A Nurse Case Management Intervention to Improve MDR-TB/HIV Co-Infection Outcomes

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Mycobacterium tuberculosis (TB) remains the leading cause of death among persons living with Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome (HIV/AIDS) in southern Africa[1]. This syndemic places an overwhelming burden on healthcare workers and the health system. Drug-resistant TB remains a growing threat to public health despite advances in treatment and diagnosis over the past decade[2]. South Africa has the world's highest rate of TB/HIV co-infection and ranks fourth worldwide for both multi-drug resistant (MDR) TB incidence[1] and HIV prevalence. Treatment of MDR-TB, defined as resistance to isoniazid and rifampin, remains challenging and its treatment course complex. Success of second line treatment regimens is considerably less likely[3;4] than first line treatment with significantly more adverse drug reactions (ADRs). Prospective cohort studies from South Africa report less than 50% treatment success (i.e. cure or completion)[5-7] and significant differences in patients with and without HIV are noted[5]. Differences in sex and gender[8;9] as well as age[10] are rarely evaluated. In addition to the management complexity and length of treatment, systems level factors such as access to care and healthcare capacity contribute to poorer treatment outcomes. Insufficient numbers of trained physicians capable and clinically competent to manage the challenges of integrated MDR-TB/HIV care are commonplace[11]. These circumstances place a heavy burden on the most abundant healthcare resource in South Africa, the nurse. Nurses with proficiency in care models for both diseases are essential to improve treatment outcomes. Our experience dictates, however, that patients endure lengthy treatment with little assessment, support or guidance from nursing professionals due to a lack of training as well as lack of evidence-based interventions and delineated models of care for MDR-TB patients.

Nurse case management (NCM) models in which a registered nurse facilitates and coordinates treatment plans to ensure that timely, evidence-based care is given improves treatment outcomes[12;13]. Presently, there is little evidence to describe such models in TB/HIV co-infected patients globally, and specifically less evidence for MDR-TB/HIV in sub-Saharan Africa. Many studies, however, have demonstrated substantial improvements in disease outcomes utilizing nurse case managers. Complex diseases such as heart failure[14], diabetes[12], HIV[15;16] and drug susceptible TB[13;17-19] are among these. Substantial gaps remain, however, in our understanding of the impact of such interventions among co-infected patients, the influence of such models among different age groups or the cost-benefit in under resourced settings. Prior studies provide strong evidence that interventions must be multi-faceted and foster system level approaches to improve treatment outcomes (i.e. NCM patient-centered care services coupled with systems level approaches to care coordination). The Chronic Care Model identifies essential elements of a health care system that encourage high-quality chronic disease care in such a systems approach[20;21]. These elements provide the conceptual model and implementation structure for the proposed NCM plus health systems strengthening (i.e. NCM-plus) intervention, a multi-faceted health systems and patient-centered intervention to improve MDR-TB/HIV treatment outcomes. The proposed 5-year cluster randomized trial, will evaluate the NCM-plus intervention on MDR-TB treatment outcomes in South Africa, the epicenter of the MDR-TB/HIV epidemic.

Primary Aim: To determine the impact of a NCM model (i.e. NCM-Plus) on MDR-TB outcomes in patients with and without HIV co-infection in South Africa through a cluster randomized trial.

Hypothesis: Nurse case management (NCM) in intervention sites will increase MDR-TB cure and completion rates (i.e. treatment success) in comparison to usual care (UC), i.e. standardized programmatic management alone, in patients with and without HIV co-infection.

Secondary Aims:

1. To conduct sub-group analysis by a) HIV co-infection; b) sex and gender; and c) age
2. To compare the frequency and time to identification of adverse drug events between intervention and control sites.
3. To conduct a costing analysis and a cost-effectiveness evaluation of the intervention.

NCM-plus, is an intervention that combines care planning and case management of MDR-TB patients with and without HIV in a health systems approach. Each cluster will be a designated MDR-TB center from which 300 subjects will be recruited. There will be 5 clusters per arm (3000 total patients), achieving 88% power to detect a difference between the arms of 0.18; a clinically meaningful difference in MDR-TB treatment outcomes. The trial incorporates distinct methods for evaluation of many of the unanswered questions including impact of the intervention on vulnerable sub-groups and a robust cost-benefit analysis. The research team and study partners (Appendix A) developed the proposed trial collaboratively. The trial is innovative and significant as it combines both health system strengthening and individual patient care approaches within the

proven Chronic Care Model framework in a low resource setting. The evaluation of such multi-faceted interventions is necessary for success, generalizability, and sustainability within sub-Saharan Africa[22], particularly with the growing syndemic of drug resistant TB in persons living with HIV and AIDS.

1. SIGNFICANCE and BACKGROUND

1A. Tuberculosis remains the leading cause of death in patients with HIV/AIDS in sub-Saharan Africa. South Africa ranks fourth worldwide for drug-resistant TB incidence[2] and has the world's highest HIV prevalence[23]. According to estimates from the South African Department of Health (SA-DOH), 60 to 70% of patients with MDR-TB are co-infected with HIV. Addressing the treatment and health system challenges of TB/HIV integration are essential to turning the tide of this syndemic. The SA-DOH has released a guideline on the decentralization of MDR-TB care[24] to address challenges in access to care for all patients with drug-resistant TB. This framework details the need to increase the number of patients who are initiated on MDR-TB treatment, thereby reducing the time from diagnosis to treatment initiation. The framework also recommends that patients quickly transfer to primary care clinics for management with outpatient follow-up coordinated by the MDR-TB treatment facility. While this policy change will improve bed capacity, it also increases the number of health centers where patients may receive follow-up care and the number of providers actively involved. This provides a growing opportunity for fragmented care. The policy document does not identify a central individual responsible for coordinating this complex care approach and a NCM model could be the solution to the lack of care coordination. Physicians are in exceptionally short supply in South Africa[25] and task sharing models for MDR-TB, unlike HIV, have not be adequately evaluated to support programmatic management. The purpose of this trial is to test a NCM-plus intervention to improve treatment outcomes in patients with MDR-TB through both individual and system level case management strategies. Such an approach is a critical strategy to reduce morbidity and mortality in patients co-infected with HIV/AIDS, and to evaluate the cost effectiveness of such a strategy. Further, the intervention provides structure to an underutilized, yet numerous cadre of healthcare workers, professional nurses. This trial specifically engages nurses in interventions to address the major evidence-based reasons for poor treatment outcomes (i.e. death, default from treatment and treatment failure; defined in Figure 2 below).

1B. Epidemiology and Treatment Outcomes for MDR-TB/HIV Epidemics; we can and must do better.

For the last decade, all MDR-TB centers in South Africa used a standardized programmatic approach to the management of MDR-TB, which includes uniform recording and reporting forms completed by physicians and nurses. All treatment and other management decisions are at the discretion of the treating clinician[24;26]. A standardized second line treatment regimen is used, which includes an initial 6 month hospital-based intensive phase of four oral drugs plus a daily aminoglycoside injection followed by 18 to 24 months (dependent on time to culture conversion) of the same regimen minus the injectable agent in the continuation phase. During the inpatient hospitalization, nurses are present daily during the intensive phase for medication administration, but conduct little patient assessment. During the continuation phase, nurses coordinate appointments and clinic flow ***but presently are underutilized with little responsibility beyond these tasks***. MDR-TB patients are seen at weekly to bi-monthly intervals by physicians during the intensive phase and monthly by physicians during the continuation phase (Figure 1). Given the ***limited number of physicians*** and therefore, limited number of patient-provider interactions, the nursing cadre remains substantially underutilized in MDR-TB care settings.

Treatment outcomes are defined using internationally recognized criteria as described by Laserson[27]. Poor treatment outcomes for MDR-TB patients are well described irrespective of HIV status, but persons co-infected have substantially greater morbidity and mortality. Shean et al evaluated treatment outcomes of an MDR-TB cohort from 1992 – 2002 and reported a 49% cure/completion rate, 16% of patients died in treatment, 6% failed treatment and 29% defaulted while on treatment[6]. MDR-TB treatment outcomes obtained from a single center in Kwa-Zulu Natal (2000 – 2003) identified successful treatment outcomes in 43%[28]. Our study team conducted a national evaluation of treatment outcomes (2000 – 2004) which demonstrated similar findings among 757 patients with known HIV status at MDR-TB treatment initiation. We found that 348 patients (45.9%) were successfully treated, 74 (9.8%) failed therapy, 177 (23.4%) died and 158 (20.9%) defaulted. Patients with HIV were less likely to have a successful treatment outcome and more likely to die. In a competing risk survival analysis, patients with HIV had a higher hazard of death (HR: 2.33, $P<0.0001$)[5].

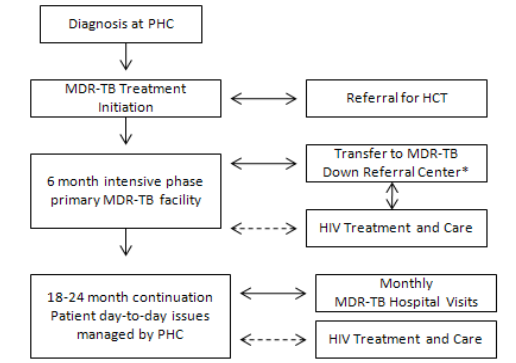
Each of these studies provides evidence of poor treatment outcomes in care models ***without access to or integration of HIV care and treatment***. Two separate meta-analyses on MDR-TB treatment outcomes

including findings from South Africa, demonstrated that treatment outcomes are exceptionally poor in areas with high HIV burden compared to areas with lower HIV burden. ***Despite this, no randomized study to date has evaluated successful programmatic implementation strategies for MDR-TB/HIV co-infected patients and the associated cost effectiveness of such intervention.***

1C. Nurse case management models for drug susceptible TB with HIV co-infection demonstrates benefit, but prior research has significant gaps. One randomized controlled trial of NCM in the United States (US) among homeless HIV positive persons with latent TB infection found that a NCM intervention (patient navigation, adherence evaluation and coaching) increased completion of isoniazid preventative therapy[18]. In Taiwan, drug-susceptible TB patients assigned to hospital-based NCM had a significantly higher rate (86.6% versus 72.8%) of successful treatment compared to patients without case management[29]. Each of these studies were conducted among drug-susceptible TB populations, provided little insight into specific measurements of the various interventions, included only patient-focused interventions and conducted no costing or cost benefit analysis – each of which are addressed in this study.

1D. Health System Factors Influencing MDR-TB Treatment Outcomes; complex care, no coordination: The MDR-TB hospital and follow-up care system is under resourced in South Africa[30]. Shortages of trained healthcare workers, particularly physicians, are commonplace[31] leaving nurses as the key implementing clinician. A national review by the World Health Organization (WHO) of South Africa's MDR-TB program in 2009 identified important gaps in the need to strengthen the healthcare system including the need for greater human capacity and support infrastructure[24]. The report specifically acknowledged challenges associated with delayed initiation of treatment, inadequate bed capacity, patient inconvenience and low cost effectiveness. A comprehensive evaluation of the South African MDR-TB treatment guidelines identifies a highly complex system of patient movement between care settings[11;32;33]. HIV co-infected patients move between a minimum of 4 centers during their MDR-TB care (Figure 1, Appendix B has a larger version). This movement between centers is haphazard with limited coordination and no single individual is held responsible for tracking patients. ***Coordination of patient movement between inpatient MDR-TB and outpatient primary care facilities and the provision of a single point person to provide continuity of care are key elements in the NCM-plus intervention and will serve to minimize fragmentation of care service and ensure communication between sites (Table 2).***

Figure 1: Process of MDR-TB Care for Patients with and without HIV Co-infection



MDR-TB, multi-drug resistant tuberculosis; PHC, primary healthcare clinic; HCT, HIV counseling and testing; dashed lines = additional requirement of HIV positive patient; * patients can move between MDR-TB Center and down referral center several times during the 6 month intensive phase based on acuity and bed needs.

1E. Patient Level Factors Influencing MDR-TB Treatment Outcomes; clinician and patient non-adherence are central: TB and HIV treatment outcomes improve with concomitant therapy and investigators within South Africa have demonstrated substantial reductions in morbidity and mortality with such models[34]. Increased access to early and appropriate anti-retroviral therapy (ART), is an urgent priority to addressing the disparity in survival for both MDR-TB patients and those with drug susceptible TB[35]. South African HIV treatment guidelines now call for the initiation of ART for any MDR-TB patient regardless of CD4 count[36]. Further, adherence to treatment guidelines is associated with improved treatment outcomes in many disease states including TB and HIV. In fact, in one US based study, 80% of persons who developed MDR-TB had at least one lapse in guideline compliance by the treating clinician[37]. ***Clinical chart audits to ensure guideline based care, accurate treatment regimens, completion of recommended clinical and laboratory evaluations, monitoring and evaluation of adverse drug reactions (ADRs) are key aspects of the evidence-based NCM-plus approach (Table 2).***

Patient non-adherence to treatment is an important reason for treatment failure and death in sub Saharan Africa [38;39]. Non-adherence is associated with longer treatment duration[40], social stigma[41] and substance abuse[42]. MDR-TB treatment is costly, and carries added burden of long-term therapy. This has a profound impact on patients and their households – e.g. job loss, loss of educational opportunities, impacts on family planning and pregnancy, and governmental grant assistance. Female-led households are often more profoundly impacted due to factors that prevent health seeking behaviors such as caring for children or the elderly within the family. Little is known about differences in treatment outcomes between men and women,

nor whether gender has an influence on time from diagnosis to treatment initiation or adherence practices. This trial will begin to address these issues through accurate documentation and analysis of gender differences. ***Training on communication strategies, mechanisms for patient tracking, and coordination of mobile injection teams as well as tracer teams will be a key role of the NCM-plus intervention. The intervention includes a comprehensive assessment of both psychosocial and gender specific barriers to adherence and interventions to address them.***

In addition to psychosocial limitations, we have identified barriers in provider-patient communication. Frequently, MDR-TB physicians are of different cultural and ethnic backgrounds than their patients. Operational evaluations during our pilot studies in KwaZulu Natal identified that care is provided by physicians who speak English and very little Zulu. In each instance, nurses translate for the physicians and a different nurse may translate at each visit. Communication difficulties between the physician and patient as well as a lack of familiarity among the translating nurses with the patient as major barriers to ensuring adequate care and patient adherence. In a study by the CDC, healthcare worker attitudes (disinterest, rudeness and lack of empathy) were identified as a major reason for MDR-TB non-adherence[43]. Language barriers[44] have been associated with a poor patient provider relationship and non-adherence. ***NCM-plus utilized nurses fluent in the patient's native language in order to bridge the gap in communication and increase continuity of care.***

1F. Adverse Drug Reactions are Common. Our analysis of the DOTS-Plus Cohort[5] demonstrated that one of the principal reasons for non-adherence and subsequent default from MDR-TB treatment is the development of adverse drug reactions (ADRs). ADRs are common occurrences in MDR-TB treatment worldwide with some studies reporting up to 72% of patients experiencing ADRs over the course of treatment[45]. Analysis of ADRs in South Africa is limited in the scientific literature. Shean et al anecdotally identified delayed side effect management as a major reason for default in their cohort [6]. During a secondary data analysis of the DOTS Plus Cohort, our research team identified a substantial underreporting of ADRs compared with published reports from other MDR-TB treatment cohorts worldwide. In our analysis of patients without concomitant ART, clinician documentation of ADRs was associated with increased odds of default (aOR: 1.63; 95% CI 1.17 – 2.28, p = <0.05) and death (aOR: 1.89; 95% CI 1.33 – 2.69, p = <0.001) controlling for age, sex, HIV status, and pre-treatment weight (unpublished data, manuscript in preparation). ***Active surveillance and reporting of ADRs to the physicians is a key element in the NCM-Plus intervention which we hypothesize will lead to earlier intervention and mitigation of these events and therefore fewer defaulters from treatment.***

1G. HIV integration remains limited. Presently, HIV counseling and testing is offered and information on previous HIV diagnoses and any prior ART is obtained from participants and medical records by lay counselors. Persons with a positive HIV test result are referred to the HIV clinicians to discuss treatment. ART is implemented outside the MDR-TB program in the majority of hospitals. Two principle ART regimens are available for use in the public sector; regimen one is efavirenz based and regimen two is lopinavir/ritonavir based in addition to two nucleoside reverse transcriptase inhibitor background regimens consisting of either lamivudine/emtricitabine, stavudine, tenofovir or abacavir. Untreated HIV remains one of the leading reasons for mortality in MDR-TB patients, and recent South African HIV guidelines recommend initiation of anti-retroviral therapy in all MDR-TB patients regardless of CD4 count[36;46]. South Africa specific guidelines recommend integration and movement toward community-based treatment programs[46-48] within the primary care system. Implementation of MDR-TB and integrated HIV care in a community-based platform is very challenging, requiring clinicians to navigate HIV and MDR-TB treatment guidelines, overlapping drug toxicities and parallel care systems potentially leading to greater fragmentation of care[32]. At no point in the MDR-TB clinical guideline, is NCM or care coordination of any type mentioned for the co-infected patient due, we believe, to a lack of evidence-based approaches. **This intervention is designed to integrate and coordinate care with specific attention to HIV co-infection through a test, refer and treat strategy.**

1H. Improvements in disease management outcomes utilizing NCM approaches are feasible. NCM interventions are effective in improving outcomes of complex diseases including HIV[15;16] and drug susceptible TB[13;17-19] in under-resourced settings. Data from these studies demonstrate that, interventions must be multifaceted and tailored to the population of interest to improve treatment outcomes. ***This study meets those requirements and will translate a proven model within the US and piloted within South Africa***

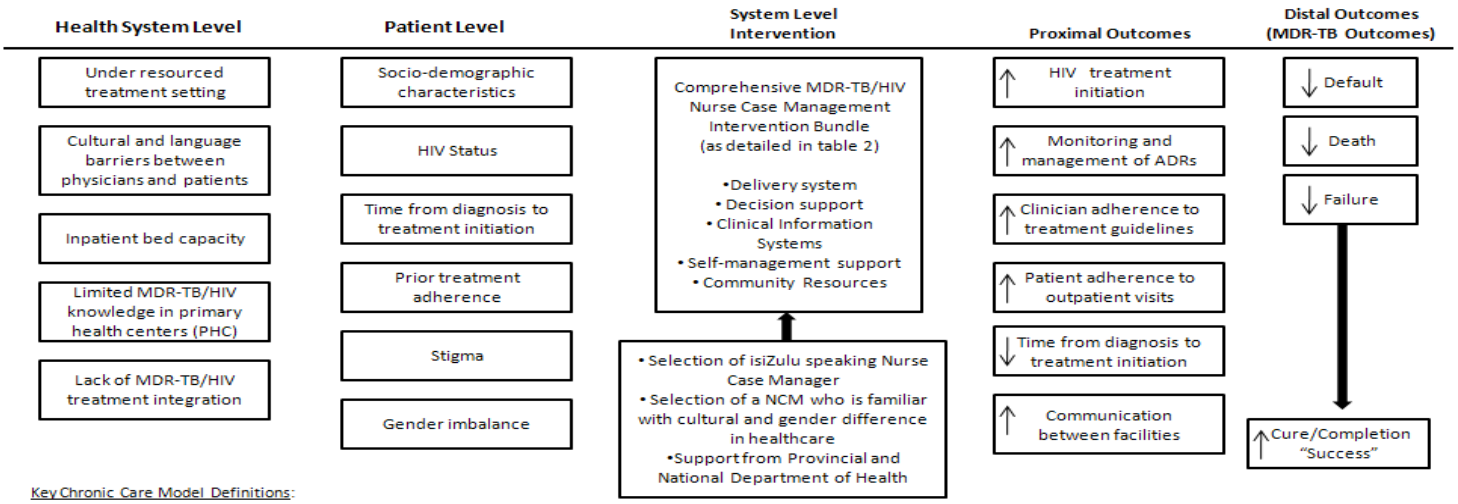
(see, Pilot Studies, below). The study is logistically feasible and programmatically congruent with the goals of the South African TB program. Nurse case managers ensure the coordinated delivery of effective, efficient clinical care, self-management support, and community resources, and in this way fit within the theoretical framework of the Chronic Care Model which guides this work. The NCM-Plus trial is particularly timely and important as economic and health system factors force changes in MDR-TB and HIV care[33]. These changes expand access to care, but also add the risk of further fragmenting care delivery. If the aims of this study are successful, the NCM-Plus intervention will provide a model of care that will ensure the best possible treatment outcomes while fostering appropriate utilization of resources and continuity of care across the MDR-TB and HIV continuum. This proposed cluster randomized trial is based on the development of a clear, proven conceptual model along with substantial process and programmatic pilot data that establish proof of concept and developed and refined the intervention protocol and data collection tools.

1I. Conceptual Framework: The proposed trial is guided by the Chronic Care Model (CCM) which identifies the essential elements of a healthcare system that support high quality chronic disease care[20;49]. Proven effective in HIV and other chronic diseases in over 500 healthcare organizations, the CCM describes the five necessary components for a systems approach to encourage and sustain productive interactions between clinicians, patients and their providers; delivery system design, decision support for clinicians, clinical information systems, self-management support and community resources. This systems approach forms the basis for the NCM-Plus intervention that has been developed (Figure 2). In our intervention, we hypothesize improvements in proximal outcomes (i.e. treatment choice, clinician adherence, etc) to be moderators/predictors of the distal outcomes (i.e. success, death, default and failure). The interventions associated with each proximal outcome are outlined in Table 2.

Application of the Chronic Care Model (CCM) in the NCM-Plus Intervention: We have designed a systems level MDR-TB/HIV NCM-Plus intervention to improve both proximal and distal treatment outcomes (Figure 2, Appendix B). Each proposed intervention addresses an issue identified either within our pilot evaluation (see Pilot Studies, below) or through existing literature on NCM models. We believe a systems level, multifaceted intervention that serves to coordinate care across inpatient and outpatient settings and within and among specialty groups will be an efficient and effective means of improving treatment outcomes. We have chosen to purposefully select nurse case managers who speak the language appropriate to the intervention site in order to enhance culturally appropriate care and limit communication barriers which were identified in pilot work.

The information that follows provides an overview of the treatment paradigm of MDR-TB care in patients with and without HIV co-infection. The application of this conceptual framework within the South African healthcare system is timely and supportive of the countries' movement toward decentralizing MDR-TB care into the primary healthcare system[33]. The reach of the proposed study will involve 10 different treatment centers and 3,000 patients, setting the stage for a highly sustainable and generalizable intervention. The study is guided by several years of ongoing research as well as recent pilot work evaluating the proposed NCM-Plus intervention in a setting with 63% HIV co-infection. The CCM has been extensively studied in high resource countries; a useful template by which to translate this intervention into an under resourced healthcare setting and into a program with a standardized treatment approach.

Figure 2: Chronic Care Model for MDR-TB & Definitions of Treatment Outcomes
(Please see Appendix B for larger version)



Key Chronic Care Model Definitions:
Delivery system – assure effective, efficient clinical care and self-management support
Decision support - promote clinical care consistent with scientific evidence and patient preferences
Clinical information systems – organize data to facilitate efficient, effective care
Self-management support - empower and prepare patients to manage their health and health care
Community resources - Mobilize community resources to meet needs of patients

Key MDR-TB Outcome Definitions:
Default – interruption of treatment for a period of 2 or more consecutive months
Death – any death while on MDR-TB treatment
Failure – A patient has failed treatment if two or more of the five cultures recorded in the final 12 months are positive, or if any one of the final three cultures is positive. Treatment will also be considered to have failed if a clinical decision has been made to terminate treatment early due to poor response or adverse events.
Cure/completion – A patient who has completed treatment and has been consistently culture-negative (with at least five results) for the final 12 months of treatment. If only one positive culture is reported during that time, and there is no concomitant clinical evidence of deterioration, a patient may still be considered cured, provided that this positive culture is followed by a minimum of three consecutive negative cultures, taken at least 30 days apart. A completion does not meet definition of cure based on availability of culture results. Success = combined cure/completion.

ADRs, adverse drug reactions – any untoward consequence of MDR-TB treatment

This trial is **significant** in: 1) targeting a health systems strengthening approach through rigorous methodological design; 2) addressing a systematic model of care that improves implementation and coordination of scarce resources in an effort to evaluate strategies that meet the need for shared responsibility and scalable interventions in HIV and AIDS care between the US and partner countries[22]; 3) developing a model that is easily modified for inclusion of non-communicable disease coordination and management; 4) including 13-17 year old subjects to address the growing concerns about MDR-TB in adolescents.

2. **INNOVATION**: The proposed NCM-Plus trial has several novel and innovative features:
   a) Nurse case management models are highly effective, however, this is the first trial to evaluate such an intervention for improving MDR-TB treatment outcomes and to integrate MDR-TB/HIV into a simultaneous systems level intervention (NCM-plus).
   b) Although designed as a holistic approach, each aspect of the intervention is tailored (Table 2) to allow clear analysis of the individual components to inform future policy, practice and cost effectiveness evaluations; this sets this study apart from prior nurse case management studies in TB/HIV.
   c) The systems level strategy utilizing the chronic care model has not been evaluated in such a low resource setting, an important novelty for this study due to the healthcare delivery system's unique challenges.
   d) This strategy is highly sustainable in that it does not change, but enhances and reorganizes, the required skill set of professional nurses providing this care.

3. **APPROACH:**

3A. NCM-Plus Pilot Studies: The proposed cluster randomized controlled trial is based on a 6 month quasi-experimental pilot study among 40 MDR-TB patients, 63% co-infected with HIV. The pilot established the proof of concept and tested the intervention's ability to effect change and improve implementation of patient centered, guideline-driven care (Table 1). This pilot included a single MDR-TB Center utilizing one full-time Zulu/English speaking nurse case manager who was easily able to enroll subjects (20 male, 20 female, 100% black South African).

Table 1: Selected^ Changes between Baseline and 6-month Intervention Period for Hospitalized Intensive Phase MDR-TB Patients (n=40)

NCM-Plus Intervention	Pre-Intervention Period	Intervention Period	Difference
Delivery System			
Percent of Patient Receiving referral/completion of Audiology Screening per guideline	30%	100%	70%
Readiness for Discharge Planning Tool Development and Utilization	N/A	100%	N/A
Decision Support			
Baseline symptom evaluation on treatment initiation	5%	100%	95%
Baseline and monthly laboratory evaluations completed, per guidelines (MDR)	10%	85%	75%
Use of co-trimoxazole preventative therapy, per guidelines n = 25 (63% HIV co-infection)	64%	88%	24%
Concordance between HIV medical record and MDR-TB medical record for HIV treatment regimen and dosing	56%	100%	44%
Average Adverse Drug Reactions (per patient) *Pre-intervention period was passive, patient self-report only	2.6 Passive	3.5 Active	35%
Adverse drug reactions acted upon by medical or nursing intervention	25%	100%	75%
Clinical Information Systems			
Weekly Goals Sheet Developed and Utilized During Inpatient Rounds	N/A	100%	N/A
^ Our pilot period did not include all of the final NCM-Plus interventions as some interventions are not necessary during inpatient hospitalization**; additional interventions were added to the final intervention from process and focus group evaluations after a review of system level requirements**; all tools identified within the appendix where piloted and refined; N/A, not applicable			

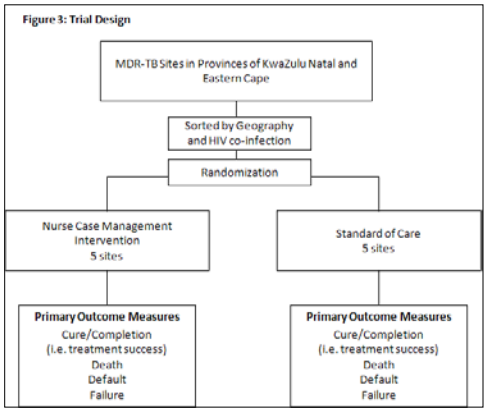
Our research team also conducted two focus group discussions with nurses (n=10 per group) in KwaZulu Natal. The themes identified were: 1) feeling ill prepared to accept responsibility for MDR-TB management; 2) belief that primary health centers are unsupported by the MDR-TB/HIV treatment facilities. Communication difficulties were cited as the most common reason for concern, specifically, a lack of communication regarding inpatient activities and follow-up plans of care. They cited the need for a single point person to facilitate care coordination, transport needs and guideline adherence.

3B. Study Design and Primary Aim: Given the substantial overlap in co-infection, addressing the challenge of TB/HIV integration is essential. This study proposes to do so by testing the effectiveness of a NCM intervention to improve treatment outcomes in patients with MDR-TB, a critical clinical strategy to reduce morbidity and mortality in patients with and without HIV/AIDS.

3B1. Primary Aim: To determine the impact of a NCM model on MDR-TB outcomes in patients with and without HIV co-infection in South Africa through a cluster randomized trial.

Hypothesis: *Nurse case management (NCM) in intervention sites will increase MDR-TB cure and completion rates (i.e. treatment success) in comparison to usual care (UC), i.e. standardized programmatic management alone, in patients with and without HIV co-infection.*

3B2. Cluster Randomized Trial (CRT) Design: The proposed NCM-Plus study is designed with randomization of MDR-TB treatment centers because care is managed within these centers by a single treating physician and healthcare team, and therefore it would be difficult to prevent contamination of the intervention if individuals were randomized. The MDR-TB treatment centers, with their adjoining outpatient HIV treatment facilities, are the unit of randomization. Because of the relatively small number of centers in the country, there is a risk of imbalance on key covariates if a simple randomization scheme is used. For this reason, we will use a highly restricted randomization approach[50], which we will design to achieve a close balance across treatment arms on the following variables: MDR-TB program size (i.e. 150 or more patients per year versus 149 or less) and geographical location (i.e. rural versus urban/peri-urban). Within each of these four categories we will randomly assign each of the centers to intervention or control arms (Figure 3, Appendix B). The intervention sites will receive the NCM-Plus Intervention (Table 2). To ensure standardized implementation of NCM-Plus interventions, each NCM will undergo a comprehensive training by the team, our consultants and research coordinator (see *Nurse Case*



Manager Intervention and Fidelity Plan, Appendix G). The control sites will receive usual care and a research assistant will record data without intervention.

3B3. NCM Intervention: Our team designed the NCM-Plus intervention (Table 2) by integrating the domains of the CCM with added attention to linkage to care, building on evidence-based guidelines and our team's pilot findings. These have been adapted for a South African MDR-TB/HIV specific context. In the design of our NCM bundle, we address the principle challenges from prior studies on NCM interventions; a lack of clarity in how elements of the interventions were measured as we provide extensive details on both proximal (moderating or predicting) and distal outcome variables. Nurse case managers will be hired as professional 3-year diploma or 4 year-degree nurses and trained (described below) to improve disease management for patients with MDR-TB and HIV. Specific measurable responsibilities will be implemented by each nurse case manager at sites randomized to receive the intervention as identified in Table 2. The NCM-patient interaction will occur at the MDR-TB treatment inpatient unit or within the outpatient department of the facility. It is important to note that the NCM-Plus intervention does not change patient interactions with physicians except to ensure guideline-based care by assisting the clinician to monitor and adhere to clinical guidelines and to streamline the evaluation through daily and monthly goal monitoring. **NCM to Patient Ratio:** The NCM to patient ratio will be approximately 1:300 over the entire 5 year period; enrolling approximately 100 – 150 patients per year. The patient panel will be built slowly as new patients are admitted to the MDR-TB centers; 10-15 consecutive patients per month until recruitment goals for the year are reached. The interactions with the patient will be 5 times per week with the NCM or a supervised designee (i.e. mobile injection team member) during the inpatient intensive phase of treatment (6-8 months) and monthly during the outpatient continuation phase. The study team will provide each NCM with a mobile phone to assist with care coordination.

3B4. Standard/Usual Care: Usual care is defined as standardized programmatic management of MDR-TB/HIV without care coordination. Nurses are present as part of the team, but with no special coordination role, leaving the MDR-TB physician solely responsible for treatment outcomes with little support. Physicians see patients weekly during the intensive phase and the patient receives basic daily nursing care without coordination of care, active monitoring of ADRs or HIV care integration. This care transitions to monthly visits with the physician in the continuation phase, again with very little nursing involvement in care coordination.

Table 2: Individual Components of Intervention Organized According to CCM Framework and Outcome Measures

Domains	NCM-Plus Interventions	Proximal Moderators of Distal Outcomes* and Measurement
Inpatient and Primary Health Care Delivery System	**Care coordination across inpatient facilities (i.e. linkage to care)** a. Evaluate readiness for discharge to down referral or outpatient management b. Prioritize admissions from waiting list based on needs c. Referral to supportive services (audiology, physiotherapy, nutritionist and palliative care as necessary)	a. Length of inpatient stay; days b. Time from diagnosis to treatment initiation of MDR-TB and HIV ; days c. Multi-disciplinary team involvement; Yes/No
	Care coordination across primary healthcare and hospital outpatient facilities (i.e. linkage to care) a. Monitor adherence to MDR-TB and HIV visits b. Identify missed appointments and assign tracing team if patient cannot be found c. Provide an ongoing resource for patients within the community via telephone triage of problems	a. Number of missed appointments; frequency b. Tracing team locates patient and re-establishes care; Yes/No c. Number of telephone calls received from outpatient; frequency
MDR-TB and HIV Decision Support	**MDR-TB and HIV Regimen selection** a. Support guideline-based regimen selection (guidelines followed) b. Monitor changes to treatment regimens (changes implemented when necessary) c. Time to ART initiation after MDR-TB hospital admission	a Clinician adherence to MDR and HIV guidelines; Yes/No b. Time from identification of need to change to changes in therapy; days c. Time to ART initiation; days
	Adherence to Guideline-Based Key Clinical Time Points for Laboratory and Diagnostic Evaluations a. Monitor frequency of MDR-TB diagnostic and laboratory evaluations (Table 3) b. Monitor frequency of HIV visits, CD4 count and viral load evaluations	a Adherence to MDR-TB and HIV guidelines; Yes/No - Laboratory evaluations - HIV evaluation
	HIV Integration: Test, Refer and Treat Strategy a. Initiate HIV counseling and testing	a. Number of patients refusing of HIV testing; frequency

	b. Refer to ART counselor, as necessary (linkage to care) c. Evaluation for first window of opportunity to begin ART after MDR-TB treatment initiation	b. Number of patients started on ART; frequency c. Time from MDR-TB treatment initiation to ART initiation (days)
	HIV Integration: opportunistic infection (OI) prevention screening & initiation a. Monitor initiation of cotrimoxazole (CPT) b. Appropriate OI and concomitant illness screening	a. Number of patients with cotrimoxazole initiation; frequency b. Number of patients who receive CD4 appropriate screenings; frequency
	Active Surveillance for Adverse Drug Reactions (ADRs) a. Active monitoring for ADRs b. Communicate event with physician c. Develop plan to remedy ADR in consultation with physician	a. ADR events; frequency b. Time from identification to management; days c. Time to resolution of ADR; days
Clinical Information Systems	**Coordination of MDR-TB/HIV Monthly Case Discussion** a. Selection of patients and coordination of clinical review with HIV team, if applicable	a. Patient review in case discussion; Yes/No b. Case review includes HIV team; Yes/No
	Interdisciplinary Communication a. Completion of Interdisciplinary Weekly Goal Sheet during Inpatient Rounds	a. Weekly goals established for patient; Yes/No
Self-Support	**Patient Coaching/Support/Skills Building to Encourage Medication Adherence During Outpatient Phases of Treatment** a. Provide education and anticipatory guidance for maintaining adherence b. Encourage self-report of difficulties with adherence	a. and b. Patients with medication non-adherence; frequency
Community Resources	**Evaluation of patients psychosocial community needs** a. Identify barriers to care and plan to remedy b. Arrange parental/guardian transport for visitation of admitted children (13-17 years)	a. Missed appointments related to psychosocial barriers; frequency b. Parental visitations; frequency
*Distal outcomes (success, death, default and failure) are defined in Figure 2 based on standardized definitions[27]		

3B5. Orientation and Training to Ensure Standardization of Documentation & Intervention:

Upon hire of the five professional nurses, they will receive a one month training course to ensure sufficient knowledge and skills. Each training session will be conducted by the PI, study coordinator and the NCM who worked on our pilot study, Ms. Ntombasekaya Mlundu, RN (see other significant contributors and biosketch). The physician, Dr. Semi Lachman, who participated in the pilot site, has also agreed to participate in the training (see, Letter of support). We have included a letter of support from a consultant, Marion Loveday, who has extensive experience in health systems operational research and MDR-TB/HIV data collection and who will assist in training (see, Letters of Support). The training, based on the Institute for Healthcare Improvement's CCM framework[49;51], has been systematically evaluated over the last 24 months in multi-disciplinary sessions with over 250 trainees and modified based on feedback. The NCM-Plus training plan has been shown to increase both knowledge and self-efficacy[52]. This 1 month training includes both didactic lectures (2 weeks) as well as problem-based clinical scenarios applying the individual components of the intervention (2 weeks). Both the research assistants (RAs) and NCMs will also undergo training on data collection, inter-rater reliability and research ethics as well as interdisciplinary communication during the second week of training. Pre-post knowledge evaluations and case-based take home materials will evaluate comprehension of clinical content. A NCM self-review along with competency evaluations from two additional reviewers (i.e. PI and MDR-TB physician) will be completed upon completion of training. We will evaluate both RA's and NCM's data collection skills through mock patient evaluations using our data collection tools. A training agenda, pre-post test and competency evaluation for both NCMs and RAs is available in Appendix C.

3B6. Description of MDR-TB Treatment Centers, their Patient Population and Study Eligibility Criteria:

MDR-TB Center Selection. Our participating 10 MDR-TB Treatment Centers were chosen in collaboration with the Provincial Departments of Health in KwaZulu Natal (KZN) and Eastern Cape (EC) Provincial Departments of Health based on inclusion criteria below. Participation will be sought from each of the centers listed in Appendix D. Prior research in these centers resulted in 100% participation (n=24)[53]. Although only 10 Centers are required based on cluster allocation requirements (see Cluster Requirements and Analysis), we have provided details on additional centers to account for possible refusal to participate in the trial. South Africa has

a total of 31 MDR-TB hospitals and additional provinces/centers could be added if needed. Each facility involved in the trial has a dedicated MDR-TB outpatient consulting area and treatment space.

Patient Characteristics. As these are public hospitals, patients are generally poor or have exhausted medical aid availability in the private sector. Racial statistics are not collected by the institutions; however, the majority of individuals receiving care in these settings are black South Africans. All racial groups will be screened for eligibility and have equal access to recruitment in the protocol. Each center will admit adolescents (13-17 years of age) to the adult unit; in the 6 month pilot, our single center admitted 4 patients in this age group.

Center and Individual Inclusion/Exclusion Criteria: The following cluster (center) and individual inclusion/exclusion criteria have been chosen after a comprehensive review of the infrastructure at each facility. We did not wish to be overly exclusive in our choice of center, as that would limit generalizability of our results. We do believe, however, that at an individual patient level, several important exclusion criteria are required.

Center (Cluster Level) Inclusion Criteria:

- MDR-TB Centers in KZN or EC, South Africa providing standardized MDR-TB regimen according to National Department of Health guidelines
- Facility has provided MDR-TB care for a minimum of 6 months at study initiation
- MDR-TB Centers with facility-based access to anti-retroviral therapy
- Facility willingness to participate in the study

Individual (Patient Level) Inclusion Criteria:

- Patients 18 years of age and older, with microbiologically confirmed MDR-TB, admitted to receive inpatient care at a participating hospital who signs informed consent within 7 days of admission.
- Patients 13 – 17 years of age, with microbiologically confirmed MDR-TB, who provide consent for study team to contact parent or legal guardian and when patient is willing and parent or legal guardian provides approval for study participation within 7 days of admission.

Individual (Patient Level) Exclusion Criteria:

- Persons who present to the MDR-TB ward who have started MDR-TB treatment prior to admission.
- Children, less than 13 years of age; only one participating center has an MDR-TB wards for children under 13.
- Persons who are unable or unwilling to provide informed consent for participation.
- Any patient enrolled in another clinical trial that changes standard MDR-TB or HIV care.

3B7. Center (Cluster) Recruitment: For enrollment, the study team will contact, via telephone or e-mail communication, each center to detail the study (see sample contact letter in Appendix E). A pre-study site visit will be conducted as necessary if written/electronic/verbal communication is insufficient. The PI has successfully used this strategy in previous studies[5;53]. With a clear understanding of the intensity of this effort, the PI has made initial strides to ensure adequate participation by the proposed centers. He has letters of support from the National Department of Health MDR-TB Coordinator as well as KZN and EC MDR-TB Coordinators which are necessary pre-requisites for obtaining center specific approval. We have letters of support from 12 of the centers demonstrating their willingness to participate in this study. We do not anticipate any difficulties with center participation, but have included more than 10 letters from our hospital list (Appendix D) as a contingency plan. Outside of the listed centers, there are currently an additional 18 possible MDR-TB centers that could be approached for participation throughout the country. These centers are not included in those proposed for pragmatic reasons related to scope of the project and funding limitations. We have conducted two prior studies within these centers. This included obtaining research approval in all 9 South African provinces as well as national ethical approval through the Medical Research Council and The Johns Hopkins University Institutional Review Board.

3B8. Patient Recruitment and Informed Consent Process: The NCM or research assistant will approach patients within 48 hours of admission, allowing up to 7 days for enrollment to facilitate obtaining parent/guardian consent for adolescents. Currently, a MDR-TB patient (adults and adolescents) signs a one-page indemnity form for standard MDR-TB treatment that details the MDR-TB treatment regimen and basic expectations associated with the treatment course. This signature is obtained by the admitting physician or nurse and the document is available in Zulu, Afrikaans, Xhosa and English. We propose adding a 2-page MRC

approved consent/ascent form to the existing consent for treatment (see Human Subjects Research Section for additional details and Appendix E for MRC approved consent document). We have completed the South African Medical Research Council ethical review process utilizing their approved consent template, as the Johns Hopkins University consent template was too challenging for a South African citizen/resident, the MRC has requested a simplified consent (see, Appendix E). The MRC consent explicitly notes that every participant may refuse to answer any questions or terminate his/her involvement at any time. The informed consent process may occur up to 7 days after admission to allow adequate time for patient consideration of enrollment. If a patient declines to participate in our research they will still receive the standard of care at that center, but research data will not be collected or analyzed for that patient. This method was utilized in our previously published cohort[5] and observational studies[53] in South Africa. Our human subjects and women and children's sections provide further detail on the consent process.

3B9. Clinical Documentation Tools and Data Collection Tools: We conducted a comprehensive review of all clinical documentation tools during our pilot and updated these tools to reflect the requirements of this proposal and, importantly, reviewed them with South African MDR-TB/HIV clinicians to ensure they accurately reflect treatment paradigms. Table 3 provides an overview of all documentation tools and the expected time of completion as well as a detailed summary of guideline-based diagnostic and laboratory evaluations; a larger version is available in Appendix B. Our clinical management form including standard operating procedures (SOPs) for NCMs and RAs are found in Appendix F.

Upon admission to the MDR-TB center, the NCM will conduct admission screenings using the Admission Assessment Form for identification of treatment history, symptoms and co-morbid diseases. This admission documentation tool provides a description of all key patient details including basic demographics, baseline clinical parameters such as height and weight, concomitant illnesses and their severity, all prescription and non-prescription agents including herbs and illicit substances, as well as comprehensive baseline symptom assessment. Day to day care will be documented on the clinical management form, which will serve as the study's main case report form and is not part of routine clinical care. Symptom review forms will describe ADRs in detail including the onset, location, duration, character, associated symptoms, relieving and aggravating factors, treatment, and severity of the individual symptom. Following the initiation of MDR-TB treatment, the NCM will begin active surveillance for adverse drug reactions. Daily assessments will occur using the Symptom Review Form during the intensive phase of treatment with monthly assessment occurring during the continuation phase. After symptom review is completed at the intervention sites, the NCM will work with the treatment team to develop a plan to mitigate this symptom using the Symptom Action Form. Control sites will simply document ADRs as reported in the medical record. All events will be reported to the National Adverse Drug Event Monitoring Center (NADEMC), a collaborating partner, using the required reporting forms modified for MDR-TB. On discharge the NCM will prepare a follow-up instructions sheet. Outside of recruitment and reporting, the RAs will only abstract data from the medical record with no direct patient intervention.

Table 3: Documentation Tools and Schedule of Clinical and Research Measures for All Patients

Data Collection Instruments	Responsible NCM/RA	Admission	Months Since Treatment Initiation																							
			Intensive Phase						Continuation Phase																	
		Hospital Admit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Admission Assessment Form	NCM	X																								
Clinical Management Form (Daily Review)	NCM/RA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Symptom Review Form	NCM/RA	X	D	D	D	D	D	D	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Symptom Action Form	NCM	X	Completed Only with Positive ADR																							
SA NADEMC Report Form	NCM/RA	X	Completed Only with Positive ADR																							
Guideline-Based Recommendations for Clinical Monitoring	LABORATORY AND CLINICAL MONITORING TIMELINE																									
Sputum Smear & Culture		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight		X	W	W	W	W	W	W	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height		X																								
BMI (body mass index)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
DST (drug susceptibility test)		X						X																		
Chest X-ray		X						X	Clinically Indicated				X	Clinically Indicated					X	Clinically Indicated					X
Serum Creatinine		X	X	X	X	X	X	X																		
Creatinine Clearance		X	X	X	X	X	X	X																		
Serum Potassium		X	X	X	X	X	X	X																		
HIV Screening		X	Every 12 months																							
CD4 testing		X	Every 6 months if HIV positive																							
Viral Load testing		X	Every 6 – 12 months if HIV positive																							
TSH (if on Eth or PAS only)		X						X					X							X						X
ALT		X	Monitor every 1-3 months if on Pyrazinamide																							
Alkaline Phosphatase		X																								
GGT		X																								
Audiometry/Hearing Screening		X	X	X	X	X	X	X																		
Pregnancy		X	Only if Clinically Indicated																							
Vision screening		X	Only if Clinically Indicated																							

Key: NCM = Nurse Case Manager; RA = Research Assistant; D = daily; W = Weekly; M = Monthly; ADR = Adverse Drug Reaction; Eth = ethionamide; PAS = para aminosalicylic acid

Standardization of Data Collection between Intervention and Control Sites: Instructions are provided throughout the various tools for reminders on how to collect each variable to ensure inter-rater reliability. We have also developed several case studies to test both groups on ability to complete the data collection tools. Data collection regarding clinical care and treatment outcomes will be standardized across intervention and control sites. There are some additional reporting requirements for NCMs to ensure documentation of the NCM-Plus intervention and outcome. The RAs and NCMs will receive identical training on data collection, reporting and data entry requirements. This process will be evaluated and overseen by the research coordinator for the study.

Day to day clinical documentation by all providers will be evaluated by the NCM and RAs at each site. We will provide all sites with a list of documentation tools that should be completed on each patient. We will create a "standardized patient chart" for both the intensive phase and continuation phases at each institution to facilitate use of these tools. An overview of the clinical documentation expected for each patient and the time points of data collection throughout the study is provided in Table 3 (larger version Appendix B). To standardize data collection, the research assistants will utilize the same clinical management forms and SOPs to document patient information as utilized by the NCMs (Appendix F). We understand that standardized documentation alone may be an intervention; however, we believe this standardization is required to make an adequate comparison between sites. All laboratory evaluations including sputum, blood and urine will be analyzed at The National Health Laboratory Service (NHLS) sites as directed by the DOH in each province. The NCMs will evaluate the clinical information collected on all subjects and will document if laboratory assessments were ordered correctly, ordered and not processed/canceled by lab, or not ordered at all. Each NHLS lab is certified as per South African requirements with an extensive internal quality assurance program associated with each treatment center (http://www.nhls.ac.za/?page=quality_assurance&id=40).

3B10. Data Management and Security: Study data will be collected and managed using REDCap (http://www.project-redcap.org) which is a secure, web-based application designed exclusively to support data capture for research. ***This database has been designed and implemented during our pilot study and is ready for use*** and the REDCap system has been validated with translational research[54]. The Johns Hopkins University is a member of the REDCap consortium and this application is freely available to consortium members. REDCap provides: 1) an intuitive interface for data entry (with data validation); 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages (SPSS, SAS, Stata, R); 4) procedures for importing data from external sources; and 5) advanced features, such as branching logic and calculated fields. To maximize quality control, staff will be trained by the PI in all data collection and entry procedures. The PI will have access to all data upon entry into REDCap. The research coordinator will monitor data collection by checking completed questionnaires for completeness and referring back to the NCM or research assistant if required. Due to the size of the study, double-data entry methods will be utilized on a 10% random sample, with checks for discordant errors, and as data are entered into the REDCap system. Study team members will have the access codes to enter and retrieve these data based on pre-determined job requirements.

3B11. Number of Centers (Clusters) Required: To determine the number of clusters necessary to achieve 80% power we selected an intraclass correlation (ICC) of 0.05. This low ICC is based on our prior work within these facilities, where we identified similar treatment outcomes across provinces and centers. We believe this is related to the standardized management throughout the country which limits between facility treatment variations[55-57]. The ICC of 0.05 provides sample sizes of 10 clusters (5 intervention/5 control) with 1500 subjects per assignment with 300 subjects in each cluster. The control group proportion is 0.60 success, based on recent data from Department of Health collaborators since the increase in availability of anti-retroviral therapy. The intervention group proportion is assumed to be 0.60 under the null hypothesis and 0.80 under the alternative hypothesis (effect size 0.18; 88% power). The test statistic used will be a two-sided Wald test from a Generalized Estimating Equations (GEE) log-binomial model for treatment success at 24 months post-enrollment with a test size of 0.05.

3B12. Outcome Measures and Analysis of Aims: *Primary Aim (Distal) Outcome Measure*:

- **MDR-TB treatment outcome by cluster allocation (NCM-Plus versus Usual Care):** Standard definitions for cure, completion, default, failure and death will be used to evaluate final treatment outcomes[27]. Cure and completion will be combined into "success". Each outcome is defined in Figure 2, Appendix B.

We have chosen the cluster randomized design given the underlying assumption of lack of independence at the patient level within each center. Our prior analyses of treatment outcomes from these centers reflect minimal between-center differences. We recognize that there are many within-cluster covariates that are specific to treatment location which may influence treatment outcomes. While we have extensive experience in the proposed MDR-TB centers, it would be impossible to account for all possible causes of between-cluster variation and therefore have prepared our cluster size and analysis approach under the assumption of between-cluster variability.

Analysis of Primary Aim: We will begin by assessing the success of the constrained randomization scheme. For these, both weighted (by cluster size) and unweighted cluster means will be used, to assess potential for discrepancies between population-averaged and cluster-specific analyses. Bubble plots of cluster outcome summaries, with bubble size inversely proportional to variance, will be used to display intervention effects and to identify outlying clusters (if any). The primary analyses will consist of risk ratios (RRs) and 95% confidence intervals (95%CIs) to assess the relationships between the NCM intervention and overall treatment outcome (i.e. cure and completion). We will conduct Generalized Estimating Equations (GEE) regression analyses[58] with log link, binomial outcome and exchangeable correlation structure, to determine the effects of NCM on final treatment outcome. As an interim analysis, similar models will be used to model the risk of modification in treatment, treatment discontinuation, default, and death at the end of the intensive phase.

Analysis of Secondary Aims: Multivariate analysis will be conducted using both incidence (binomial or Poisson-based GEE models, as appropriate) and time-to-event data (Cox models with gamma frailty component, or log(days) regression models if there is minimal censoring) to investigate the intervention effect and then, determine factors associated with adverse drug reactions and each outcome of interest. Statistical significance will be identified when $P<0.05$.

Sub-group analysis: a) Patients with HIV co-infection: after evaluation of overall cohort outcomes the data will be stratified by HIV status to determine relationship of NCM-Plus intervention in those with and without HIV. The PI and collaborators have recently published a cohort analysis of MDR-TB treatment outcomes from SA stratified by HIV status and have noted expertise on this type of evaluation[5]; b) Gender: although, our previous work did not demonstrate significant differences in treatment outcomes between men and women, in this study we will examine the impact of gender and the following variables: head of household status; time from diagnosis to treatment initiation; number of transfers between facilities; and age to determine if any relationship exists. We hypothesize that women will have a longer time to treatment initiation and that women led households will experience an even longer delay between diagnosis and treatment initiation than men; c) Age: the sample will be analyzed by appropriate age categories to determine the impact on treatment outcomes. This will enable evaluation of important groups such as those 13 – 17 and those over 60 years of age.

Adverse Drug Reactions (ADRs). First, we will evaluate differences between the NCM-Plus intervention and control arm to determine differences in frequency of each of the most common ADRs. Our prior analysis demonstrates a substantial influence of ADRs on treatment outcomes. We plan to assess ADRs to determine if they serve as a mediator of treatment outcomes. Rather than just putting them in a regression and seeing how much the treatment effect diminishes upon their inclusion, we will form principal strata based on the potential ADR event categories and randomization assignment, and then investigate the role of ADRs and the direct effects of the intervention[59]. Such an analysis adjusts for the non-random distribution of ADRs across the study arms. We anticipate there will be a substantial lead time 'bias' with respect to ADR identification--this is one of the goals of the NCM-Plus intervention, to detect these earlier and more often, with the hope that this will lead to lower default and higher cure rates. We will compare ADR rates across the study arms, as a process check, to see if there are resultant increases in reporting, as we would expect from an active reporting system (compared to the passive one in the standard of care arm).

Costing analysis and a cost-effectiveness evaluation of the intervention. We will conduct a costing of the intervention and a cost-effectiveness analysis. The costing will involve micro-costing, an ingredient based approach, which results in a line item analysis of each resource (including labor) required. The data describing the quantity of resources used will be drawn from project records and reports from the staff including the time of the trainer and the nurses being trained as NCMs during training (attendance sheets), the nurses' time during the intervention (staff reports for one day each at regular intervals), any supplies used during the training and intervention (project records), and any medical care received by the study subjects (study subject

records). Wages will be based on average wages in SA for these types of personnel available from the South African government. If the costs averted are found to be greater than the cost of the NCM program so that NCM-Plus intervention saves money and is more effective, then it can be described as dominating: a more effective, less expensive then it is economically the correct choice. In contrast, if the NCM-Plus intervention is more effective and yet more expensive, then we will calculate an incremental cost-effectiveness ratio (i.e., $(Cost_{NCM}-Cost_{Usual\ care})/(Effect_{NCM}-Effect_{UsualCare})$) that describes the extra costs necessary for each additional cured case of TB. Sensitivity analyses varying by assumptions made for modeling as well as bootstrapping to determine how robust the cost-effectiveness conclusions are will be performed. An overview of anticipated cost items is provided in Appendix H.

Approach to Attrition: In our previous work[5] we identified a 20% default rate among patients with and without HIV co-infection under standardized programmatic conditions. Due to severe adverse drug effects, length of treatment and inconvenience of the MDR-TB care model we do anticipate some patient attrition. ***Default from care is a measurable MDR-TB distal outcome and all patients will be included in our analysis.*** It is important to recognize, however, that a patient may default from MDR-TB care, but remain engaged in HIV care. Once the primary outcome of our trial is obtained, in this case default, the patient would no longer be followed in this protocol. Center attrition can also occur at any point throughout the study. We have additional hospital facilities that can provide alternative centers as needed.

Anticipated Challenges and Approach to Overcome:

1. Number of available MDR-TB Centers. In the two chosen provinces (EC and KZN) there are 15 MDR-TB sites in which this study could occur. The PI has obtained letters of support from the Department of Health in each province (see Appendix D). Should difficulties arise with site recruitment, we will use our well established collaborations with our SA partners to extend to sites outside of the selected provinces.
2. Intervention fidelity. We recognize the importance of standardization of the NCM intervention. To that end, we developed a comprehensive Intervention Fidelity Plan (Appendix G). We have divided this intervention fidelity plan into five principal areas; trial design, hiring and training, intervention delivery and receipt, analysis and enactment[60]. This plan will enable the results to be widely and rapidly implemented.
3. Contamination. Contamination occurs in a CRT when responses in one site/cluster are distorted because of contacts with individuals from outside the site/cluster and may lead to the dilution of the differences between arms. The geographical isolation between many of our sites will limit contamination as they are often great distances apart. Any enrolled patient who transfers between sites will be excluded.
4. New Investigator. Dr. Farley and his co-investigators recognize the complexity and ambition of the proposed study. Dr. Farley has developed a substantial team of partners in South Africa, published robust analysis in this area, and will be advised by a Scientific Advisory Board of persons with significant expertise. The study also includes the use of the NIH Data Safety and Monitoring Board (DSMB).

TIMELINE AND MILESTONES: Many key elements are presently in place to make this trial highly feasible, but space prevents representation here. Our team has developed a comprehensive overview of the prospective timeline and milestones which details how this trial will proceed to meet future milestones and trial related timelines (Appendix I).

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