristics as outlined in Paper V are indeed more useful or more widely used in decision-making than are more typically explanatory trials. This is work that we are currently formulating for future funding applications and will yet undertake, starting with questions such as: for trials which declare their intent to support decision-making, what are their pragmatic characteristics?

The work outlined in this thesis is designed to change the world, in a small way and hopefully for the better, not merely to study it for curiosity or academic purposes. In being arrogant enough to seek change, I feel it is vital to be humble enough to acknowledge my uncertainty that the effects of these efforts for change have been, on balance good. In these circumstances, the pragmatic randomised trial is a useful tool. Efforts to promote wider availability of the skills to use this tool, that is, to conduct pragmatic trials, are already underway. As a consequence of the PRACTIHC framework grant, there is a web based "textbook" on pragmatic trials available free for non-profit use at www.practihc.org . To date it has been used as a basis for over a dozen short (three day) courses in the design and conduct of pragmatic trials for researchers, including one at KI; but we plan to add more interactive resources to the web based package, and test the feasibility of running global courses using the resource, with live interactions among the class and students taking place through web based videoconferencing.

## 9. ACKNOWLEDGEMENTS

*Chapter 9 contains acknowledgements of the many people without whom this thesis and the underlying intellectual developments could not have happened.*

This thesis has been almost like a child- certainly in the length of time taken to bring it to independent existence. And children owe their existence to families. I would like to express my deep gratitude to the several families who helped bring this child to independence.

Beloved **Bettina** and our boys, **Max** and **Sander** (whose development is more or less contemporaneous with the thesis and the studies in it), my thanks for their support and encouragement, as well as their tolerance of my work related abscences.

In this thesis I frequently use the word “we”; the people who follow are that “we”. They are my work family from around the world, who have led me into and helped me through this work:

**Judy Dick**, who tolerated my crass commitment to narrowly defined scientific evidence, and who skillfully and generously incorporated me and my ideas into a delicate set of relationships that she had painstakingly built with policymakers, while trying to nurture in me the seeds of an effective health care quality improvement activist.

**Hennie Schoeman**, whose gentle nature, and courage in the face of powerful opposition to our joint research is memorable and inspiring, and whose tenacious commitment to excellence is almost entirely responsible for the quality of our randomised trials on Nurse and LHW care in TB.

**Marina Clarke**, the most modest and most determined community health activist, and scientist I have ever met.

**Carl Lombard**, a statistician of global stature, principled and wise in the ways of data analysis, clear in his explanations, and more attuned to real world relevance of research than almost any scientist I know. Carl is responsible for all of the analysis on all the RCTs in this thesis. He is solely responsible for the biostatistics which I do understand; I am responsible for the large remainder.

**Hester van der Walt**, a qualitative researcher of exquisite sensitivity, insight and honesty, who opened my mind to methods of research outside of numbers and helped me learn how to integrate trials and qualitative information.

**Lara Fairall**, my close collaborator on the PALSA and PALSA Plus trials, an extraordinarily talented and stylish scientist, trialist, educator, organiser and lobbyist.

**Ron Chapman**, a uniquely bold and determined health system manager, whose modest ways hide an extremely successful designer of health care innovation.

**Max Bachmann**, my longstanding friend, comrade in anti-apartheid organisations, and fellow scientist, with whom I have shared many jaundiced and skeptical late night hours –discussing people, parenting, politics, research and healthcare design.

**Andy Oxman,** another committed activist, scientist, humorist and sceptic, from whom I have tried to learn how to spend more time thinking, writing and doing than talking.

**Dave Sackett,** who inspired me, during his visit to South Africa in its darkest apartheid years, by helping me see that science was anti-authoritarian, and that it could make a difference to life and death; and who has remained accessible and supportive all these 30 years.

**and especially to Vinod Diwan,** a scientific leader in knowledge dissemination for development, and in randomised trials of complex interventions, head of the Division of International Health (IHCAR) and Chairman of the Karolinska International Research and Training Program (KIRT). In my long years registered at KI, I sorely tested his legendary patience and generosity. Vinod, my apologies; and everlasting gratitude for your advice and unwavering support.

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