

Addressing Challenges in Scaling Up TB and HIV Treatment Integration in Public Health Settings in South Africa.

Short title: *Scaling up TB HIV integration (SUTHI)*

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ABBREVIATIONS AND ACRONYMS

AIDS	Acquired Immunodeficiency Syndrome
ART	Anti-retroviral treatment
ANC	Antenatal Clinic
ART	Antiretroviral Therapy
BRHC	BroadReach Health Care
CCG	Community Care Givers
CDA	Clinical Doctor Advisor
CAN	Clinical Nurse Advisor
COACH	Context Assessment for Community Health
CPT	Cotrimoxazole Preventive Therapy
DOH	Department of Health
DOT	Directly Observed Therapy
DR-TB	Drug resistant TB
GEE	Generalized Estimating Equation
HBCs	High burden countries
HCT	HIV Counseling and Testing
HIV	Human Immunodeficiency Syndrome
HSSM	Health Systems Strengthening Manager
ICF	Intensified Case Finding
IPT	Isoniazid Preventive Therapy
KZN	KwaZulu Natal
NDOH	National Department of Health
NSP	National Strategic Plan
OSS	Operation Sukuma Sakhe
PHC	Primary Health Care
PLWH	People living with HIV
PMTCT	Prevention of Mother to Child Transmission
QI	Quality improvement
SANAC	South African National AIDS Council
Statssa	Statistics South Africa
SUTHI	Scaling up TB/HIV integration
TAO	Technical Assistance Officer

TB	Tuberculosis
UKZN	University of KwaZulu Natal
UNAIDS	United Nations
W H O	World Health Organization
XDR-TB	Extensive Drug resistant TB

PROTOCOL SCHEMA

Full Study Title	Addressing challenges in scaling up TB and HIV treatment integration in public health settings in South Africa
Short Study Title	Scaling up TB HIV Integration (SUTHI)
Primary Objective	The primary aim of this study is to test the effectiveness of a peer mentor-led, quality-improvement model of service delivery of integrated HIV-TB treatment on mortality in HIV-TB co-infected patients treated in rural primary health care clinics in KwaZulu-Natal.
Study Design	Cluster randomized control trial where clinics, with all their HIV-TB patients, are randomized as a group but the trial outcome is measured in individual patients at each of these clinics.
Study Population	HIV or TB infected suspects and cases attending primary healthcare facilities located in rural, South Africa
Sample Size	40 primary healthcare facilities in the Ugu and uThungulu Districts
Study Intervention	A quality improvement model of service delivery for integrated HIV-TB treatment: a peer-led, mentored and supported comprehensive model of integrated TB and HIV services at a primary health care level aimed at improving TB and HIV outcomes at a programmatic level and individual patient based level.
Study Outcomes	All-cause mortality among TB and HIV patients Time to ART initiation among HIV infected TB suspects and cases HIV testing rates in TB patients Number of HIV-TB co-infected patients receiving co-treatment for TB and HIV at the same facility Number of HIV-TB co-infected patients that are retained in care at 12 months Number of HIV-TB co-infected patients that are virologically suppressed at 12 months TB treatment outcomes in HIV-TB co-infected patients Hospitalisation rates among patients receiving co-treatment for TB and HIV
Study Duration	Each clinic will be included in the study for an 18 month period

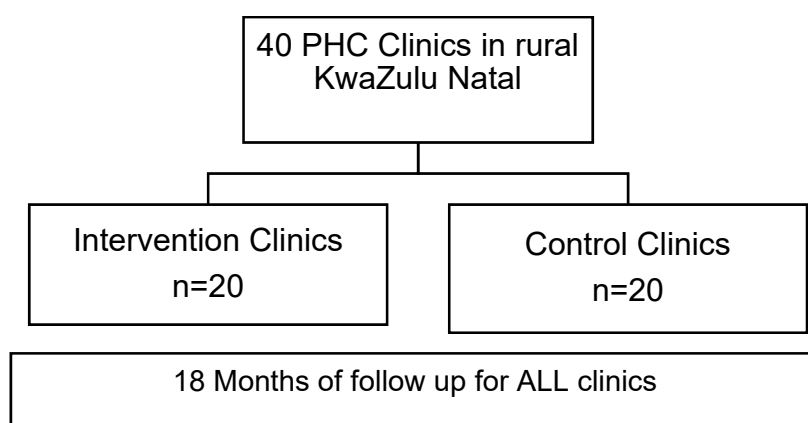


Figure 1: SUTHI Trial Study Schema

CHAPTER 1: INTRODUCTION

1.1 BACKGROUND

The World Health Organization (WHO) Global Tuberculosis (TB) estimates that there were 9.6 million new TB cases in 2014, which is an equivalent of 133 per 100 000 population¹. A third of the cases, 28%, are reported to have occurred in the African Region with the high burden countries (HBCs) contributing 83% of all the estimated incident cases worldwide¹. The high global burden of TB is concerning, considering that TB is potentially curable. In addition, TB is the most frequently encountered opportunistic disease and cause of mortality among HIV patients in developing countries, accounting for approximately 25% of all HIV associated deaths each year.² Globally, people living with HIV (PLWH) are 26 times more likely to develop TB disease than HIV negative individuals. In 2014, between 1.1 and 1.4 million (11-13%) of the 9.6 million incident cases were HIV positive individuals.^{2,1} The risk of developing active TB disease after infection with *Mycobacterium tuberculosis* is relatively low, although this probability is much higher among people infected with HIV. Mortality in TB-HIV co-infected patients is usually due to complications from overwhelming TB disease or to impaired immunity from advancing AIDS.^{3,4} Over a period of 14 years (1990-2004), there was an estimated 5% increase in HIV prevalence and a corresponding 2.5-fold increase in the incidence of TB in sub-Saharan Africa.⁵ In addition, the overall prevalence of HIV-TB co-infection in Africa has been estimated by the WHO to be 38%, with some regions experiencing levels of co-infection approaching 80%^{6,7} TB and HIV infection are individually major global public health concerns but the two intertwined epidemics are a devastating and deadly combination, responsible for more deaths than any other condition. HIV co-infection is thought to be a risk factor for acquisition of drug resistant TB (DR-TB), with increased risk of mortality among HIV individuals who acquire extensively drug resistant TB (XDR-TB), despite viral suppression with ARTs.⁸

TB in South Africa, contributes to unacceptably large numbers of illness and death. Mortality rates excluding HIV positive TB patients was estimated at 44 per 100 000 population in 2014, an equivalent of 24 000 cases. South Africa is ranked among the top six countries as having the largest numbers of incident TB cases in 2014, estimated at 834 per 100 000 population (450 000 cases).¹ Despite a decline in TB mortality 2011-2013, with cases estimated at 55 102 (10.7%) in 2011, 48 409 (9.9%) in 2012 and 40 542 (8.8%) in 2013, TB remains a leading cause of death in South Africa. ⁹ South Africa remains at the center of the global HIV epidemic, with an estimated 6.8 million people reported to be living with HIV in 2014, an increase from 5.3 million people in 2013. There were 469 000 new infections recorded at the end of 2012, with high incidence levels among young women of ages 15-24 years. Between 2011 and 2013, HIV shifted from the seventh most common cause of death in 2011 to being third in 2013, accounting for 5.1% of all natural deaths in 2013.^{9,10}

The intertwined epidemics of HIV and Tuberculosis (TB) have contributed disproportionately to morbidity and premature mortality in South Africa. Levels of HIV and TB co-infection are high with as many as 61% of patients having HIV-associated TB in the country with TB mortality rates estimated at 134 per 100 000 population (72 000 cases) among HIV positive patients compared to the 44 per 100 000 population (24 000 cases) of HIV negative individuals¹. The scale of these epidemics has hindered efforts to achieve the United Nations' Millennium Development Goals targets set for 2015. Consequently combating HIV/ AIDS and decreasing the burden of disease from TB has been articulated by the South African health sector within the Negotiated Service Delivery Agreement, as a priority implementation activity aimed at improving the health status of the entire South African population. It is clear that this dual epidemic calls for a comprehensive approach that is patient – centered and fully integrates TB and HIV services within both curative services¹¹.

CHAPTER 2: LITERATURE REVIEW

A desktop review was conducted on all publications emanating from sub-Saharan Africa examining various aspects of TB/HIV integration in primary health clinics during the ten year period 2003-2013. Among the 30 articles that were reviewed, the non-clinical operational challenges identified in 22 articles¹²⁻³³ include: issues with directly observed therapy (DOT) coverage and TB treatment adherence; staffing issues and lack of clinical supervision and mentorship; poor recording / missed opportunities in CPT administration; low uptake of HIV HCT in TB patients; poor recording of CD4 results-difficulties/ shortcomings in monitoring and reporting ; delays in initiating ART in TB patients; drug stock-outs; funding constraints; problems in communication between collaborative services; issues with implementation of IPT and issues with implementation of ICF protocols/ diagnostic challenges.³⁴⁻³⁵ While the plethora of publications underpin both the need for, the benefits of and the best practice evidence based approach to HIV-TB service integration, there has been no collation of evidence that translates to a readily implementable HIV-TB service integration package suitable for a primary healthcare (PHC) level facility, where most of the service delivery occurs³⁶.

These findings highlight the need for a study that will explore the scope of the challenges with the current TB/HIV service delivery model in health care facilities. This study will map out problems and describe the extent of the challenges from various perspectives, thus, enabling the development of evidence informed strategies to improve the care of all those infected with **HIV, TB or both in the clinics of Ugu and UThungulu districts.**

In 2004, the WHO published an interim policy on collaborative TB/HIV activities.³⁷ This policy stipulates that for TB/HIV services to be considered as “integrated” the following activities must be carried out:

- Isoniazid Preventive Therapy (IPT)
- Intensified case finding and infection control and for TB,
- HIV counselling and testing (HCT)
- Cotrimoxazole preventive therapy CPT
- Care and support and antiretroviral therapy (ART) for those with HIV-associated TB ³⁶

South Africa has taken progressively determined measures to stop the tide of the epidemics and alleviate the impact of HIV and TB co-infection. The country has made integration of services an all-encompassing policy both in the context of transformation of the health system and primary health care re-engineering. TB /HIV integration was endorsed by the South African National Aids Council (SANAC) in 2009, and consequently, the DOH has since April 2010 prioritized ART availability at PHC level and integration with TB control fully incorporated into the mandate of SANAC alongside those of HIV and STIs resulting in the launching of a National Strategic Plan (NSP) on HIV, STIs and TB (2012-2016). There is successful, functional integration of HIV and TB, using the “one stop service” approach at the facility level. A Joint Review of the HIV, TB and PMTCT Programmes was commissioned by the NDOH to be undertaken in 2013, the main purpose of which was to assess performance of the programmes and provide options for improvement. The focus of the Review was on issues critical to effective delivery and impact of HIV, TB and PMTCT services, to assess progress made after the recommendations from previous Reviews, identify challenges and highlight the best practices .³⁸

While the country had made impressive advances in the implementation, the Joint Review found that there were some areas still lagging behind and these include, for the TB/HIV collaborative activities; poor infection control and a consistent gap in integrating IPT TB prevention and TB screening ; diagnosis in pre-ART car; low HIV and TB treatment coverage among children and adolescents including declining retention rates with each year after initiation – which was a major concern and that key populations were not yet reached with HIV and TB services. There were also high rates of patients defaulting from care, a challenge in retention of patients on treatment in both the TB and HIV programmes and low ART coverage initiation in TB co-infected patients compared to non TB co-infected patients. Among the recommendations from this Review, was that a QI programme and support for the use of data at a facility level be implemented ³⁸. QI is believed to raise morale among staff and patients as they see barriers to care they face each day being addressed and they realize they can participate in the work to remove them. ³⁹

A few studies that have been conducted on QI include one that was conducted in Cape Town. In this study, quality was defined as adherence to local protocols and standards for TB care. The objective was to use a QI approach to improve access to and quality

of TB diagnosis and care. Integrated HIV/TB/STI tools were developed and routinely implemented in all the health care facilities. HAST coordinators were providing support to the primary health care facilities and the primary services were offered by the local and provincial authorities who collaborated to ensure efficient service delivery. After five audits were performed, poor capacity and weaknesses in quality and continuity of care were identified and strategies were put in place. Among the quality gains were the improved cure rates, from 67% to 80% (2004-2009) and in one district from 52% to 78%⁴⁰.

In another study involving QI, the objective was to quantify TB/HIV integration at three primary health clinics in Johannesburg. In this study, routinely collected TB and HIV data were collected over a three month period and reviewed. The results from activities to reduce the incidence of TB among people living with HIV (PLWH), revealed that newly diagnosed patients with HIV were not screened for TB, newly diagnosed patients with HIV were not offered IPT even though most might have been eligible. ART coverage among patients with TB could not be ascertained as ART was not documented in the TB register or on the TB treatment card. Of biggest concern was the poor quality of routine data given that the primary clinics are expected to compile from these data sources for aggregation at the district and national levels³⁸

2.1 JUSTIFICATION OF THE STUDY

KwaZulu Natal (KZN) is one of the six out of the nine provinces of South Africa that had the highest proportion (11.9%) in the number of deaths observed in 2013. It was followed by Mpumalanga and Limpopo with 10.6% and 9.8% respectively, figures that were higher than the national coverage of 8.8% in the same year⁹. KZN is also considered the DR-TB hotspot, with all the districts in the province reporting proportions of rifampicin resistance higher than the national coverage. The districts that reported the highest proportions in the country are also in KZN, UMkhanyakude and Zululand with 13.2% and 12% respectively. HIV was the second leading cause of death in KZN accounting for 7.3% of deaths in the province. The province has also consistently experienced the highest prevalence level of HIV among the 15-49 year olds at 37.4% in 2011 and 2012 followed by Mpumalanga and the Free State with prevalence rates greater than the 30%. It is also reported to have performed the poorest on the TB/HIV co-infected client on ART indicator with the lowest rate of 74%. This is concerning as the province has the highest HIV and TB rates in the country, however, KZN along with Gauteng are reported to be the two provinces that are continuing to improve their cure rates with KZN having moved from 79.6% in 2012 to 82.8% in 2013.⁹

Ugu and UThungulu, the two districts where the study will be conducted, carry a heavy burden of TB and HIV in KZN. Ugu is reported to be one of four districts in the country that have TB incidence of over 1000 per 100 000 population, estimated to be 1 044 per 100 000 population. In this district TB was the cause of the majority of deaths across all age groups with the exception of the under five year olds where it was the seventh leading cause of death accounting for 13% of all deaths along with HIV. The district performed well with regards to some of the indicators, ranking among the best in the country. These indicators include ANC initiated on ART and HCT including ANC. The district however, also ranked among the worst performing for indicators such as TB rifampicin resistant confirmed client rate. Process and poor infrastructure, poor data quality from poor recording and record keeping have been cited as some of the challenges resulting in slow HIV/TB integration, resulting in poor management of HIV/TB patients and IPT roll-out. The district is also plagued by MDR-TB and cure rates that remain low at 74.7% due to high numbers of defaulters. Poor data quality from poor recording and record keeping has also been cited as a challenge in this district.^{10, 41}

The incidence of TB in UThungulu is estimated at 847 per 100 000 population, a figure that is also higher than the national 687 per 100 000 population in 2012. HIV and TB were the leading cause of death across all age groups with the exception of under-fives where it dropped from fourth position to sixth, among the 65 year olds and older. Although there have been improvements in data quality, decreased TB incidence and HCT testing rate which is presently at 99%, the district has increased incidence in MDR-TB and ANC sero-prevalence increased from 33.4% to 38.5% in 2012. Inadequate infrastructure has also been reported as being a challenge.^{10, 42} Our hypothesis is that although the clinics have integrated HIV and TB services, the interventions are not done holistically and or the policies, guidelines or documents that cover issues pertaining to HIV/TB integration are not adhered to. Conducting this study in Ugu and UThungulu, will help report on the challenges in the scaling up of TB and HIV treatment in public health settings in South Africa. The study will highlight programmatic weaknesses and indicate further necessary improvements.

2.2: RATIONALE FOR INCLUSION OF EACH OF THE COMPONENTS OF THE INTERVENTION

2.2.1 Intensified Case finding for TB in HIV infected patients

Although theoretically possible, one expects a 100% patient coverage for intensified case finding (ICF) for TB in patients with HIV-infection at the PHC level to be hindered by logistical and operational factors which might not be present at a tertiary level. One study demonstrated operational feasibility and sustainability of an ICF programme when integrated into routine TB and HIV care.¹⁴ This study found that ICF in community clinics was potentially more accessible to an underserved, rural population and was as effective as the hospital service in

detecting smear positive TB. In our review, we noted that the use of TB symptom screening is widely implemented as the method of choice for TB screening, with improvements in TB detection gained through the addition of TB smear and culture to the screening process. While the addition of GeneXpert technology to the TB diagnostic algorithm is likely to increase TB case finding, this technology may not be accessible by all rural PHC facilities in the near future. Interestingly, regular TB screening among HIV-infected patients is recommended to increase TB case detection. Data reporting the proportion of HIV-positive patients who receive anti-TB treatment subsequent to intensified case finding processes at PHC level is scant.^{14, 33} Greater efforts should be made to include this important data element during the development of data collection tools.

2.2.2 IPT for HIV-positive patients that screen TB negative

Although published literature on the implementation of IPT in PHC clinics is scarce, the efficacy of IPT in reducing incident TB is well established. Additionally, good adherence to the course of IPT, up to 86%, has been demonstrated in an African study,²¹ which is similar to adherence rates described in a Spanish cohort which was described in a meta-analysis.⁴⁴ Furthermore, one study showed the benefit of prolonged IPT to 36 months compared to 6 months in reducing TB incidence.⁴⁵ Despite these documented benefits, implementation of IPT in resource-constrained settings, which includes most of sub-Saharan Africa, has been limited.⁴⁶

2.2.3 Testing and counselling for HIV in all patients with TB, including children and pregnant women

Various studies demonstrated that integration of TB and HIV care in PHC facilities contributed to improved TB and HIV outcomes including reduced mortality,^{34,47} improved TB treatment outcomes,¹⁶ earlier and more prioritized ART initiation in ART-naïve HIV-infected TB patients,^{24,27,29-31} and a decrease in the time to initiation of ART, especially in patients with low CD4 counts.¹⁶ The high HIV testing rates among TB patients indicate that patients co-infected with the two diseases are entering into the continuum of treatment for HIV infection, and that service integration has the potential to ensure their appropriate management.⁴⁸ Evidence suggests that implementation of routine provider initiated HIV testing and counselling by the TB nurse or health care worker at the primary health care centre results in a higher test uptake compared to referral of patients with TB to freestanding voluntary counselling clinics, and is feasible and acceptable to TB patients and TB suspects.²² When offered to TB suspects, provider initiated testing identifies large numbers of persons requiring HIV care. It is also important to note that community sensitisation, staff training, multitasking and access to HIV care contribute to a high acceptance of HIV testing.²² Clear directives are nevertheless required to change practice. Pregnant women and children with TB will be tested for HIV, following the same guidelines as other patients.

2.2.4 Cotrimoxazole therapy for HIV-TB co-infected patients

HIV-infected TB patients should be counselled and supportively encouraged to seek additional treatment that will reduce illness, death, and improve their quality of life. One key intervention available to patients is CPT. Cotrimoxazole taken daily reduces the risk of serious opportunistic infections and death in HIV-infected persons.⁴⁹⁻⁵² Cotrimoxazole is safe, effective, and well-tolerated. Serious side effects are rare.^{47, 53-54} Cotrimoxazole is currently being provided free of charge to HIV-infected persons with tuberculosis at PHC clinics in South Africa.

2.2.5 ART initiation in HIV-TB co-infected patients

Studies have found ART initiation during TB treatment in HIV-positive patients to be associated with high levels of treatment adherence, TB cure and treatment completion rates, and improvement in patient immunologic and virologic parameters. However, patient and programme data from comprehensive HIV-TB integration studies at PHC level is still lacking. The ART coverage amongst pregnant women in the province of KwaZulu-Natal, which has an HIV prevalence of 38.7% among public sector pregnant women, is poor (estimated at 43%).⁵⁵ There has also been little improvement in the number of children receiving ART, with no significant gains being observed in South Africa for the period 2004-2011.⁵⁶ Hence, there is also a special need to increase timely access to ART among children and pregnant women with TB and HIV.⁵⁵⁻⁵⁷

2.2.6 A fully integrated model of service delivery – adopting the one patient, one appointment, one file, and one data management system approach

One study has recommended a 'one patient, one file, one appointment' principle – a practical approach worthy of consideration and piloting.²⁰ A fully-integrated services approach would seem to offer the best solution to the challenges of ART and TB integration. However, while ART and TB treatment under one roof appears to facilitate ART initiation for HIV-positive TB patients,²⁰ the co-location of services alone might be insufficient to permit timely initiation of ART for all patient populations.²⁹

Paper-based ART registers are complicated to manage and to extract data needed to report on TB and HIV program indicators. Current manual and electronic data reporting systems do not merge HIV and TB programme indicators despite the WHO's HIV and TB Departments defining a core set of indicators for monitoring and evaluating collaborative TB-HIV activities⁵⁸.

2.2.7 Enhanced retention in care strategies including the use of community care workers for retention and for community-based management of selected patients

Improved integration of HIV-TB testing and treatment beyond the health facility represents an opportunity to further promote the timely diagnosis and treatment of co-infected patients, with the aim of controlling the HIV-TB syndemic. To this end, future programs should include active TB and HIV case finding not only in the clinic but also in the community. Community health workers and other community systems can improve linkage to ART services and provide

integrated follow-up for defaulters from both TB and HIV treatment programs. Community-based distribution of HIV and TB treatment offer the ability to scale-up the number of patients in treatment while not overwhelming health systems. Improving the diagnosis, care, and outcomes for HIV-TB co-infected patients is an important step toward turning back the tide of HIV. ⁵⁹

2.2.8 Enhanced ART and TB treatment adherence strategies

A. The use of community care workers for adherence support, retention and community based management of patients

Community Care givers (CCGs) are at the core of OSS as their role is to connect households and communities with clinics, health and social services. This study aims to harness the presence, experience and reach CCGs have in the clinics and catchment populations in Ugu and UThungulu for adherence support, retention and community-based management of patients.

CHAPTER 3: STUDY OBJECTIVES

3.1 GOAL OF THE STUDY

The goal of the study is to identify and develop a set of interventions, change ideas, tools and approaches that can be used to scale up the adoption, implementation and sustainability of integrated HIV-TB services across South Africa and in other resource constrained settings.

3.2. Primary objective

The primary aim of this study is to test the effectiveness of a peer mentor-led, quality-improvement model of service delivery of integrated HIV-TB treatment on mortality in HIV-TB co-infected patients treated in rural primary health care clinics in KwaZulu-Natal.

3.3 Secondary objectives

Specific Aim 1: To determine the impact of a QI-mediated HIV-TB service integration on patient mortality. All patients that access services in intervention and control clinics, via either the TB entry point or via the HIV entry point will be tracked during clinic follow-up visits or, through a community care giver, and will have their vital status ascertained 12 months after clinic randomization

Specific Aim 2: To determine the effectiveness of peer-led Quality Improvement (QI) to integrate HIV-TB services. The effect, on HIV-TB integrated processes of care, of the deployment of a QI approach (systems view, data driven decision making, culture of continuous improvement, trained peer mentors) to ensure uniform implementation of an essential package of evidence based HIV-TB interventions that support HIV-TB integration. The impact on clinical outcomes of using QI methods to implement

integrated HIV and TB management will be assessed using the following indicators: Time to ART initiation among HIV infected TB suspects and cases; HIV testing rates in TB patients; Number of HIV-TB co-infected patients receiving co-treatment for TB and HIV at the same facility; Number of patients infected with HIV or TB that are retained in care at 12 months; Number of HIV patients that are virologically suppressed at 12 months; TB treatment outcomes; Hospitalisation rates among patients receiving co-treatment for TB and HIV.

Specific Aim 3: To identify clinic-level factors that impact on integrated HIV-TB services. Understanding the context (environmental, social and political factors) in which we are working is essential to identifying factors that promote or inhibit the implementation of the intervention. We will use the COACH tool (Context Assessment for Community Health) to collect data and assess the organizational context and the influence of factors such as organizational culture, leadership, resources and HCWs remuneration etc. on the intervention

Specific Aim 4: To determine the cost-effectiveness of implementing HIV-TB services using Quality Improvement methodology (Intervention Clinics) versus the control clinics implementing HIV-TB services independently.

Specific Aim 5: To identify a set of interventions, change ideas, tools and approaches that can be used to scale up adoption, implementation and sustainability of integrated HIV-TB services across South Africa and in other resource constrained settings.

CHAPTER 4: METHODS

4.1 Study setting

The study will be implemented in 40 Primary Health Care (PHC) clinics in the Ugu and uThungulu districts of KwaZulu Natal. The Ugu and uThungulu districts are large and relatively rural districts. Table 1 below, illustrates that in terms of their respective demographics and geographical characteristics, the districts are very similar to each other.

Both districts have many Primary Health Care facilities selected will also be representative of typical primary health care facilities in South Africa with respect to size, infrastructure, population served and staff complement etc.

The Ugu and uThungulu districts carry a heavy burden of TB and HIV. Table 2 illustrates the disease burden in both districts. TB and HIV remains the main causes of death in Ugu (35.8%) and uThungulu (35.4%). The performance of the districts in meeting the UNAIDS 90-90-90 target is sub-optimal as demonstrated by the proportion of TB-HIV patients initiated on ART (below 90%).

Table 1: Ugu and uThungulu District characteristics



Figure 2: A Map of the KwaZulu Natal Province, South Africa

Characteristics	Ugu	uThungulu
Total population	722,484	907,519
Geographical size	5047km ²	8213km ²
Men (%)	46.94%	46.25%
Women (%)	53.06%	53.60%
IsiZulu speaking (%)	82.7%	89.1%
English speaking (%)	8.26%	5.1%
Black African (%)	90.6%	94.4%
White (%)	4.9%	3.2%
Indian (%)	3.4%	1.6%
Coloured	0.8%	0.6%
Health Facilities		
No.# PHC clinics	54	67
No.# CHC clinics	2	1
No.# District Hospitals	5	7
No.# Tertiary Hospitals	0	1
Main Support Partner	BRHC	BRHC

Table 2: HIV and TB profile of Ugu and uThungulu Districts

	Ugu	uThungulu	South Africa
HIV prevalence among antenatal women	41.7%	33.4%	29.5%
Diagnosed cases of TB for 2013	1044	888	593
Number of patients on ART in 2015	67 381	91 157	3 103 902
Proportion TB-HIV co-infected patients on ART in 2013	79%	83.3%	78.9
Proportion of deaths from TB and HIV in 2013	35.8%	35.4%	27.9%

In KwaZulu Natal all South African Department of Health (DoH) Primary Health Care clinics are overseen by Primary Health Care (PHC) Coordinators. The PHC Coordinators are the link between PHC clinics and the South African Department of Health higher level structures. They are mandated to oversee the PHC clinic performance against set targets, implementation of clinical guidelines review clinic data to identify gaps and weaknesses in performance and

supervise the clinic nurse manager to ensure smooth clinic operations. One PHC coordinator can oversee 3-5 Primary Health Care facilities in 1 District. In addition to the SA DoH staff supporting PHC clinics, the vast majority of South African Department of Health facilities are well supported by local not-for-profit organizations in terms of point of care health systems strengthening, mentoring and coaching of the DOH front line workers and managers. One such noteworthy organization is BroadReach Healthcare (BRHC) which has a strong footprint and established relationships within the KwaZulu Natal Department of Health as a provider of supervision and onsite technical mentorship support for healthcare workers.

4.2 Study Design

This study is a cluster randomized controlled trial (RCT). Forty (N=40) Primary Health Care (PHC) clinics from 2 districts in KZN will be selected for the trial and n=20 clinics will be assigned to the intervention group and n=20 clinics to the control group.

4.3 Randomization

In the interests of future scale up initiatives and minimizing cross contamination between clinics, the randomization of clinics will be at the level of the PHC Coordinator. The PHC coordinators play a critical role in mentoring the PHC Operational Managers (Facility Managers) and overseeing the implementation of SA DOH policies and practices in facilities at a sub-district level. The Ugu district has 6 PHC coordinators and the uThungulu district has 8 PHC coordinators. Each PHC Coordinator is responsible for a group of clinics. If a PHC coordinator is randomized to the intervention group then all clinics reporting to that PHC coordinator will receive the intervention. A graphic presentation of the study design is reflected in Figure 2 below:

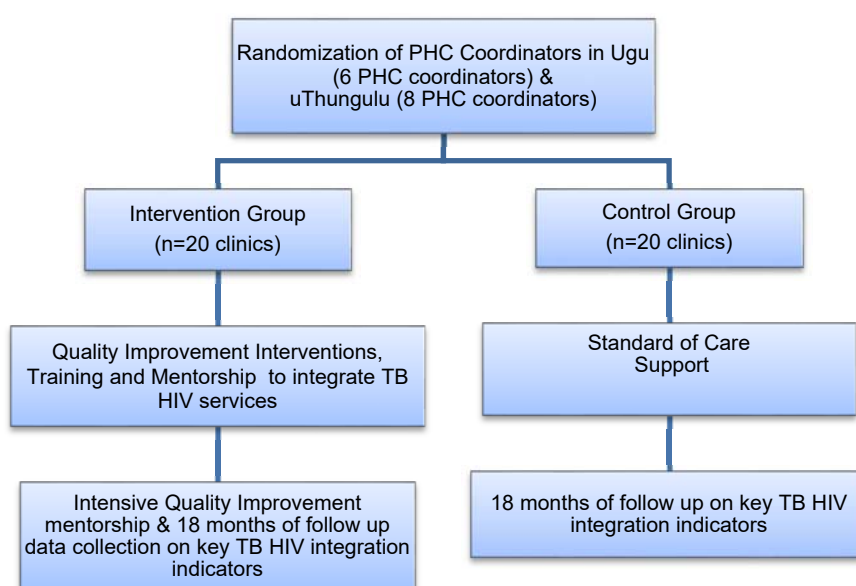


Figure 3: The SUTHI study randomization process and study groups

4.4 Study Groups

4.4.1 The Control Group

The BroadReach Health Care (BRHC) organization has been supporting clinics in the Ugu and uThungulu districts to enhance PMTCT, HIV and TB services as well as impacting clinics by supporting the SA DOH district management structures. All BRHC activities will continue as per normal in control clinics. The following package of health systems strengthening and mentorship will be provided in both districts at the control clinic sites. At the clinic level there is onsite mentorship and coaching provided by the BRHC team. This team consists of 1 Technical Assistance Officer (TAO), 1 Clinical Nurse Advisor (CNA) and a Clinical Doctor Advisor, with expertise either in TB, HIV or PMTCT.

- **Technical Assistance Officer (TAO)** - supports and mentors the existing Department of Health data captureurs to input complete and accurate data into the TIER.net¹ system. TAOs offer training on data entry, generating reports of Tier.net, correcting errors and where necessary they escalate certain issues to higher structures within the DoH (e.g. PHC Supervisor). The TAO reports to a Clinical Nurse Advisor.
- **Clinical Nurse Advisor (CNA)**
The CNA is a Professional Nurse whose core responsibility is to mentor, coach and support the Operations Manager (OM) of the PHC clinic with respect to patient flow, data flow and in meeting targets for UNAIDS 90-90-90 strategy targets.
- **Clinical Doctor Advisor (CDA)**
The CDA is a medical officer that provides mentorship and coaching on clinical issues with respect to diagnosis and patient management through clinical audits which highlight gaps in services in terms of missed tests, infection control and clinical governance.
- **The Health Systems Strengthening Manager (HSSM)**
The HSSM is the direct interface between BroadReach Health Care and SA DoH at the District level. All the above BRHC personnel report to the HSSM who in turn feeds back to the district and provincial Department of Health on the findings of clinical audits and major issues that impede clinical services or the achievement of targets.

¹ TIER.net is the Department of Health's patient data management system. It is a facility-based software program designed for ART clinics and has the capacity to include TB-related data.

4.4.2 The Intervention Group

Intervention group clinics will receive the standard BroadReach supported service and in addition PHC coordinators assigned to the intervention group will be trained, mentored and skilled to provide a Quality Improvement approach to significantly enhancing and improving service delivery with specific focus on TB-HIV service integration in their assigned PHC clinics. Historically PHC coordinators have been mandated to provide a supervisory role to PHC operations managers and staff. Overseeing the achievement of TB HIV-related targets and clinical governance are core priorities of the PHC coordinators yet the tools and mechanisms for how to manage and direct clinic teams is not a part of the skill set for PHC coordinators who were themselves Professional Nurses before being transitioned to more of a Managerial/Supervisory role ¹

4.4.2.1 The Quality Improvement Approach in Intervention Clinics

Quality Improvement consists of continuous actions that lead to measurable improvement in health care services and ultimately the health status of the targeted patient groups ². One of the defining principles of QI is that it focuses on continuous improvement of systems and processes used in an organization in contrast to Quality Assurance (QA) which focuses on episodic survey of performance, with no attempts to changing the status quo. The QI intervention for this proposed study will entail training, mentoring and coaching the PHC Coordinators to identify gaps in performance in TB-HIV service delivery and systematically test change ideas to close performance gaps. They will also examine patient flow, systems and processes –mainly for the HIV/ART and TB patients. The study will use the Plan-Do-Study-Act (PDSA) model, shown in Figure 3 below, to test proposed changes and identify those that yield positive results.

The QI methods promote front-line staff engagement in the identification of the problem and rapid testing of possible solutions. This improvement process will be led by the PHC coordinator and guided at the local clinic sites by a QI Team leader, an assigned member of the clinic nursing staff who will play a key role in monitoring the weekly performance of key processes and indicators being improved and working with a team of clinic staff –who together form a clinic quality improvement team. This team will be supported by a study appointed QI mentor, who will join clinic QI meetings on regular basis. The QI Team will be given basic training on QI methods and how to undertake the process of analysing gaps in care, generating new ideas for improvement and iteratively testing those ideas on a small scale, and monitoring progress.

The QI mentor will be supported by skilled quality improvement advisers from CAPRISA, who will train the QI teams and QI mentor. The change in performance resulting from these activities will be tracked through a set of indicators that will be

collected, collated and reported weekly at first, and monthly for continued monitoring. The effectiveness of these change ideas will also be assessed by project staff, who will generate a set successful interventions and tools that will be used for the scaling up phase of the intervention.



Figure 4: The Plan-Do-Study-Act model of Quality Improvement²

The TB-HIV Package of Clinical Services implemented in the Intervention Groups

Intervention clinics in this study will be directed (via the QI approach) to implement the following package of integrated TB-HIV services as per the algorithm in Figure 4 below.

- Intensified Case finding for TB in HIV infected patients
- Isoniazid preventative therapy (IPT) for HIV-positive patients that screen TB negative
- Testing and counselling for HIV in all patients with TB, including children and pregnant women
- Cotrimoxazole therapy for TB-HIV co-infected patients
- ART initiation for all HIV and TB co-infected patients
- A fully integrated Data Management system – adopting the one patient, one appointment, one file, and one data management system
- Enhanced retention in care strategies including the use of community care workers for retention and for community based management of selected patients
- Enhanced ART and TB treatment adherence strategies including the use of community care workers for adherence support and for community based management of selected patients.

CHAPTER 5: INCLUSION AND EXCLUSION CRITERIA

Primary Health Care clinics will be included in this study if:

- They are South African Department of Health Primary Health Care clinics supported by BroadReach Healthcare (BRHC)
- They are of reasonably similar size. The number of HIV infected patients reported by the clinics will be listed and clinics falling within the same range of patients will be selected.

Clinics will be excluded if they are:

- Hospitals and Gateway Clinics
- Mobile clinics
- Clinics with only one nurse
- Clinics that do not offer ART services on site

CHAPTER 6: DATA COLLECTION AND MONITORING

6.1 Patient Clinical Outcomes

In this cluster randomized trial, data will be analyzed at an individual patient level taking clustering into account. For each outcome analyzed the appropriate sample of eligible patients in the clinic will be determined and calculated. For example the primary objective is to analyze mortality in patients infected with HIV and TB. Therefore all patients infected with either of these diseases will be included in the sample analyzed. The primary outcome of mortality will be analyzed using survival techniques through Cox regression with random effects (frailty models). These models will take the clustering by clinic into account through the random effects. The secondary objectives of time to ART initiation will also be analyzed using survival techniques already described. TB treatment outcomes will be classified as either successful completion or not successful completion and will be analyzed using Generalized Estimating Equation (GEE).

6.2 TB-HIV Process Outcomes

TB-HIV Process Outcome Process outcomes, for example, HIV testing rates in TB patients will be analyzed using GEE. All patients with TB will be included in the sample. Patients who tested for HIV will be assigned a 1 and patients who did not test for HIV will be assigned a 0 in the GEE analysis. GEE allows one to take the effect of clustering into account and the fact that patients at one facility are likely more similar to each other than patients at other facilities. The same analysis will be done for the secondary objectives: number of HIV-TB co-infected patients receiving co-treatment for TB and HIV at the same facility; number of patients retained in care; and number of patients who are virologically suppressed. Due to the geographic distribution of clinics in rural areas, we think that contamination between intervention and control clinics is highly

unlikely. Analyses will be conducted by CAPRISA study statisticians using SAS statistical software version 9.4 or later.

6.3 Contextual factors affecting the Quality Improvement Intervention

Data will be collected from both the intervention and control clinics which could explain why the QI intervention was successful or not. Contextual factors that impact the intervention refers to organizational structural factors, work culture in clinics, geographical setting and location and leadership and management support (please see figure 4 below). The study team will create or identify tools to ensure the impact of contextual factors but where this is not possible (e.g. unexpected changes in staffing) then detailed process and observational notes will be taken to describe the relationship that contextual factors have on the QI intervention

Tool to be used for this data collection include the listed validated tools/questionnaires below:

- Informed consent
- Socio demographic and work experience of the health workers
- Clinical profile questionnaire to obtain information on the clinic profile which includes infrastructure, staff, amenities, culture, TB/HIV service delivery
- Context assessment for community health (COACH)
- TB/HIV integration survey tool to measure degrees of TB HIV service delivery
- Work related quality of life tool to measure the quality of life of the health workers
- Quality improvement tool to evaluation the intervention being carried out

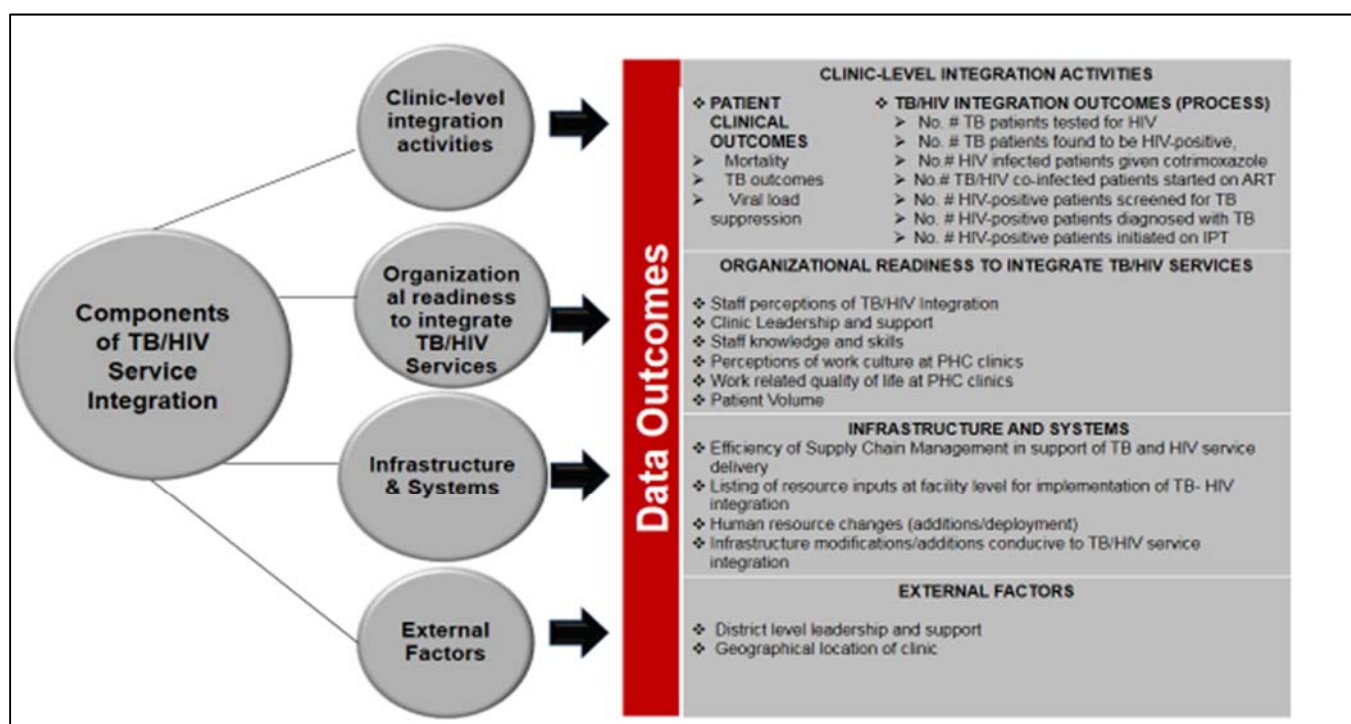


Figure 4: Domains of Health systems Performance and anticipated data outcome

Clinic-level characteristic	Measure/Tool to be used
TB/HIV Service Integration Survey	Degrees of TB HIV Service Integration Survey developed by Uyei et al Uyei J, Coetzee D, Macinko J, Weinberg SL, Guttmacher S. Measuring the degree of integrated tuberculosis and HIV service delivery in Cape Town, South Africa. <i>Health Policy Plan</i> 2014; 29 (1): 42-55.
Infrastructure supporting TB/HIV integration at PHC clinics	A CAPRISA-designed tool to observe infrastructure at clinics (E.g. availability of extractor fans, open windows, N95 masks etc.)
Clinic Culture	The COACH Tool designed by Bergstrom et al.2015 Bergstrom A, Skeen S, Duc DM, et al. Health system context and implementation of evidence-based practices-development and validation of the Context Assessment for Community Health (COACH) tool for low- and middle-income settings. <i>Implement Sci</i> 2015; 10 (1): 120.
Clinic Leadership	The COACH Tool designed by Bergstrom et al.2015 Bergstrom A, Skeen S, Duc DM, et al. Health system context and implementation of evidence-based practices-development and validation of the Context Assessment for Community Health (COACH) tool for low- and middle-income settings. <i>Implement Sci</i> 2015; 10 (1): 120.
Staff Work Related Quality of Life	WHO Work-related Quality of Life Scale
Staff Knowledge and Skills on TB/HIV integration	CAPRISA –designed questionnaire to test HCW knowledge and skills on TB/HIV service integration
Treatment guidelines/ Policies for TB HIV integration	CAPRISA –designed questionnaire to determine the presence of TB and HIV polices and guidelines in the clinic

Table 3: Domains of Health systems Performance and anticipated data outcomes

Table 4 : Schedule of Evaluations

Study Activity	Pre-intervention period	Study Entry Assessments (Baseline)	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12	M13	M14	M15	M16	M17	M18
			ALL CLINICS																	
Retrospective collection of 6 months of TIER.Net Data prior to Quality Improvement Implementation	X																			
Retrospective collection of 6 months of TB HIV Process Outcome Data	X																			
TIER.Net Data Downloads		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
DHIS Data Collection		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinic Profile Questionnaire		X																		
TB/HIV Service Integration Survey		X						X						X						X
Work Related Quality of Life Survey		X						X						X						X
Context Assessment Questionnaire		X						X						X						X
Clinic Resources Tracking Tool		V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V
Intervention Clinics Only																				
Quality Improvement Orientation Workshop	X																			
Quality Improvement Sessions		X	X	X	X	X	X	X	X	X	X	X	X	X	Follow up and exit					

V= Optional form, used as needed

6.4 Data management

Data management systems will be put in place in all the clinics, including control and intervention clinics. Dedicated study staff will be placed in each clinic to ensure the collection and quality control of all data collected on patient files and captured in the data management system.

As far as possible data management systems supported by DoH will be used (such as TIER.net and ETR.net). Information required that cannot be collected with these systems will be collected on an additional electronic data management system implemented at each clinic. Data will be captured in this system from the patient files by the study staff member at each facility.

Database files will be password-protected, and access to the files will be limited to authorized study staff members only. Quality control and validation checks will be performed and data cleaning steps will be undertaken prior to finalizing the study database for analysis.

Data downloaded for analysis purposes will be de-identified and will not contain personal information in order to protect the anonymity of the patients.

CHAPTER 7: ETHICS AND REGULATORY CONSIDERATIONS

Clinics will be randomised to the intervention or control arms. No patients will be randomised. Consent will be obtained from the Department of Health to conduct the study in the clinics and to obtain clinic and patient records for data collection. No individual patient consent will be obtained. This study will not include any direct patient contact with research staff, rather the processes in the clinic will be changed and research staff will work with the clinic staff to implement the interventions. We will seek permission to collect data from patient charts prospectively.

7.1 Regulatory and ethical review

This initiative is conceived and led by CAPRISA in conjunction with BroadReach Healthcare to improve patient outcomes through improved TB HIV service integration in facilities within the BroadReach Healthcare supported target districts. All interactions with patients will be provided as part of routine care and exclusively by Department of Health staff. De-identified patient and program data will be analysed to determine health outcomes by randomised arm. Formal ethics permission will be sought from the Biomedical Research Ethics Committee of the University of KwaZulu Natal.

7.2 Informed consent

Letters of Support have been obtained from the District Managers of the Ugu and uThungulu districts. Informed consent will be sought from clinic staff for the purposes of interviewing staff/administering structured questionnaires. See Annexure I

7.3 Risks and benefits

This study does not involve the use of experimental drugs or invasive procedures. There is therefore no additional risk to patients. The entire public health clinic might benefit from the intervention if it is shown that the health systems strengthening improves outcomes in primary health care clinics.

Should the intervention package of services be shown to significantly improve HIV and TB health outcomes for patients in intervention facilities, BroadReach Healthcare will work with the Department of Health and District and Clinic management teams to ensure the continued delivery of that package of services and level of care in those facilities following completion of this study.

7.4 Confidentiality

Within the clinic patient confidentiality will be protected by the rules governing medical professionals. Patient data will be de-identified before being released for data analysis.

CHAPTER 8: REPORTING

A final report from the trial will be completed by CAPRISA including key results and conclusions and recommendations for adaptations, scale-up and roll out of the intervention on a national scale. CAPRISA will provide technical input based on the evidence of this study to BroadReach Healthcare to package the recommended integrated TB HIV services programme to enable wide-scale roll-out of the intervention. In addition, manuscripts for peer-review publication will be drafted in collaboration between CAPRISA and BroadReach and abstracts for scientific conference presentations will be prepared and submitted to appropriate journals and conferences. Biannual study reports will be submitted to the University of Kwazulu-Natal Biomedical Research Ethics Committee for review. Presentation and publication of the results of this study will be governed by CAPRISA's publication policies.

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ANNEXURE I: INFORMED CONSENT FORM

INFORMATION SHEET/CONSENT FORM FOR PARTICIPATION IN A STUDY

Centre for the AIDS Programme of Research in South Africa (CAPRISA)

Title of Study: Addressing challenges in scaling up TB and HIV treatment integration in public health settings in South

Research Ethics Committee's approval number: BF108/14

Sponsor(s) of research: The United Kingdom and South African Medical Research Council

PART A: Information Sheet

Dear Healthcare Practitioner,

You are requested to be part of a research project. Research is a way to find solutions and answers to questions. We are researchers from the Centre for the AIDS Programme of Research in South Africa (CAPRISA). The main investigator for this study is Dr Kogieleum Naidoo. We are conducting this study to better understand how clinic teams can be assisted to provide integrated TB and HIV services.

Why we have invited you to participate in this study:

You have been selected because you play an important role in the integration of HIV-TB service delivery at this primary care health clinic (PHC). Please feel free to ask questions as we go through this information with you.

Your participation in this study is voluntary. You can choose not to be part of this study or withdraw consent during the study. There will be no consequences for not wanting to participate in the study.

Procedure: One of our well trained staff will approach you for permission to ask questions about yourself and your work at this clinic. There are a couple of questionnaires on your socio-demographics, training, experience and TB/HIV integrated services that we require you to complete.

Participation in the study: This study team should not take more than an hour and half of your time to complete these questions. Please be as honest as possible in your answers. No information that can identify you will be collected (i.e. staff number, SA ID number, name)

Risks and Benefits of participating in the research: There is no direct benefit to you for being part of this study. Your participation in this research will enable us identify challenges to TB/HIV service integration as well as impact in public health settings and address program weaknesses. There is little risk to you for participating in the study. There are some questions regarding your thoughts and mood in the work place that may cause you some feelings of embarrassment. You are free to refuse to answer questions that make you uncomfortable. You will be treated the same no matter what you decide.

Cost and voluntariness of joining the research: Your participation in this research will not cost you anything, aside from your time, and is completely voluntary. Thus you are free to withdraw your consent to participate in the study.

Compensation: There is no monetary compensation for being a part of this study. You may be provided with very light refreshments after the interview process.

Confidentiality: All information you provide in this study will be kept confidential in accordance to rules governing medical professionals. Every caution will be taken to ensure your details are confidential. We can't guarantee privacy. Your information can be disclosed if required in a court of law. The interview forms will not contain information that could identify you (e.g. Staff numbers, SA ID, addresses etc). Researchers from CAPRISA and the University of KwaZulu-Natal ethics committee providing oversight to the study are the only people who will know your identity.

Sharing the results when the research is over: The knowledge gained from this research will be shared with the department of health, stakeholders other relevant health bodies. Confidential information about you will not be shared. Only a summary of the data that we collect is distributed. We also intend to publish the results to showcase best practices and improve on identified gaps.

PART B: Certificate of consent

I have fully explained this research to _____ and have given sufficient information, including about risks and benefits, to make an informed decision.

DATE: _____ SIGNATURE: _____

NAME: _____

Statement of consent from participant:

I have read the description of the research or have had it explained in a language I understand. I understand that my participation is voluntary. I have received a copy of document to keep for myself.

I hereby consent to take part in the study. Components marked "yes" and refuse to consent to participate in the components marked "no".

Interview at start -	YES	NO
Interview during periodic visits -	YES	NO

DATE: _____ SIGNATURE/THUMBPRINT: _____

NAME: _____

WITNESS' SIGNATURE (if thumbprint): _____

WITNESS' NAME (if thumbprint): _____

Ethics approval: This research has been reviewed and approved by the Research Ethics Committee of University of Kwazulu-Natal, Durban-South Africa. Any inquiries can be directed to the contact(s) below.

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