PROTOCOL: NKATEKO TRIAL

Treating hypertension in rural South Africa: A clinic-based lay health worker to enhance integrated chronic care

Principal Investigators

Margaret Thorogood, Professor of Epidemiology[1], & Honorary Professor[2],
Jane Goudge, Director of the Centre of Health Policy[2],

Co-Investigators (Alphabetical)

Melanie Bertram, Health economist [2]
Tobias Chirwa, head of the Division of Statistics and Epidemiology[2],
Sandra Eldridge, Professor of Biostatistics[3],
Xavier Gómez-Olivé, Research Manager, MRC/ Wits Rural Public Health and Health Transitions Research Unit[2]
Eustasius Musenge, Statistician[2]
Stephen Tollman, Director, MRC/Wits Rural Public Health and Health Transitions Research Unit[2]
Rhian Twine, Head of LINC Office, MRC/Wits Agincourt HDSS Unit[2]

Trial Steering Committee

Chair:	Helen Schneider, Professor [4]
Members:	Obioha Ukoumunne, Senior Lecturer in Medical Statistics[5]
	Naomi Levitt, Professor [6]
	Simon Lewin, Social Scientist[78]
Observers	Jill Jones, International Strategy Manager,
	UK Medical Research Council, representing the trial funder
	Debbie Greer, Research Development Officer.
	University of Warwick, representing the trial sponsor

[1] Warwick Medical School University of Warwick, UK
[2] School of Public Health, University of the Witwatersrand, South Africa and INDEPTH Network, Ghana
[3] Queen Mary University of London, UK
[4] School of Public Health, University of the Western Cape, South Africa
[5] University of Exeter, UK
[6] Division of Diabetic Medicine and Endocrinology, University of Cape Town, South Africa
[7] Norwegian Knowledge Centre for the Health Services, Norway
[8] Health Systems Research Unit, Medical Research Council of South Africa.

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Trial Sponsor University of Warwick
Contact Dr Peter Hedges, Director of Research Support Services.
University of Warwick, Coventry CV4 7AL United Kingdom

Neither the trial funder nor the sponsor will have any role in the study design, analysis or reporting of the findings.

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A. SCIENTIFIC ABSTRACT

South Africa has a high and rising prevalence of hypertension. Previous research in the rural Agincourt sub-district, covered by a high-functioning health and demographic surveillance system (HDSS) has found a prevalence of 61% in adults, many affected individuals not using any medication and very few of them (9%) with controlled blood pressure. Until recently, primary care clinics focused on management of acute conditions, but recent government initiatives are shifting the focus to management of chronic disease including HIV and hypertension. This cluster randomised controlled trial will test the effectiveness of a new clinic-based lay health worker to supplement government initiatives and support care of chronic disease. Eight health facilities that provide care for the population of the Agincourt sub-district, together with the communities they serve will be randomised to usual care or to the provision of one or more chronic-care focused lay health workers. The principal outcome will be the percentage of people who have a blood pressure and risk profile that indicates Moderate or greater Added Risk of cardiovascular disease as defined by a modified version of the South African Hypertension Guideline 2011[1].The principal outcome will be assessed in two population level surveys at baseline and at the end of the intervention. A clinic/census link set up in all clinics will provide detailed information on changing patterns of clinic use, and an extensive realist evaluation of processes will provide greater understanding of the barriers and facilitators to effective management of hypertension. The finding from this trial will be relevant for improving the care of all chronic diseases,

B. LAY SUMMARY

In South Africa, it is very common for people to have hypertension. We have found that over half (61%) of adults in the Agincourt Health and Demographic Surveillance System Site (HDSS) have hypertension and in only a few (9%) of those people is the blood pressure well controlled using medication. Hypertension is a chronic condition requiring long term medication but until recently the primary care clinics in South Africa were only organised to deal with short term conditions. The government has recognised the problem and is reorganising clinics to also deal with chronic conditions, such as HIV and hypertension. We will test whether providing an extra lay health worker, to work alongside the nurses in the clinics focusing on the care of chronic conditions, will help to improve the care of people with hypertension. We will carry out research in eight clinics that provide care to the people living in the Agincourt HDSS. We will randomly choose four clinics where we will provide the lay health workers for 15 months. We will test the effect of these lay health workers by doing two population surveys of blood pressure, one before we start the intervention and one as soon as we finish. In addition we will set up a clinic/census link so that we can find out which people (age, sex, place of residence, etc.) are using the clinics and whether that changes when the intervention is introduced. We will also carry out a number of interviews with different people during the intervention to identify some of the barriers and facilitators to providing good care of people with hypertension. The finding from this trial will be relevant for improving the care of all chronic diseases.

C. BACKGROUND

C1. Introduction

South Africa has a high and rising prevalence of hypertension, affecting between a quarter and a half of its population[2, 3], within the context of the complex epidemiological and demographic transition underway in South and sub-Saharan Africa. In low-resourced South African rural settings, fewer than half of those affected are aware they have hypertension, and only a small percentage achieve appropriate blood pressure levels[4]. There is marked variation in the quality of clinical management due to poor functioning of primary care services, which centre on the management of acute, rather than chronic conditions. Adherence to medication is sub-optimal, long-term patient retention is low, and little attention is paid to potential co-morbidities[5]. South Africa's antiretroviral treatment (ART) programme, the largest worldwide with recent notable increases in coverage, has generated substantial knowledge likely to be relevant to other chronic illnesses on adherence support, tracing defaulters, and enabling patient participation through treatment literacy and patient support groups[6].

This trial builds on the Department of Health initiatives for integrated chronic care. The aim of the trial is to reduce population levels of uncontrolled hypertension, especially in those individuals at greatest risk, by supporting and strengthening the management of hypertension in primary care clinics. The intervention is appropriate and relevant to a rural, resource constrained setting. In collaboration with the Department of Health, the trial will compare the effectiveness of the 'usual care', with an intervention where a clinic-based lay health worker (LHW)[i] supports the provision of chronic care. This will be a cluster randomised trial[7] and realist evaluation[8] taking advantage of the well-established health and demographic surveillance system (HDSS) in the Agincourt-Bushbuckridge sub-district.

C2. Research objectives

The specific **research objectives** are to:

i. Compare the effectiveness of a quality improvement intervention involving use of clinic based lay health workers to 'usual care', in improving access to care, adherence to treatment, and management of hypertensive patients, in rural South Africa;
ii. Conduct a realist (or process) evaluation to clearly understand the patient, intervention, implementation, health system and community barriers and facilitators that explain patient outcomes in the intervention and 'usual care' clinics;
iii. Contribute specific recommendations to strengthen policy and practice in similar rural settings of South and Southern Africa.

[i] In this document, the phrase 'lay health worker' refers to all non-professional staff based either in the clinic or conducting outreach work; 'community health worker' refers to a lay health worker conducting outreach work in the community. In South Africa both are paid for their services.

C3. Primary and Secondary Outcomes

The Nkateko trial is a pragmatic trial aiming to provide information that will enable policy makers to improve the management of hypertension.

The **primary outcome** is a population level measure of hypertension control and will be derived from cross-sectional surveys carried out before and after the intervention. This primary outcome will be the change between the two surveys in the percentage of people in the population who have elevated blood pressure that is combined with other factors resulting in a risk profile that indicates moderate or greater added risk of cardiovascular disease. This is described in more detail below (section F2)

Secondary outcomes are:

- change in proportion of the population with undiagnosed hypertension,
- change in the proportion of the population reporting they had had their blood pressure measured,
- change in the proportion of the population reporting that they are using medication for hypertension
- changes in the proportion of the population at different levels of blood-pressure-related cardiovascular risk by age group and sex
- Change in the proportion of people in the population reporting that they have attended a clinic in the last year.
- the proportion of people with diagnosed hypertension using primary care clinics who are adherent to prescribed medication, defined by recorded collection of prescriptions.
- Retention in care of people with diagnosed hypertension defined by the proportion of appointments kept during the study period.

C4. Scientific justification

Conceptual frameworks for chronic disease care emphasise the need for productive interactions between patient, provider, and the broader health system (See Figure 1)[9]. Delivery systems need to include: a reliable drug supply; robust systems for patient records to monitor care over time and assess clinic performance; provision of quality care close to the community; and adequately staffed clinics (Figure 1, Box 1). Health workers need to be able to: diagnose and prescribe; have access to clinical advice when necessary; and, have understanding and knowledge of the local community to provide effective adherence support and counselling (Figure 1, Box 2). Lastly, effective chronic care requires patients with: sufficient self-efficacy to manage their illness; support from their social network; and, financial and physical means to attend the health facility (Figure 1, Box 3).

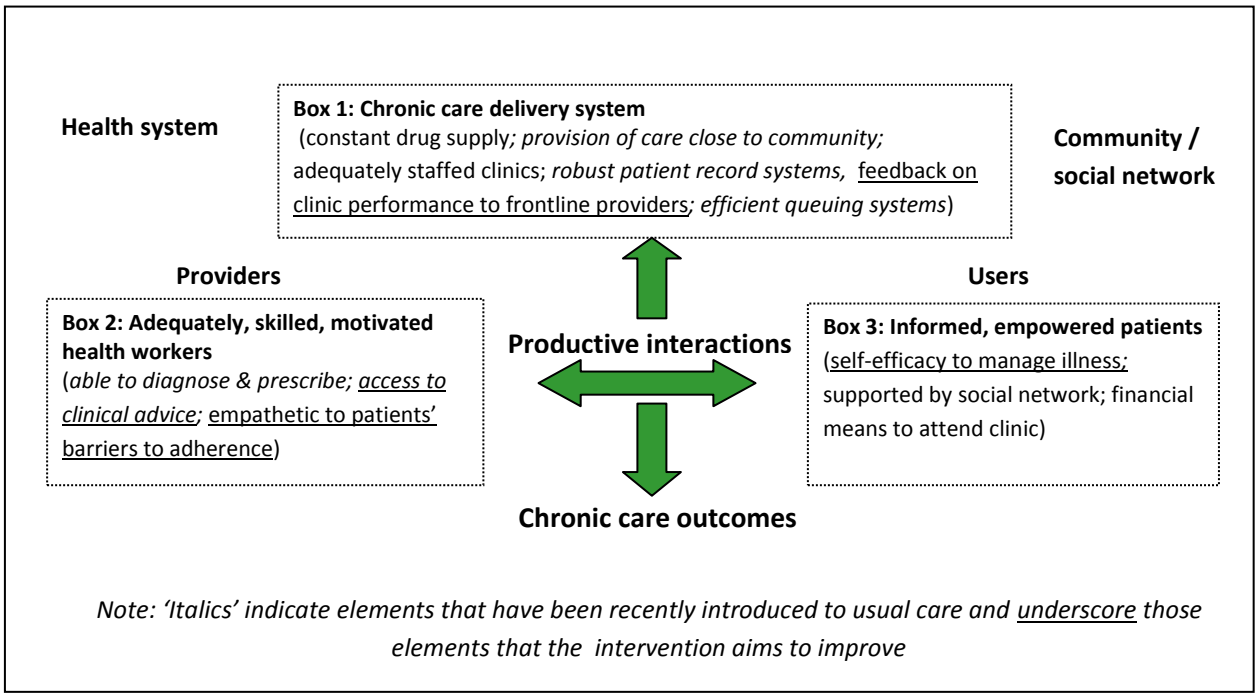
Efforts to strengthen chronic disease management in low and middle income countries have focused primarily on HIV & TB treatment, often with heavy reliance on lay health workers to support patient adherence, varying from the often didactic directly observed therapy (DOTS) to adherence counselling. In South Africa, LHWs have played a crucial role in the provision of effective HIV and TB care and in scaling-up treatment by: a) pre and post-test counselling; b) providing adherence counselling; c) administering treatment; d) assisting

patients to navigate their engagement with health staff and the various processes in a facility, and; e) tracing defaulters[10-13].

There is evidence on range of strategies carried out by LHW or other cadres to improve retention in care, self-management by patients, and accountability to patients. For example, a recent systematic review of RCTs concluded that text messaging received good acceptance and showed early efficacy in most studies, improving medication adherence, and health behaviour modification[14ii]. Lay health workers (behvaraz) in Iran aggregate patient data to on a year-long wall chart to monitor health outcomes (such as pregnancy outcomes, maternal and child mortality and causes). This is displayed on a wall of the clinic to enable both staff and patients to assess clinic performance. It is an important method to facilitate accountability of service providers to the local community[15]. Patient held 'health passports' have been shown to be feasible at the MRC/Wits Agincourt site, with nurses using the passport as a reliable source of information to update clinic records[16] facilitating patient 'ownership' of their health status. In discussion with the DoH and clinic staff these strategies will be considered as possible intervention activities for the clinic-based LHWs.

[ii] By 2007, 85% of the population in the MRC/Wits Agincourt research sub-district had access to a mobile phone.

Figure 1: Dimensions of chronic disease care (Adapted from Wagner model)



Note: 'Italics' indicate elements that have been recently introduced to usual care and underscore those elements that the intervention aims to improve

D. METHODS

D1. Methodological approach

As set out in the research objectives (section C2), this study will include a cluster-randomised controlled trial, to measure the effectiveness of the intervention in changing population level outcomes, and a realist evaluation to examine how context, actors, and process influence patient outcomes. Experimental methods answer the question: 'What interventions work best and have the most impact?' and make the assumption that the intervention will be transferrable since the study population is representative of a broader population. By contrast, in a critical realism approach the predominant question is: 'what works for whom under what conditions' and acknowledges that pre-existing health system structures and processes affect, and are affected by, the intervention actors. Given the importance of context, process and actors in the performance of the health system[17], it is not sufficient to assume the findings from a health systems randomised controlled trial are transferrable to other settings. Examining how context, process and actors shape outcomes, and building middle level theories to explain this influence, allows theoretical generalisation and an understanding as to whether, and how, an intervention may work in similar contexts, and what adaptations might be necessary.

The combination of a pragmatic cluster-randomised trial and a realist process evaluation poses a methodological dilemma: that the intervention will be affected by, and affect, activities in the local health system. To ensure that the LHW intervention achieves the best possible outcome, the implementation manager will aim to increase clinic staff's awareness of patient constraints; adapt LHW activities to suit the local context; and obtain local commitment. This engagement may change the local context (e.g. the perceptions and

functioning of the existing clinic staff). The local context and the intervention are likely to co-evolve; hence it will be important to document this interaction to understand whether outcomes are due to impact of the intervention or other changes (albeit probably minor and temporary) to the local context.

We will separate implementation activities from those of the evaluation by allocating these responsibilities to different teams. A researcher (the Project Site Manager) will be responsible for the realist evaluation, studying the implementation processes, as well as the overall day-to-day project management. An Implementation manager will be responsible for establishing the intervention, supervising and supporting the implementation staff (the LHWs), using best practice in implementation science as a guide. The role and contribution of the Implementation manager will be documented, by the researcher, in addition to how much the local context has changed as a result of the study. In this way we hope to understand the importance of the Implementation manager in improving patient outcomes. The role of the Implementation manager is justified as a sustainable component of the intervention, as any health system reform requires either a temporary 'change manager', or for existing managers to take on such a role. Should our understanding of, and response to, these methodological dilemmas change over the course of study, this will be documented.

D2. Study site

The trial will be based in the Agincourt sub-district of Mpumalanga Province, South Africa. Since 1992 the MRC/Wits Rural Public Health and Health Transitions Research Unit (Agincourt) has collected population data, with vital events (pregnancy outcome, death, migration) updated yearly. The total population under surveillance is about 90,000 people (52,592 older than 18 years) who live in 15,500 households in 26 villages within a rural, former Bantustan area, with high labour migration. A population-based survey at the site of 4230 adults over 18 years in 2010 found the prevalence of hypertension was 61%, diabetes 3% and HIV 27%. Moreover, 36% of the population had at least moderate risk of cardiovascular disease as a result of their blood pressure and other risk factors. (Gómez-Olivé pers. comm.) The public health system in the sub-district consists of five clinics and one health centre. For this trial a further health centre and clinic together with the population they serve (a population partly in the HDSS area) will be included. The eight facilities with their associated communities will comprise the clusters, with a ninth clinic used as a pilot site.

The Agincourt LINC office improves local, district and provincial access to, and use of, research findings. This office supports an active Community Advisory Group as well as Chronic Disease sub-committee, with representatives from each village, which review and advises on research.

D3. Study design

We will conduct a cluster-randomised trial in tandem with a detailed realist evaluation, drawing on global experience of evaluating complex interventions[18, 19]. The unit of randomisation will be a health facility and its surrounding catchment population. We propose to randomise eight clinics, four of which will receive the intervention. To achieve our primary outcome, we aim to both increase the proportion of the population under active management for their hypertension as well as reducing the level of blood pressure in those patients already receiving care. For this reason the outcome of the trial will be measured at population level, and we estimate that the trial has a power of above 80% to detect an 11% to 13% reduction in the proportion of the population at moderate or greater cardiovascular risk as a result of their blood pressure and other risk factors. Realist evaluation will provide data on adaption of the intervention to the context, individual and organisational processes of change as well as contextual factors that influence outcomes[8] Collecting data for the 15 months after the intervention has been introduced in each clinic will provide data on the sustainability of the intervention. The detailed study methods are described in the following sections.

E. DEVELOPING AND IMPLEMENTING THE INTERVENTION

E1. Developing the study intervention

An initial phase of community engagement will obtain the communities' permission to conduct the study (Fig 2; Box 1). A situation analysis within all the included clinics (Fig 2; Box 2) will gather information on the existing provision of care, and community and providers' understanding of hypertension, diabetes & HIV (Fig 2; Box 3) to ensure this study builds on prior work and that the intervention is appropriate. A separate proposal has been developed and an ethics application submitted for this early part of the study. The objectives are:

1. To describe chronic care as currently provided in primary health clinics in the Agincourt HDSS;
2. To understand what factors have facilitated effective chronic care from the perspective of the clinic nurses, district and province staff and whether any barriers remain;
3. To understand, from the patient's perspective, the key factors that have facilitated (or continue to hinder) access to care, and being adherent to medication;
4. To use the findings from objectives 1-3 to design possible activities of a clinic-based lay health worker intervention to support chronic care, particularly for those with hypertension;

In order to get further refinement of the intervention we will hold meetings with a range of stakeholders (national, province, district, sub-district, and clinic staff) to provide feedback the results of the situation analysis as well as the planned intervention. The discussion at these meetings will lead to further refinement of the intervention.

Figure 2: Phases of implementation

Exploration > adoption > development > installation > initial implementation > full operation

Box 1: Project set up phase (Month 1-2)	**Box 2**: Situational analysis of usual care (Month 3-5)	**Box 3**: Community engagement (Month 4-5)	**Box 4**: Intervention & material development; staff recruitment; and training; (Month 4- 6)	**Box 5**: Pilot & refinement of intervention (Month 7-9)	**Box 6**: Setting up intervention (Month 10)	**Box 7**: 15 months of full operation (Month 11-25)	**Box 8**: Data cleaning and analysis (Month 26-33)

Baseline population survey at month 5-6

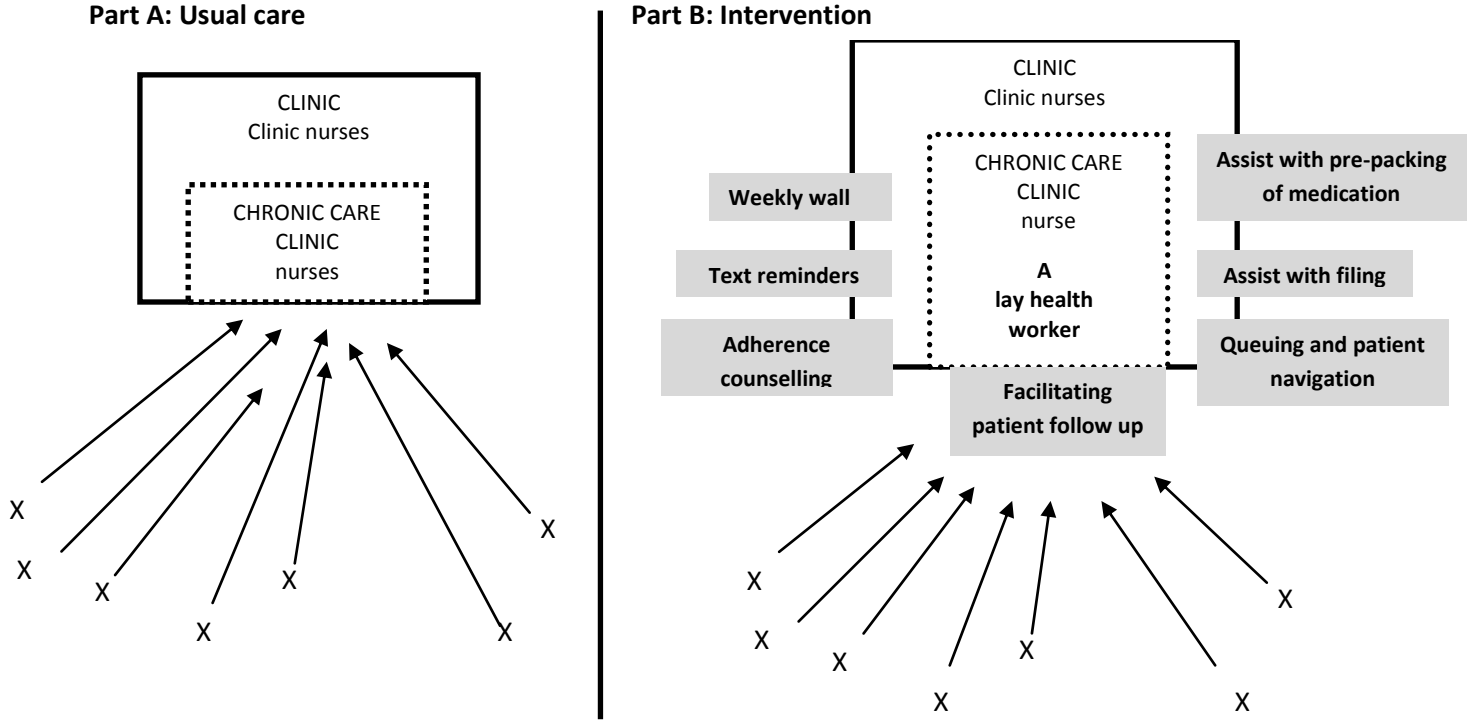
Follow up population survey at months 24-25

E2. Usual care and likely components of the intervention

Procedures in control clinics: 'Usual care' (Fig 3 Part A**)**

A recent programme, led by the national Department of Health, in three provinces (50 clinics, including the Agincourt-Bushbuckridge sub-district) has strengthened and integrated the provision of chronic care. The programme provided: focused training of nurses in chronic disease management; an equipment audit and replacement; human resources audit and supplementation; improving drug supply; and, re-organising the patient flow. Following these efforts, usual care within clinics now includes routine screening for hypertension, diabetes and HIV as well as prescription and dispensing of medication. All clinics (both intervention and control) will continue to implement Department of Health policy, including integrated care for chronic conditions.

Figure 3: Comparing usual care with intervention



Procedure in intervention clinics: 'Clinic-based lay health worker (LHW) providing support to chronic disease patients' (Fig 3 Part B)

The study intervention, broad components of which are outlined here, will be developed after the situation analysis has been conducted in partnership with local communities, health staff and the Department of Health. The intervention will function as part of the integrated chronic care system. It will focus on a LHW based in each clinic, who will act as a 'health system navigator'. Building on experience with lay counsellors in ART delivery[10], we expect that LHWs will provide adherence counselling, help to improve treatment literacy, use text messaging to remind patients of appointments[iii,20] , and assist with filing of patient records. LHWs will aggregate data from patient records on a weekly basis onto a yearly wall chart to enable staff and patients to monitor their facility's performance. The LHW will be supervised by an implementation manager, as well as the senior clinic nurse.

Table 1 below sets out the pathway of care, likely barriers to care, and suggested intervention activities aimed at reducing these barriers.

E3. Preparation for implementation

Intervention development will encompass material development including the aggregated data sheets to display on each clinic wall, tracking systems for collection, delivery, appointments, and defaulters, training materials for nurses and LHWs, mobile phone text health and adherence messages, and interview schedules (Fig 2; Box 4). Recruitment of the LHWs and data clerks will use behaviour vignettes as well as role plays to assess social interaction skills, receptivity to training, and ability to establish constructive relationship with patients. A pre-service training programme, led by the co-PIs and implementation manager (IM), will allow LHW and clinic staff to discuss system barriers to the provision of care, review existing patient-provider relationships, understand the aims and hypotheses underlying the intervention; practice required skills, as well contribute to further refinement of the intervention.

Before the trial is started we will test out the procedures for the trial in a pilot site close by (Fig 2; Box 5). This pilot site will start three months earlier, allowing time for lessons learnt to be applied as the full trial is started. The pilot clinic will continue to run for a full 15 months, allowing us to test each stage of the trial in the pilot clinic before full implementation. After any necessary modification to the tools and materials, the intervention will be introduced and established at four of the eight clinics (Fig 2: Box 6). The Implementation manager will be responsible for training the lay health workers and providing them with on-going support.

[iii] Already by 2007, some 85% of the population in the Agincourt research site had access to a mobile phone (Gómez-Olivé pers comm.).This study will not assess the cost-effectiveness of mobile technology in supporting adherence directly; instead it will assess the effectiveness of a package of activities of which mobile technology is one component.

Table 1: The pathway of care, likely barriers to care, and intervention activities.

Pathway of care	Problem along pathway that leads to loss of patient from care	Data collection methods for situation analysis	Likely LHW intervention activities to improve management of hypertension
Step 1: Hypertensive patient in the community	**Problem 1:** Doesn't go to clinic for hypertension or for any other reason	Focus group with community	Not the focus of the intervention, but: a) Knowledge of LHW snowballs out to those beyond the clinic; b) Survey – inform respondent of their BP& refer to clinic;
Step 2: Patient goes to clinic, for hypertension or another reason	**Problem 2:** BP not measured	Interviews with senior nurse Clinic checklist Interview with receptionist and existing lay health workers; Clinic observations Focus group with community;	LHW potentially to measure BP if not being done by receptionist;
Step 3: BP taken by receptionist or health care worker	**Problem 3:** BP not recorded; **Problem 4:** Patient and/or nurse not told BP level **Problem 5:** Patient not given medication, adherence counselling, and/or lifestyle advice, **Problem 6:** no return appointment made		a) Purchase cuffs or batteries for BP machines b) Training by nurse trainer; c) LHW to assist patients with navigation; d) Improving patient flow to ensure, for example, patient gets drugs;
Step 4: Given diagnosis, medication, and/ **OR** asked to come back for another test	**Problem 4:** Doesn't come back (no money, doesn't think it is serious) **OR** only comes irregularly (because of money, access, ill health, migrant worker)	Focus group with community	Will be followed up by LHW, with text reminders
Step 6: Comes back regularly >> but various problems prevent access to care or deter patient from regular attendance	**Problem 6:** Drug supply is erratic; **Problem 7**: Patient file is lost, so don't know patient history; **Problem 8:** Long queues / no drugs **Problem 9:** Nurses are overwhelmed by HIV patients, pay little attention to HT patients; **Problem 10:** Nurses are rude to patients /indifferent to needs to patients	Interviews with senior nurse Clinic checklist Interview with receptionist and existing lay health workers; Clinic observations Focus group with community;	LWH to assist with a) Ordering of drugs; b) Filing of patient record; c) Queue management; d) Facilitate patient pathway for (non-HIV) chronic patients; e) Workshop for nurses to increase their understanding of patient barriers to care organised by implementation manager; f) Wall chart to increase accountability
Step 7: Comes back regularly	**Problem 11:** Collects but doesn't take pills (BP is not reduced)		a) Counselling by LHW b) LHW send reminders /texts.
Step 8: BP is reduced			

E4. Implementing the intervention in a complex adaptive health system

Participating clinics

We intend to approach the following clinics to participate in the trial: Agincourt, Xanthia, Kildare, Lillydale, Justicia, Belfast, Cunningmore A and Cork . The clinic at Arthurstone will be approached to act as a pilot clinic, while the clinic at Oakley is a reserve clinic in case a clinic drops out early in the trial. Oakley, Cork, and Arthurstone clinics are situated on the borders of the study area and their catchment area includes villages in the study site.

Patient inclusion and retention

Adults over 18 years and residing in the Agincourt sub-district will be eligible for inclusion. All adults attending a clinic will be screened and offered treatment as usual by clinic staff, which, for those with hypertension, usually involves monthly clinic visits (or 3-monthly for stable patients).

Individual health records

As part of the intervention, if necessary, the LHW will assist with maintaining patient record filing system. If this assistance is insufficient and patient data is not maintained, a patient-held passport will be considered. Patient data from the records, collected by the lay health workers, will be used to populate clinic wall charts.

Quality control of implementation of intervention

In line with current implementation science[21], the implementation manager will: assess the alignment between intervention and the community; pay careful attention to the quality of communications between clinicians, trainers and implementing staff, and permit modification of non-core components (for example, design of LHW patient record system) to encourage local ownership. Core non-modifiable components are: appropriate staff selection, pre-service and in-service training, ongoing consultation and coaching, staff and programme evaluation. Key issues to enable full operation (Fig 2; Box 7) at each site will include establishing:

i. a data management system that is simple and easily replicable, given resources in similar rural settings;
ii. a culture of team working (between the nurses, LHW, and CHWs) and,
iii. collective responsibility for health outcomes and clinic performance.

The implementation manager will be responsible for facilitating the development of a functional relationship between the LHW and clinic staff as well as the performance management and evaluation of the LHW.

Competencies required to intervene in a complex adaptive system(CAS)

Despite the growth in organisational level interventions to improve the delivery of chronic care and patient outcomes, these strategies have met with varying success. There is evidence that the variation in outcomes is due to the fact that interventions often do not take into account the complexity of the clinical systems in which patients receive care[22]. The complex

adaptive systems (CAS) framework has been used to describe clinical micro-systems as a theoretical model to improve our understanding[23 24]. This framework suggests that clinical settings are environments in which individuals learn, inter-relate, self-organise and co-evolve in response to their internal and external environments. This framework individuals ability to achieve these competencies (learn, inter-relate, self-organise and co-evolve) are critical considerations in designing, and implementing interventions. Using this framework, Table 2 sets out the elements of a complex adaptive system, and Table 3 lists, as examples, skills and competencies the implementation manager and the lay health worker will have to demonstrate to effectively work with the existing clinic team and implement the possible activities listed in Table 1 and Figure 3. .

Table 2: Characteristics of a complex adaptive system Source: Leykum 2007

Characteristic	**Definition**
Agents who learn	People who can and will process information, as well as react to changes in information
Interconnections	Change in patterns of interactions, including non-verbal communication among agents
Self-organisation	Order is created in a system without explicit hierarchical direction
Co-evolution	The system and the environment influence each other's development

Table 3: Intervening in a complex adaptive system: Examples of the implementation manager and lay health worker

CAS charac-teristic	**Competencies and activities within the complex adaptive system (CAS) of the clinic setting**	
	Implementation manager (IM)	**Lay health worker (LHW)**
Learning	The IM will have to learn / understand the processes and systems for providing chronic care in each of the 4 clinics, the peculiarities of the specific clinic, the patient context and constraints, the health system context and constraints, and the intention of the intervention;	The LHW will have to learn / understand the existing processes and systems for providing chronic care in his/her clinic, the patient context and constraints, the intention of the intervention, and how to carry out the specific activities (e.g. updating the wall chart)
Inter-connecti ons	The IM will have to engage with the clinic supervisors, senior nurse and clinic staff in order to develop a workable intervention, in a way that ensures team functioning. The IM will have to recruit, train, supervise, mentor and appraise the work of the LHWs, interacting effectively to support the LHW to deal with challenges, and to ensure a culture of team work and collective responsibility;	The LHW will have to work with the clinic staff, other CHWs, facilitating a team culture. The LHW will have to work with patients, understanding their challenges, encouraging their regular attendance at the clinic and adherence to the medication (through for example, counselling and text reminders).
Self-organisat ion	The IM will have to organise the use of her/his time effectively, taking initiative in response to health system constraints or features of the patient context, without explicit hierarchical direction, in order to train, supervise, mentor, and appraise the work of the LHW.	The LHW will have to organise the use of her/his time effectively, taking initiative in response to health system constraints or features of the patient context, without explicit hierarchical direction, in order carry out the intervention activities
Co-evolution	As clinic supervisors, senior clinic staff, and LHW work with the IM to develop a feasible	As LHW works with the clinic staff and patients the intervention activities, and relationships

CAS charac-teristic	Competencies and activities within the complex adaptive system (CAS) of the clinic setting	
	Implementation manager (IM)	**Lay health worker (LHW)**
	and useful intervention, the intervention itself, and relationships between staff will co-evolve, hopefully leading to effective team functioning to improve the provision of care;	between staff will co-evolve. The LHW will have to adapt to changes, and assist in steering those changes so they lead to further improvements rather than deterioration (e.g. a fluctuation in nursing staff at the clinic; or a change in data collection procedures at the clinic.)

E5. Staff recruitment, training and replacement

Recruitment of the lay health workers, data clerks and qualitative field workers will use behaviour vignettes as well as role plays to assess social interaction skills, receptivity to training, and ability to establish constructive relationship with patients.

Before the trial is launched, a one-day workshop led by the co-PIs and Project Site Manager will allow all the research staff (lay health workers, data entry clerks and qualitative field workers) and some of the clinic nurses to discuss system barriers to the provision of care, and review existing patient-provider relationships, as well contribute to further refinement of the intervention. Two further days of training for all the research staff will concentrate on the background to the research question, the aims and hypotheses underlying the intervention, and the skills that will be required of research staff. The Implementation manager, supported by the management team and the Project Site Manager, will lead a further two days training for just the lay health workers focusing on their role in the clinics. If LHW need to be replaced during the study, additional training sessions will be conducted.

E6. Standard operating procedures

All staff will be provided with written job descriptions setting out their responsibilities. Written standard operating procedures (SOPs) will be prepared for the individual activities.

F. EVALUATION OF EFFECTIVENESS

F1. Randomisation

Randomisation will take place in the community, probably at a meeting of clinic staff and members of local clinic committees. Eight primary health care facilities will be randomised. After showing sheets of paper with the names of the clinics to the meeting, they will be put into sealed envelopes, several community members will be invited to shuffle the envelopes, which will then be put into a bag and seven other community members will each in turn choose one envelope, and the chosen clinic allocated to a slot in the order of intervention clinic, control clinic, intervention clinic etc..

F2. Study outcomes

The primary outcome of the trial reflects the concepts behind the 2011 SA guidelines[1] and focuses on the prevalence in the population of people at moderate or greater cardiovascular risk. However, we are constrained by the practicalities of measuring all the variables used in the SA Guideline in a population based survey, (for example, we do not have the resources to make a diagnosis of target organ damage or of the metabolic syndrome). We will therefore use a modified definition of people at moderate or great added risk which is shown in Tables 4 and 5 below. The **primary outcome** will be the change in the percentage of people in the population who have elevated blood pressure that is combined with other factors resulting in a risk profile that indicates moderate or greater added risk of cardiovascular disease. as indicated by the shaded cells in Table 4. This includes individuals with either: a systolic blood pressure of 160 and above, diastolic of 100 and above, systolic blood pressure of 140-159 plus one or more risk factors, or diastolic blood pressure 900-99 plus one or more risk factors. These data will be obtained from two population surveys (one before the start of the trial and one after the trial ends).

Table 4. Modified South African Guideline: Stratification of cardiovascular risk in patients with hypertension (defined as SBP>139 or DBP>89)

Blood pressure (mmHg)	**Presence of risk factors or other conditions**			
	No risk factors	One or two risk factors	Three or more risk factors or diabetes	Associated clinical conditions
SBP 140 -159 or DBP 90-99	Low Added Risk	Moderate Added Risk	High Added Risk	Very High Added Risk
SBP 160 -179 or DBP 100-109	Moderate Added Risk	Moderate Added Risk	High Added Risk	Very High Added Risk
SBP 180 + or DBP 110+	High Added Risk	Very High Added Risk	Very High Added Risk	Very High Added Risk

Table 5 .Modified South African Guideline: risk factors and associated clinical conditions

Risk factors	Associated clinical conditions
Age/sex: Men >55 yrs, Women> 65 yrs	Self-reported coronary heart disease
Smoking at least every day	Self-reported heart failure
Dyslipidaemia	Self-reported Stroke or TIA
Family history of CVD* (M<55yrs, W<65yrs)	
Waist circumference M>94cms, w>80cms	

*Cardiovascular disease

Secondary outcomes obtained from the population surveys will be:

- change in proportion of the population with undiagnosed hypertension,
- change in the proportion of the population reporting they had had their blood pressure measured,
- change in the proportion of the population reporting that they are using medication for hypertension
- changes in the proportion of the population at different levels of blood-pressure-related cardiovascular risk by age group and sex
- Change in the proportion of people in the population reporting that they have attended a clinic in the last year.

Secondary outcomes obtained from data collected in the clinics will be:

- the proportion of people with diagnosed hypertension using primary care clinics who are adherent to prescribed medication, defined by recorded collection of prescriptions.
- Retention in care of people with diagnosed hypertension defined by the proportion of appointments kept during the study period.

Gender and age of attendees and patterns of health seeking behaviour for hypertension treatment will also be recorded.

F3. Statistical power

The two cross-sectional surveys, which will be used to assess the effectiveness of the intervention, will each include at least 4000 participants, giving approximately 500 people in each cluster. We adopted the use of the coefficient of variation (standard deviation of the cluster means divided by the overall mean) as used in similar study settings when we cannot get a good intra-cluster variation[25-27]. For a background prevalence of 36% and a coefficient of variation of 0.132 (error margin 4.5% (0.132±0.045)) based on data collected in the same site in 2010, different scenarios of proportions of moderate or greater risk patients at the end of trial in the control and intervention arms and their associated power are shown in Table 6. Based on the scenario of a 15% difference (i.e. 36% control vs 21% intervention), the highest power will be 97.4%. and we will have power of above 80% (94% and 88% respectively) to detect an 11% to 13% absolute reduction of people at moderate or greater cardiovascular

risk. These calculations assume that the coefficient of variation will be similar in the two groups and that effects of the interventions are similar across clusters.

Table 6: Power matrix of different scenarios

	Control	**"36%" No change**
	CV	**0.132**
Intervention	"5% difference" 31%	**20.7**
	"10% difference" 26%	**68.6**
	"12% difference" 24%	**85.4**
	"15% difference" 21%	**97.4**
	Control	**"34%" 2% change**
	CV	**0.132**
Intervention	"3% difference" 31%	**10.5**
	"8% difference" 26%	**52.7**
	"10% difference" 24%	**75.4**
	"13% difference" 21%	**94.2**
	Control	**"32%" 4% change**
	CV	**0.132**
Intervention	"1% difference" 31%	**4.3**
	"6% difference" 26%	**35.2**
	"8% difference" 24%	**58.4**
	"11% difference" 21%	**87.7**

F4. Population surveys

Two population surveys will be carried out (one before the intervention starts and one after it finishes) to estimate the primary outcome of the trial. In each survey a random sample of 5000 people aged over 18 years will be selected from census records, to allow for 20% attrition, so that 4000 individuals will be included in each survey, contributing approximately 500 people in each of the 8 clusters. From previous experience in this research setting, we expect good participation (~80%) and long term follow-up rates of ~90%. The sample will be disproportionately stratified to ensure adequate representation of males and older people. This is necessary because the population pyramid is heavily weighted to younger people and there are fewer men than women amongst older adults due to labour migration.

Each consenting participant in the surveys will have their blood pressure measured by trained field staff three times using a BOSO blood pressure machine. (BOSO machines are already in use for other research projects on the site and are approved for research use by WHO). The questionnaire will be brief, so as to allow the survey to be completed within a ten week period before the start of the intervention. Information will be collected on respondents' use of

primary care clinics in the last 12 months, and their preferred clinic. Information on factors related to cardiovascular risk will be collected and respondents will also be asked if they have had their blood pressure checked by a doctor or nurse in the last year, if they have ever been told they have hypertension, and if they are using medication for hypertension.

F5. Calibration and servicing of automated BP machines

All the blood pressure machines used for the survey will be calibrated and serviced as necessary before each of the two population surveys. To avoid interruptions in the survey due to machines breaking down we will purchase two extra machines.

F6. Data entry, management and storage

All quantitative data will be entered in the field site by Agincourt staff, using double data entry. All personal identifiers in the quantitative data will be encrypted once the data has been entered and cleaned. Encryption codes will be held securely in the Agincourt under the guardianship of the Data Manager**.** After completion of data collection, cleaning and encryption, the data files will be placed with other legacy data on the data warehouse server in the Agincourt research site. Data held here are backed up daily, with a supplemental weekly back-up transferred to an offsite location. In addition copies of the dataset will be transferred to DVD and held in a secure location.

F7. Analysis

A full analysis plan will be agreed with the Management Team and the Trial Steering Committee before starting analyses. The primary analysis will be on intention to treat and will be carried out using STATA software. Descriptive analyses will report distributions of categorical variables and summary measures of continuous variables. Baseline values in the intervention and usual care arms will be described.

To allow for confounding, analysis of the primary outcome (binary, as defined above) will use the two stage regression model described by Hayes & Moulton[28]. Firstly, two logistic regression models for control and intervention clusters that include covariates will be fitted separately. Covariates in the two models will be both cluster level factors (e.g. clinic size) and aggregated individual level factors (e.g. gender and age). Secondly, observed and fitted values for each cluster will be compared by computing residuals. Where there are residual differences, a t-test at the cluster level will be done to test the effect of the intervention. Secondary outcomes will be analysed as described above for the primary outcome. They will include: proportion of population in each cluster screened (data from the population survey), adherent to medication and retained in care (from records of clinic activity). Adherence will be defined by using the records of pharmacy refills.

We expect relatively few missing values, especially for individual demographic data, because this trial is taking place in a health and demographic surveillance site. Multiple imputation methods for cluster randomised trials with few clusters are not well developed,

although this is a growing research field. We will therefore only analyze complete cases but when drafting the analysis plan we will also check the literature for appropriate methods of imputation in sensitivity analyses if relevant.

F8. Clinic Census Link

Although the two population surveys described above will sample respondents from each geographic cluster, patients often attend a clinic in a neighbouring community. Part of the data collection for this trial will involve monitoring which respondent attends which clinic. Data entry clerks in both the intervention and control clinics will be responsible for collecting identifiers of all consenting clinic attendees to allow their identification on the Agincourt census database. The linked data will enable us to understand patterns of clinic use which may not be geographically determined, as well as differential clinic use associated with gender, age, and relative wealth of clinic users and to monitor whether patterns of clinic use change over the 15 months. From a previous study in the area it is known that the most important identifiers to do the posterior link with the census are: name, surname, age or date of birth, sex, village, cell phone number, national ID number, and name of another person living in the house. The system will be piloted in early 2013 in two clinics to the refine the details of how the computerised system will best be implemented.

G. REALIST EVALUATION OF INTERVENTION AND IMPLEMENTATION

G1. Background

In addition to collecting the outcomes described above, we will conduct a theory-driven evaluation to understand the causal processes leading to change (or the lack of change); to explain 'why' and 'how'. To guide the evaluation, the study will draw on the 'health policy triangle' framework[17] in which the context, process, actors as well as the policy or in this case the intervention, are acknowledged to influence outcomes. In addition, the study will take a realist approach and explore the 'mechanism' by which the intervention has its effect[29]. Here the study will draw on theory of complex adaptive systems[22 30] in which the non-linearity of the implementation-outcome relationship is seen as due to the adaptability (or unpredictability) of actors and the wide range of influencing factors within a complex adaptive system. Experience, learning, context, and inter-dependencies are assumed to influence the extent to which the implementation teams and patients are able to learn, inter-connect, self-organise and co-evolve, and hence improve patient outcomes (as described in Tables 1 and 2 above).

G2. The objectives

The objectives of the realist evaluation are:

1. To examine how the different aspects of the intervention function (e.g. wall chart, text reminders) in the different clinics and the mechanisms by which the intervention was (un)able to increase the proportion of patients whose hypertension was better controlled;
2. To examine the extent to which the actors (implementation manager, LHW, clinic supervisors, clinic staff and patients) were (un)able to work within the context of a complex adapting system (by learning, interacting, self-organising and the co-evolution of the team) to establish sustained improvements in care;
3. To explain how the implementation processes (e.g. quality of engagement with clinic & district staff, training & recruitment of staff, activities of implementation manager) shaped the intervention and its functioning;
4. To explain the role of the local context (including the organisational culture within the clinic, the motivation and values of the staff, local health system functioning, and the influence of sub-district and district staff) in determining outcomes;

The evaluation will aim to determine whether failure to improve patient outcomes is due to: a) core implementation factors (inadequate staff selection, pre-service and in-service training, on-going consultation and coaching, feedback to staff of their performance while the intervention is on-going, as well as retention of staff); b) the unsuitability of the intervention to the local context (i.e. patient, health system and community factors); and/or c) intrinsic weaknesses in the intervention, such that it is likely to fail in other settings. The evaluation

will also aim to explain any difference in patient outcomes between clusters (clinics). It will also aim to identify which particular contextual factors are likely to be important to consider when transferring the intervention to other settings.

G3. Study design and sampling

The evaluation will use a case study design, with each clinic and its attending population being a single case. The study will use a range of qualitative methods including interviews and observation. As is standard in qualitative methods, sampling will be purposive, designed to ensure representation of a range of views and inputs. The figures provided below on sample sizes are preliminary; interviews and observations will continue until a point of redundancy is reached (i.e. no new information is emerging). Sampling strategies will be designed to include those who know their diagnosis but have withdrawn from treatment, migrants who struggle to maintain regular clinic attendance, as well as regular clinic attendees.

G4. Data collection methods

Observation of clinic activity and patient pathway

We will carry out three 3-day observation visits, spread over the 15 months of the intervention in all nine clinics in the study (n=81). The aim will be to observe the operation of the intended intervention activities, to describe the patient pathway in each clinic, and to describe the health system facilitators and barriers to hypertension care. We will also observe the functioning of the clinic, its organisational culture, the relationship between nurses, the lay health worker, and the patients. We are interested in the points in the patient pathway where there are barriers to access to care, for example, whether, where, and when blood pressure is measured of patients not attending the chronic disease clinic, whether results of measurement are recorded, and what action is taken with respect to blood pressure levels above the normal cut-off.

Table 7 sets out the eight steps in the pathway of care (as in Table 1 above), showing the evaluation data to be collected along the pathway. The first column details the steps on the pathway from a patient with hypertension in the community through to the patient successfully on medication with lowered BP. The second column details the various problems along the care pathway that can cause to the patient being lost from care. The third columns indicates the likely intervention activities by the LHW in order to improve retention in care; the fourth and fifth the data collection in the evaluation to understand barriers and facilitators to intervention activities achieving the intended improvements.

Interviews with lay health workers and the implementation manager

Throughout the 15 months of the intervention, the LHWs and the Implementation manager will be interviewed once a month by the Project Site Manager, at a convenient time after the clinic has closed (n=19x15). The aim of these interviews will be to explore: functioning of the intervention, the usefulness of the intervention activities, adaptations to the context, barriers and facilitators to care, the functioning of the clinic (routines, drug stock outs, staff turnover,

equipment), different actor assumptions of the nature of the problems and how best to address them, the relationship between the various actors, and other changes are taking place in the clinic. The interviews with the implementation manager in addition will examine: quality of communication during community engagement and implementation; suitability of staff appointments, training, coaching; staff performance assessments; and the team's success in removing any system barriers.

Patient exit interviews

We will carry out brief exit interviews both with patients who have attended the chronic disease clinic and have a diagnosis of hypertension. We will interview five patients per observation day, leading to a total sample of 405 (5x3x3x9). We will ask whether they had their blood pressure measured, what advice they have been given, whether they have been given any medication (drug stock-outs are reportedly a problem), and whether a return visit has been booked.

Patient cohort interviews

We will identify three cohorts of patients that we will aim to interview with a semi-structured topic guide twice across the 15 months period; at around 3-5 months and again at around 12-15 months.

i. One cohort will be recruited through the LHW in the intervention clinics and will comprise both patients who only intermittently adhere to their medication and patients who have a high level of adherence (n=36).
ii. The second cohort will be recruited from the results of the baseline population survey and will comprise individuals who report that they normally attend one of the clinics in the control arm of the study and report that they have hypertension when interviewed (n=36).
iii. The third cohort will also be recruited from the baseline survey and will include individuals with raised blood pressure on measurement who either do not report that they have hypertension, or who know their diagnosis but are not taking treatment. For ethical reasons, this group will be informed at the time of the baseline survey that their results indicate that they may have hypertension, and should seek care (n=36).

We will stratify the recruitment of the three cohorts by age group (two groups), gender and household asset scores (two groups) and aim to recruit 4 patients in each of the eight strata. The semi-structured interviews with all three cohorts will explore experience of care including the LHW service, patient and health system barriers to care, patient costs of accessing care, in order to explain differential access to health care.

Interviews with health personnel

We will carry out two interviews with the senior nurse in clinics, clinic supervisors & PHC programme staff once early in the trial period and once as the trial comes to an end. The baseline interviews will include exploring changes to clinic routines, their expectations of the research, and any concerns they have, as well as their perception of how the clinic currently manages patients with hypertension, problems and how best to address them The final

interview will explore their experiences of taking part in the research and their perceptions of whether there has been any change over

Table 7: Pathway of care showing points at which the effective management of hypertension can fail

Pathway of care	**Problem along pathway that leads to loss of patient from care**	**Likely LHW intervention activities to improve management of hypertension**	**Process evaluation data collection methods**	
			Intervention clinics	**Control clinics**
Step 1: Hypertensive patient in the community	**Problem 1:** Doesn't go to clinic for hypertension or for any other reason	Not the focus of the intervention, but: a) Knowledge of LHW snowballs out to those beyond the clinic; b) Survey – inform respondents of their BP, and if necessary refer to clinic);	Identified during survey, and a small sample followed up for more detailed interview	
Step 2: Patient goes to clinic, for hypertension or another reason	**Problem 2:** BP not measured	LHW potentially to measure BP if not being done by receptionist;	a) Clinic observations; b) Interviews with LHWs	a) Clinic observations;
Step 3: BP taken by receptionist or health care worker	**Problem 3:** BP not recorded; **Problem 4:** Patient and/or nurse not told BP level **Problem 5:** Patient not given medication, adherence counselling, and/or lifestyle advice, **Problem 6:** no return appointment made	e) Purchase cuffs or batteries for BP machines f) Training by nurse trainer; g) LHW to assist patients with navigation; h) Improving patient flow to ensure, for example, patient gets drugs;	a) Monthly interview LHW; b) Two interviews with senior nurse in 15 months; c) Patient exit interviews; d) Cohort interviews	a) Two interviews with senior nurse in 15 months; b) Patient cohort interviews;
Step 4: Given diagnosis, medication, and/ **OR** asked to come back for another test	**Problem 4:** Doesn't come back (no money, doesn't think it is serious) OR only comes irregularly (because of money, access, ill health, migrant worker)	Will be followed up by LHW, with text reminders	a) From census clinic link and patient record data; b) Patient cohort interviews to understand why	
Step 6: Comes back regularly >> but various problems prevent access to care or deter patient from regular attendance	**Problem 6:** Drug supply is erratic; **Problem 7**: Patient file is lost, so don't know patient history; **Problem 8:** Long queues / no drugs **Problem 9:** Nurses are overwhelmed by HIV patients, pay little attention to HT patients; **Problem 10:** Nurses are rude to patients /indifferent to needs to patients	LWH to assist with g) Ordering of drugs; h) Filing of patient record; i) Queue management; j) Facilitate patient pathway for (non-HIV) chronic patients; k) Workshop for nurses to increase their understanding of patient barriers to care organised by implementation manager; l) Wall chart to increase accountability	a) Monthly interview with LHW; b) Exit interviews; c) Two interviews with senior nurse; d) Patient cohort interviews;	a) Two interviews with senior nurse; b) Patient cohort interviews;
Step 7: Comes back regularly	**Problem 11:** Collects but doesn't take pills (BP is not reduced)	c) Counselling by LHW d) LHW send reminders /texts.	Patient record data in both intervention and control clinics	
Step 8: BP is reduced				

the 15 months. Clinic staff, supervisors and sub-district staff will be asked to complete a structured questionnaire on motivation. These interviews will be carried out in English (all health professionals are fluent in English). We will also carry out interviews with the district and sub-district staff once during the study to determine their perceptions of the intervention and its usefulness.

Table 8 links study objectives with the data collection methods and data that will be used to achieve the objectives.

Table 8: Objectives, data collection methods and data

Objectives	Data collection method	Data
1. To explain how the different aspects of the intervention function in the different clinics and the mechanisms by which the intervention was (un)able to increase the proportion of patients whose hypertension was better controlled;	Observation of clinic activity; Interviews with LHW & IM, clinic staff, sub-district & district staff; Patient exit interviews; Patient cohort interviews;	Explanatory descriptions of: • routine and intervention activities within the clinic; • patient pathways and points at which patients 'fall out' of care; • how intervention activities influence health outcomes; • patient experience of clinic routines & community factors that affect health outcomes
2. To examine the extent to which the actors were (un)able to work within the context of a complex adapting system (CAS) (by learning, interacting, self-organising and the co-evolution of the team);	Observation of clinic activity; Interviews with LHW, IM, clinic staff, sub-district and district staff	Explanatory descriptions of • behaviour and interaction of staff, work patterns, and changing behaviour over time; • role and influence of sub-district & district staff in supporting (or not) to operate as effective agents in a CAS;
3. To explain how the implementation processes shaped the intervention and its functioning;	Observation of clinic activity; Interviews with LHW & IM, clinic staff, sub-district & district staff;	Explanatory descriptions of: • implementation processes, how they differ across clinics and their effect on clinic routine and intervention activities;
4. To explain the role of the local context (including the organisational culture, motivation, values, local health system functioning, and the influence of sub-district and district staff) in determining outcomes;	Observation of clinic activity; Interviews with LHW, IM, clinic staff, sub-district and district staff using tools to assess organisational culture & motivation	Assessments of how staff motivation and organisational culture varies from clinic to clinic; Explanatory descriptions of routine health system functioning & its influence on the effective of intervention activities & associated outcomes

G5. Data entry, management and storage

All qualitative data will be recorded as either field notes, or on tape during interview and later transcribed for electronic storage. Transcripts of taped interviews in Shangaan will be simultaneously translated and transcribed by the field workers involved. Transcripts of

interviews in English will also be transcribed by the interviewer involved. Field note books, tapes with data and electronic databases will be stored at the Centre for Health Policy, with access limited to researchers named in the consent forms. Anonymised data will be entered in Atlas.ti. Transcriptions of qualitative data will be anonymised, with all identifiable names removed and with codes used to identify the participants and placed in the data archive described above (F6).

G6. Analysis

A case study approach will be used to compare and contrast experience in the four different clusters. Combining qualitative and quantitative data will allow the development of within- and across-cluster analyses to explain and interpret outcomes. Individual data from the census-clinic link (gender, age, location, health seeking behaviour) will be matched with data from the clinic records (clinic attendance, BP, medication and adherence), and data from patient exit interviews and the patient cohort interviews will be added, where available for specific patients. This analysis will enable individual health outcomes to be explained by information on patient barriers. The patient data, aggregated to clinic level, will be linked to information on clinic factors (such as staff turnover, motivation, organisational culture, drug stock outs, as well as availability of equipment) as well as descriptions of how the various aspects of the intervention function in order explain outcomes. This will be complemented by descriptions of the various actors roles and behaviour within the complex adaptive system, including their ability to learn, inter-connect, self-organise and co-develop useful behaviours, as well as the role of implementation processes in shaping local actor responses.

Initial analytical themes and categories will be determined *a priori* from existing conceptual frameworks including relevant literature (on complex adaptive systems, street level bureaucracy, organisational culture, health seeking behaviour, retention in care, and key health system elements in the provision of chronic care), the research aims and objectives, as well as issues emerging from the raw data. To strengthen validity, two researchers will independently develop their own coding categories, followed by a discussion of similarities and differences. A process of returning to the original data to confirm emerging analyses will ensure the robustness of analytical interpretation and development of middle range theories. At each stage of the analysis, both patient and clinic level data will be compared and contrasted within and across cases. Where information gathered by different methodologies or groups is contradictory rather than complementary, divergences will be outlined and discussed in meetings and – where necessary – reports. The process of analysis will be collaborative, conducted iteratively, with regular sessions to discuss emerging analyses.

H. COMBINING EVALUATIONS OF EFFECTIVENESS AND PROCESS WITH COSTS

In the final analysis, the aggregated patient data and the qualitative descriptions of clinic functioning will be linked with the results from the relevant cluster of the population survey, to determine whether the intervention and clinic performance has improved population level outcomes. A cost-consequence analysis will be undertaken showing an array of output measures alongside the costs. As there is potential for multiple, key outcomes that cannot be aggregated into a single outcome, this will enable us to show the trade-offs associated with each scenario. We will collect patient level costing data, examining the cost implication for the public sector as the funder of primary health care, and costs to the patient of participating in the intervention. The comparator for the analysis will be current practice as assessed by the situation analysis which will include a detailed costing study. Costs (South African Rand) will be collected over the course of the study, and inflation used to adjust all prices to the final year of the study. As there is likely to be a range of patient-level costs and outcomes, non-parametric bootstrapping will be used to assess the effect of variation in patient-level outcomes on the costing results.

Table 9 lists the study outcomes and shows which data collection method will collect specific data on each outcome.

Table 9: Study Outcomes and Data Collection Methods

Data	Population survey	Clinic link	Patient records	Clinic obs	Exit int'views	Patient int'views (Cohort)	LHW int'views	Health worker int'views	Community advisory group
Change in population control of BP	X								
No. with undiagnosed BP	X								
Self reported screened	X				X				
Self-report on medication	X								
No. of people with BP measured			X	X					
No. of people who have BP recorded			X	X					
Adherent to treatment [a]			X						
Retention [b]			X						
Inequities in clinic use	X	X				X			
Clinic functioning incl. drug stock-outs, filing system				X	X	X	X		
Functioning of follow up tracking system				X	X	X	X		
Functioning of wall chart				X			X		
Patient experience of care (barriers to access)					X	X			
Experience of implementation & intervention					X	X	X	X	X
Cost of intervention				X				X	
Patient costs of access					X	X			

[a] Defined by recorded collection of medication over study period

[b] Defined by proportion of appointments kept during study period

J. RESPONSIBILITIES OF APPLICANTS AND PROJECT STAFF

J1. Principal investigators

Prof. Margaret Thorogood will be responsible for overall oversight and co-ordination of activities. Dr Jane Goudge, the South Africa based co-PI, will be responsible for the design and implementation of the evaluation.

J2. Co-applicants (alphabetical)

Dr Melanie Bertram, will be responsible for designing and leading the cost-consequence analysis. She will be assisted by Mandy Maredza, who will be responsible for collecting the costing data and conducting the analysis. Prof Tobias Chirwa will provide advanced statistical support in South Africa, and will be responsible with Prof Eldridge for preparation of the statistical analysis plan. Prof Sandra Eldridge will be responsible for the oversight of the statistical analysis and preparation of the statistical analysis plan. Dr Xavier Gómez-Olivé will be responsible for the implementation and coordination of all field activities and will also assist in the analysis and interpretation of study results. Eustasius Musenge, will carry out the statistical analysis of the outcome data with the support of Chirwa and Eldridge. Prof Steve Tollman will be responsible for overseeing an effective knowledge translation strategy, Rhian Twine, will take the lead in seeking the engagement of community and service providers in the process of developing the intervention

J3. Project implementation staff

The intervention staff will include one or more lay health workers at each intervention clinic, and an Implementation manager (a health professional) responsible for all five intervention clinics who will train and provide support to the LHWs, and other clinic staff where requested.

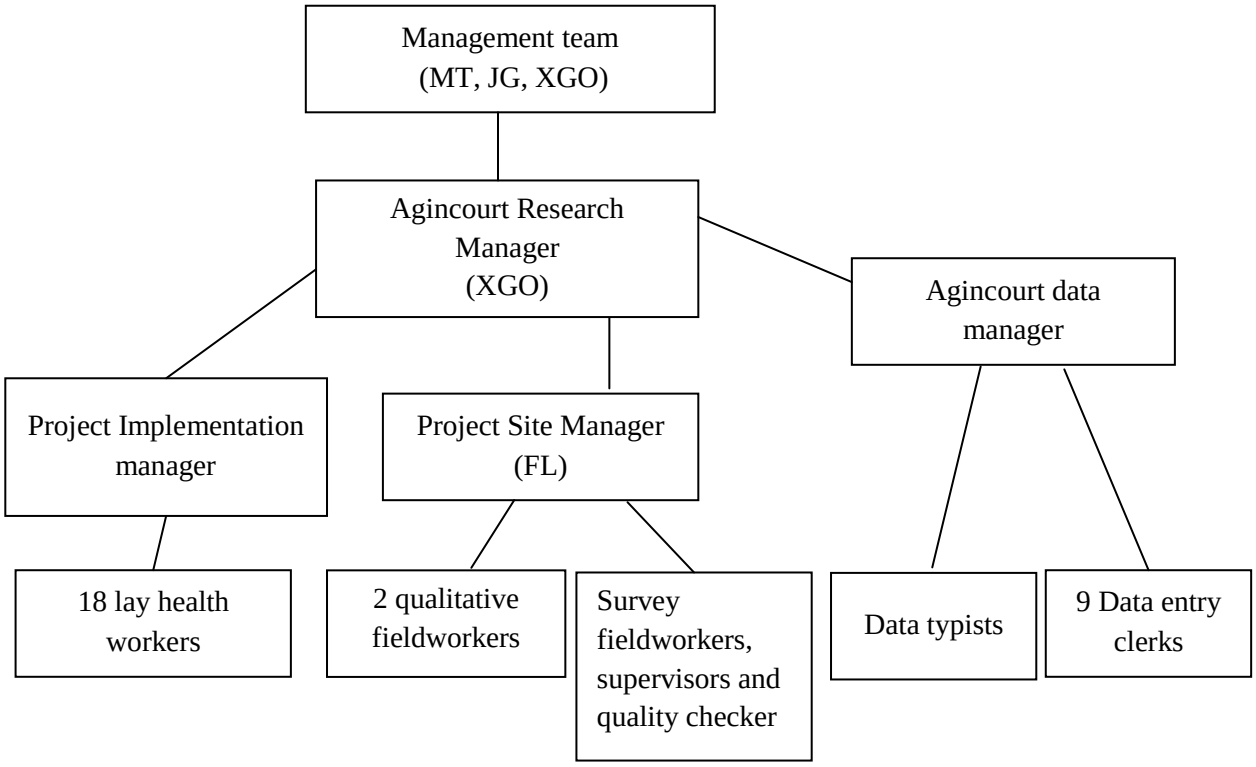
J4. Project research staff

The research team will consist of a Project Site Manager (Felix Limbani) who will have responsibility for the daily management of the study and for the realist evaluation. He will be assisted by two qualitative field staff. This team of three will conduct semi-structured interviews and observations. Nine data entry clerks (one per clinic) will be responsible for the clinic-census link and collecting patient record data, and will report to the Project Site Manager. The population surveys will be conducted by fieldworkers from the core Agincourt team, supported by the site data manager, with the Project Site Manager having overall responsibility for the surveys. The Project Site Manager will also be responsible for logistics such as transport, meeting organisation and so on.

J5. Management structure

The Management Team (Thorogood, Goudge, Gómez-Olivé, Limbani) will have weekly phone conference calls. Overall supervision at the site will be provided by the Agincourt Research Manager (Gómez-Olivé), with the Project Site Manager and the Implementation manager reporting to the Management Team, but on a day-to-day basis to Gómez-Olivé. Schedules of activities and data collection points will provide a detailed plan for the implementation and research teams throughout the trial. Progress will be reviewed monthly by the management team.

J6. Organogram



K. DISSEMINATION

K1. Workshops and symposia

Stakeholder workshops will engage key potential users of the research to obtain their involvement in the research design, the intervention, outcome measures, and the process evaluation; and their interpretation and responses to initial analyses. The stakeholders will include potential users of the research, primarily staff from the Chief Directorate of Chronic Diseases and Primary Health Care at National and Mpumalanga provincial departments, as well as the Bushbuckridge district and facility managers,(such as the PHC Clinic Coordinators and the Sub District Health and Chronic Diseases Managers.) External experts who have experience in a range of approaches to patient outreach, as well as those involved in design of current SA policies, will also be invited to participate in the meetings. A full day event with 20-25 people will allow thorough debate of the issues.

We will use the Centre for Health Policy (CHP) current half-day mini-symposia to present the proposal and findings to decision makers and practitioners in the national and provincial departments of the health, local and district health authorities, academics and civil society. Through these mini-symposia we aim to build a community of practice of district managers and practitioners, who can share experiences in their own district, and discuss innovative strategies as being investigated in this study with their peers elsewhere in the country. The possibility of extending this to a virtual community of practice through the CHP website will be explored. The mini-symposia will also engage civil society from the Rural Health Advocacy Project (RHAP), the Rural Doctors Association of South Africa (RUDASA), the Centre for Rural Health, Soul City (a health edutainment organisation that produces a TV series and has done formative work in the Agincourt HDSS), Section 27 (a health and social rights advocacy organisation), the Patients' Health Alliance of Non-governmental Organisations (PHANGO), and appropriate associations such as the SA Hypertension Society and the Public Health Association of SA. Involving this sector in the early phases and when we have findings will facilitate broad exposure and feedback to the researchers. Presentations will be made at local conferences such as PHASA, RUDASA, and the Gauteng Department of Health Research Conference.

K2. Written output

We will publish the findings of this study in open access academic journals and expect to produce at least five peer reviewed papers. Written outputs will also include information flyers for dissemination at symposia and academic conferences; media releases to lay and technical press and 2-page policy briefs to Parliament's Health Portfolio Committee and policy-makers. Other distribution and monitoring channels will include info-mediaries such as the DFID-funded R4D, Eldis Gateway, and Meltwater. The CHP, Agincourt, Warwick university websites will post regular updates of the project's progress.

K3. Authorship agreement

A collective discussion of possible papers will allow a sharing of opportunities for lead-authorship among the study team. For each paper generated by the study, the individual or individuals who take the lead in drafting the paper will be the lead authors. Everyone whose contribution meets the international standards for authorship will be listed as authors, and authorship lists should end with the phrase 'on behalf of the Nkateko Trial Team'.

K4. Open access to data

All data sets derived from this project will be made publically available within 1 year of the data collection and cleaning being completed. Secondary data users will submit a request for data access to the data custodians, appointed by the project PI's by completing an online form. If the request falls with the bounds of appropriate data access requests as specified in the 'MRC Principles for access to, and use of , MRC funded research data.' Then it will be approved. Collaboration with the original investigators in resulting publications will be encouraged.

L. ETHICS AND RESEARCH GOVERNANCE

L1. Review and ethics boards' approvals

The study proposal and reports will be submitted to the Committee for Research on Human Subjects (Medical), University of the Witwatersrand, the Biomedical Research Ethics Committee, University of Warwick, and Mpumalanga Province Research and Ethics Committee. Once formal permission has been granted, we will meet with the Ehlanzeni District health department (contact person Ms TZ Madonsela) and the Bushbuckridge sub-district (contact person Mr. I Mtungasi) before approaching clinic staff.

L2. Community advisory committee

The MRC/Wits LINC office (Learning, Information Dissemination and Networking with the Community) based in the Agincourt sub-district will manage a community advisory group specific to this trial which will meet at specified intervals to receive reports on the progress of the trial and to advise the study team. We will obtain the communities' permission to conduct the trial, and get information on community and providers' understanding of hypertension, diabetes & HIV, and patient and system barriers to provision, access, and adherence to care. For the duration of the study, LINC will further engage with these groups, giving verbal and printed (one page information sheets and posters) updates at annual community meetings, and occasional village leadership and clinic meetings. All information will appropriately translated and packaged, with the assistance of the communications officer from the Centre for Health Policy (CHP). LINC will recruit and manage a community advisory group specific to this trial which will meet at specified intervals to receive reports on the progress of the trial and to advise the study team.

L3. Trial steering committee

A Trial Steering Committee (TSC) has been set up to provide expert advice independently of the principal investigators. The members are listed on page 1. The TSC will meet, by electronic communication, at six-monthly intervals. Representatives of the funder (UK MRC) and the sponsor (University of Warwick) will be invited to meetings and will receive copies of all minutes and documents submitted to the TSC. TSC meetings will also be attended by the principal investigators together with other co-applicants or trial staff as appropriate. The TSC will meet to approve the final version of the protocol before the trial starts, and will later review the statistical analysis plan and any future amendments of either the protocol or the statistical analysis plan.

We do not propose to set up a separate data management committee. The primary outcome data for the trial will be based on two population surveys, neither of which will be analysed until after the trial is complete. For this reason there will be no data available during the trial of a data management committee to consider.

L4. Obtaining informed consent

This cluster randomised trial is a Type A trial as defined in the 2002 MRC document on cluster randomised trials[7]. The decision to consent to organisational change in a clinic cannot

depend on the consent of users of the clinic. Instead, consent will be sought from the National, Provincial and District authorities, and implementation within a clinic will take place in discussion and partnership with the clinic staff.

Individuals will be asked for written consent to being included in the research process on the following occasions:

i. When individuals, using the clinic, are asked to participate in the study. Consent will also be request for the lay health workers to access their records and extract data. An individual's continued willingness to provide this information will be sought on each return visit to the clinic.
ii. When an individual is approached to participate in the cross sectional surveys.
iii. When an individual is approached to participate in a semi-structured interview or a focus group;

In addition:

iv. For the purposes of observation of general clinic activity, a staff meeting will be held and posters displayed in the area where the observation is taking place.
v. Each individual and health worker in order to observe a consultation.

L5. Protocol amendments

This protocol won't be finalised until the details of the intervention have been decided. Once finalised, should important protocol changes become necessary, they will be discussed first with the Trial Steering Committee and will then be submitted for approval to the Committee for Research on Human Subjects (Medical), University of the Witwatersrand; the Biomedical Research Ethics Committee, University of Warwick, and Mpumlanga Province Research and Ethics Committee. If consent is given, the funder and the sponsor will be given formal notification of the change.

L6. Recording adverse events

Any incidents or accidents which are related to the conduct of this trial including the delivery of the trial intervention, or which affect trial staff while at work will be recorded and copies of the report sent to all three members of the Management Team and the Chair of the Trial Steering Committee. The Chair of the Steering Committee, in consultation with the Management Team, will decide whether any further investigation or action is necessary.

L7. Conflicts of interest

None of the co-applicants have any conflicts of interest. Should such conflicts arise they will be discussed with the Chair of the Trial Steering Committee to decide on appropriate action.

L8. Study Timetable

We started the study on April 22nd 2013

Date	Month of study	Activity
April 2013	1	Project Site Manager takes up post
April	1	RITA meeting (resource planning meeting)
June-August	3-5	Situational analysis of clinics & analysis
June-July	3-4	Community Engagement
July-August	4-5	Intervention and material development
June - August	3-5	Preparation of ethics committee applications
July	4	Implementation manager in post
August	5	Recruitment of LHWs and survey staff
September	6	Staff training
September-November	6-9	Baseline population survey
October - December	7-9	Pilot intervention site starts
November-January	8-10	Refinement of protocol with lessons learnt from pilot
December - January	10	Christmas break
Jan 2014 – March 2015	11-25	Full intervention period
Feb – April 2015	24-26	Follow-up population survey
April – December 2015	26-33	Data cleaning and analysis

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