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Evaluation of the National Adherence Guidelines for Chronic Diseases in South Africa Using Routinely Collected Data

SECOND ENROLLMENT REPORT

31 JANUARY 2017

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BOSTON UNIVERSITY

Health Economics and Epidemiology Research Office
HE²RO
Wits Health Consortium
University of the Witwatersrand

Evaluation of the **Adherence Guidelines for Chronic Diseases in South Africa** Using Routinely Collected Data

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ACRONYMS

AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral treatment
ARV	Antiretroviral
CBO	Community based organization
CRF	Electronic case report form
DMD	Decentralized medicine delivery
EAC	Enhanced adherence counseling
FSW	Female sex worker
FTIC	Fast track initiation counseling
HIV	Human Immunodeficiency Virus
NCD	Non-communicable diseases
NGO	Non-Governmental Organization
KP	Key Population
MSM	Men who have sex with men
NDoH	National Department of Health
NHLS	National Health Laboratory Services
PHC	Primary health care
TB	Tuberculosis
TBHD	TB, Hypertension and Diabetes
TRIC	Tracing and retention in care
TROA	Total remaining on ART

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EXECUTIVE SUMMARY

Now that enrollment has been completed for the HIV cohorts, this report describes the complete enrollment into the HIV cohorts for protocol 1 for the Evaluation of the National Adherence Guidelines for Chronic Diseases in South Africa Using Routinely Collected Data. The study is evaluating short-term and long-term effects of five interventions being implemented by the National Department of Health (NDoH) in South Africa to improve adherence to HIV care and chronic disease care in general: Fast track initiation counselling (FTIC), decentralized medicine delivery (DMD), adherence clubs (AC), early patient tracing (TRIC) and enhanced adherence counselling (EAC). The study uses a randomized evaluation design to compare health facilities where the intervention was rolled out with facilities where it was not. After completing data enhancement activities at each of the 24 sites (12 intervention and 12 control sites in 4 provinces in South Africa), the teams began enrollment into 7 study cohorts (5 HIV intervention evaluation cohorts and 2 TB, hypertension and Diabetes (TBHD) observational cohorts).

Enrollment began on 20 June 2016 and was stopped as of 16 December 2016 for the HIV cohorts. Enrollment for the TBHD cohorts is ongoing (with expected completion by March 2017). While the team faced several challenges to completing enrollment the team developed approaches to overcoming the enrollment obstacles for nearly all cohorts by working with the World Bank and NDoH co-principal investigators. In addition to the barriers reported in the first enrollment report, the team encountered some additional barriers: 1) additional delays in rollout of the interventions; 2) an insufficient number of patients provided with the interventions at some sites; and 3) delays in implementation of the interventions which meant we could not continue to prospectively enroll subjects and still meet our endpoints within the appropriate time frame. To overcome these barriers and achieve the targeted sample size for all but one cohort (EAC), the team employed three main strategies: 1) increasing the duration of enrollment through nearly the end of December 2016; 2) overenrolling patients at some sites; and 3) shifting to including some retrospective enrollment, whereby sites with additional numbers of eligible patients for enrollment prior to December 2016 overenrolled patients. While these strategies mean we do not have even enrollment across sites, this allowed us to achieve or nearly achieve our total sample size in nearly all cohorts. The exception to this is the EAC cohort, where either not enough subjects were offered the intervention or the intervention was offered and not documented sufficiently to allow completion of enrollment within this cohort.

Passive follow up has now begun for patients in the HIV cohorts through monitoring data collection systems (TIER.net and NHLS) and patient files for study outcomes. Much of the work by the local team has now shifted to focus on protocol 2 where qualitative data is being collected to supplement the quantitative analyses that will result from protocol 1.

1 BACKGROUND

For antiretroviral therapy (ART) for HIV and treatments for other chronic diseases to be effective, patients must remain in care for longer periods of time, initiate treatment as early as allowed under prevailing guidelines, consistently achieve high levels of adherence to their treatment regimen and, as a result, exhibit low and stable monitoring test results and/or treatment completion. In the case of HIV, treatment is lifelong and requires consistent, nearly complete adherence to sustain an undetectable viral load. Numerous studies and reviews have indicated that retention in care and adherence to ART in South Africa are sub-optimal and pose a serious threat to the long-term success of the national HIV response. Although there is less evidence on hand, these same problems almost certainly also pertain to tuberculosis (TB), for which treatment completion and cure rates do not approach global targets and to non-communicable diseases (NCDs), for which almost no treatment adherence data are available.

To address this challenge, in 2014 the NDOH developed the "National Adherence Guidelines for Chronic Diseases (HIV, TB and NCDs)" with rollout in 2015/2016. The guidelines address the provision of a minimum package of interventions to increase linkage to care, retention in care, and adherence to treatment. The minimum package of interventions includes five interventions that are being evaluated under this study: 1) fast track initiation counseling (FTIC); 2) enhanced adherence counseling for unstable patients (EAC); 3) adherence clubs (AC); 4) decentralized medicine delivery (DMD); and 5) early tracing of all missed appointments to improve retention in care (TRIC). The study was designed as a matched cluster randomized study in 24 clinics, 12 of which would receive early implementation of the minimum package and 12 would delay implementation and serve as control sites. Clinics were matched on clinic characteristics: total remaining on ART, clinic size, setting, location and viral suppression. This design was achieved for all of the interventions except for DMD, where a national decanting strategy meant that many of the control sites implemented DMD.

2 STUDY AIM AND OBJECTIVES

The overall aims of this study are to assess the impact of a subset of the National Adherence Guidelines' (AGL) minimum package of interventions on HIV patients' treatment outcomes at public sector clinics; estimate the costs of the interventions; and describe the cascade of care for TB, hypertension, and diabetes at these same clinics.

The study has 8 specific aims which are detailed in the two study protocols entitled "Evaluation of the National Department of Health's National Adherence Guidelines for Chronic Diseases in South

Africa Using Routinely Collected Data" and "Process Evaluation of the National Department of Health's National Adherence Guidelines for Chronic Diseases in South Africa". The objectives are:

- Among HIV-infected patients newly eligible for antiretroviral therapy, evaluate the impact of Fast Track Treatment Initiation Counselling on initiation and viral suppression.
- Among HIV-infected patients who are stable on antiretroviral therapy, evaluate the impact of Adherence Clubs on ART adherence and viral suppression.
- Among HIV-infected patients who are stable on antiretroviral therapy, evaluate the impact of decentralized medicine delivery on ART adherence and viral suppression.
- Among HIV-infected patients who have poor adherence to antiretroviral therapy, evaluate the impact of EAC on treatment adherence and viral suppression.
- Among HIV-infected patients in antiretroviral therapy programs who miss a scheduled appointment by 5 days or more, evaluate the impact of Early Patient Tracing on retention in care.
- For each clinic included in the study, evaluate the overall impact of the Adherence Guidelines on patient outcomes.
- Estimate the incremental and total cost of each of the interventions listed above compared to standard of care.
- Describe the current status of the cascade of care and adherence to treatment for tuberculosis, hypertension, and diabetes, for the purpose of tailoring the minimum package of interventions to these conditions in the national rollout.

3 PURPOSE OF THE REPORT

We previously wrote an enrollment report which covered enrollment up through October of 2016. Since that time enrollment has closed for all of the HIV cohorts. The purpose of this report is to describe the complete enrollment for protocol 1 which was completed for the HIV cohorts at the end of December 2016 (December 16th). Enrollment is still ongoing for the TB, Hypertension and Diabetes cohorts and this report provides updated enrollment data for those cohorts as well. In addition, we describe the additional challenges we faced since the last report to completing enrollment and document the strategies that we used to complete our enrollment for the HIV cohorts. As with the previous report, we describe the data sources used to collect baseline information on the cohorts, review the eligibility criteria for each cohort and describe the methodology used to identify eligible subjects for each cohort. Finally, we review the final enrollment data within each HIV cohort and describe the cohorts in terms of their basic clinical and demographic characteristics.

4 ELIGIBILITY CRITERIA

For all cohorts, we created general eligibility criteria that focused the study on non-pregnant adults. All cohorts used these general eligibility criteria, including the TBHD cohorts. Below we describe the general inclusion and exclusion criteria which applied to all cohorts within the study.

4.1 General inclusion/Exclusion criteria

Inclusion criteria

- ≥ 18 years old
- Meet the inclusion criteria for one or more of the cohorts

Exclusion criteria

- Not resident in the facility's catchment area
- Recorded intention to transfer care to a different facility within 12 months
- Pregnant and eligible for prevention of mother to child transmission (PMTCT)

4.2 Cohort specific inclusion/exclusion criteria

Within each cohort, specific inclusion/exclusion criteria were developed to ensure enrollment of appropriate subjects. The enrollment criteria followed the December 2014 national guidelines for HIV care and ART and November 2015 National Adherence Guidelines for Chronic Disease (HIV, TB and NCDs) with some updates based on the August 2016 version of the Guidelines. Below we describe inclusion/exclusion criteria applied to each cohort.

Cohort 1: Fast track treatment initiation inclusion criteria (Patients newly eligible for ART)

- Determined to be eligible to start ART under prevailing national guidelines (before September 2016, CD4 count < 500, WHO Stage 3 or 4 condition, no TB or cryptococcal meningitis; September 2016 and after, anyone HIV positive and considered eligible by the sites)

Cohorts 2 and 3: Adherence clubs or decentralized medicine delivery (Patients stable on ART)

- On same ART treatment regimen for at least 12 months
- Most recent viral load taken in past 3 months
- Two consecutive viral loads undetectable (<400 copies/ml[3])

Cohort 4: Enhanced adherence counseling (Patients on ART with poor adherence)

- On first-line ART for at least 3 months
- Poor adherence as indicated by an elevated viral load (>400 copies/ml[3])

Cohort 5: Early patient tracing (Patients lost from ART programs)

- Initiated ART
- Failed to return for a scheduled appointment within 5 to 90 days from their scheduled appointment date

Cohort 6: TBHD cohort (Tuberculosis, hypertension, and diabetes patients)

- Screened for TB, hypertension or diabetes at last visit during enrollment period June-December 2016 or diagnosed with TB or hypertension between June-December 2016, or diabetes between January-December 2016.
- Does not have existing TB, hypertension (diagnosed before June 2016) or diabetes (diagnosed before January 2016)

5 OVERVIEW OF STUDY SITES

The study is being conducted at 24 primary health care clinics (PHCs) in South Africa. In consultation with the NDoH, the study team chose six clinics from one district each in Gauteng, KwaZulu Natal, Limpopo, and North West Provinces giving a total of 24 sites. These provinces were chosen because in most cases they are high HIV burden provinces with high burden districts and high volume clinics.

Each site was required to meet the following criteria: 1) a high volume site as defined by having its Total Remaining on ART (TROA) being above 1000 patients; 2) not already be a National Health Insurance pilot site; 3) generating computerized TIER.net Phase 2 (all HIV patient data captured electronically including back capture of historical data) essential for the evaluation outcomes; and 4) not participating in any other adherence-related studies or pilots. Sites were chosen so that they could be matched with another site within a district roughly on TROA, proportion of patients virally suppressed, setting (rural/urban/formal/informal) and location (sites near each other).

After choosing the 12 pairs of sites (24 total), NDoH, World Bank, Boston University and HE[2]RO randomly allocated one site within each pair to be an intervention site and the other to be a control site. Table 1 below describes the study populations at each facility using data from TIER.net and DHIS on patients who were active in care (i.e. had visited the clinic within the last four months) and

who would have been eligible for enrollment by virtue of having met our eligibility criteria. Catchment population and PHC headcount are from DHIS while the eligibility data come from TIER.net data.

Table 1 Population data (facility headcount and total active patients) at each facility and total numbers eligible by intervention (I) and control (C) for each intervention

Facility	2015 catchment population	Total PHC headcount, monthly 2015 average	Total active on ART on 30 June 2016 N	FTIC eligible June 1-30 N	AC/DMD** eligible 30 June 2016 N (%)*	EAC eligible June 1-30 N (%)	TRIC eligible 30 June2016 N (%)
EKURHULENI							
I: Motsamai Clinic	12681	2701	1563	43	486 (31%)	53 (3%)	86 (6%)
C: Tamaho Clinic	18686	3980	1741	18	366 (21%)	8 (0%)	374 (21%)
I: Phola Park CHC	70047	14920	3434	17	1422 (41%)	97 (3%)	259 (8%)
C: Ramokonopi CHC	76257	16242	3502	63	999 (29%)	146 (4%)	190 (5%)
I: Khumalo Clinic	26255	5592	2587	22	808 (31%)	66 (3%)	185 (7%)
C: Zonkizizwe 1 Clinic	21856	4655	1614	35	528 (33%)	55 (3%)	121 (7%)
EKURHULENI TOTAL	**225782**	**48090**	**14441**	**198**	**4609 (32%)**	**425 (3%)**	**1215 (8%)**
MOPANI							
I: Grace Mugodeni CHC	22533	5 212	2061	15	982 (48%)	31 (2%)	158 (8%)
C: Motupa Clinic	17263	4 511	1708	23	546 (32%)	17 (1%)	204 (12%)
I: Giyani CHC	25982	7 149	2184	30	621 (28%)	60 (3%)	363 (17%)
C: Dzumeri Clinic	23644	5 753	1597	10	598 (37%)	16 (1%)	253 (16%)
I: Tzaneen Clinic	17258	4265	1851	19	700 (38%)	2 (0%)	334 (18%)
C: Nkowankowa CHC	22629	4 881	1132	10	233 (21%)	6 (1%)	97 (9%)
MOPANI TOTAL	**129309**	**31771**	**10533**	**107**	**3680 (35%)**	**132 (1%)**	**1409 (13%)**
BOJANALA							
I: Letlhabile CHC	69554	9825	3855	43	1729 (45%)	31 (1%)	487 (13%)
C: Wonderkop Clinic	21236	3200	1848	49	875 (47%)	28 (2%)	272 (15%)
I: Hebron Clinic	32352	4301	1714	29	870 (51%)	34 (2%)	130 (8%)
C: Majakaneng Clinic	21539	3259	1431	24	751 (52%)	12 (1%)	136 (10%)
I: Tlhabane CHC	79290	15130	5202	86	1330 (26%)	50 (1%)	667 (13%)
C: Bafokeng CHC	62149	10810	3113	37	1252 (40%)	36 (1%)	520 (17%)
BOJANALA TOTAL	**286120**	**46525**	**17163**	**268**	**6807 (40%)**	**191 (1%)**	**2212 (13%)**
UTHUNGULU							
I: King Dinizulu Clinic	24456	6058	2528	28	1152 (46%)	22 (1%)	420 (17%)
C: Nkwalini Clinic	10434	2573	1089	11	609 (56%)	11 (1%)	232 (21%)
I: Thokozani Clinic	42678	10657	3875	65	220 (6%)	15 (0%)	722 (19%)
C: Nseleni CHC	71060	18273	6218	83	2118 (34%)	6 (0%)	1021 (16%)
I: Buchanana Clinic	21944	3574	1323	12	722 (55%)	10 (1%)	239 (18%)
C: Ntambanana Clinic	19103	3323	1416	17	769 (54%)	8 (1%)	99 (7%)
UTHUNGULU TOTAL	**189675**	**44458**	**16449**	**216**	**5590 (34%)**	**72 (0%)**	**2733 (17%)**
TOTAL	**830 886**	**170 844**	**58586**	**789**	**20686 (35%)**	**820 (1%)**	**7569 (13%)**

Note: *Percent of total active on ART, 30 June 2016; **DMD has different intervention and control sites.

As can be seen, by design the sites were very different in terms of geographic location, size and number of eligible subjects within each of the intervention cohorts. For most cohorts, this did not pose any major challenges. Over the time period described, for most cohorts and sites a sufficient number of subjects became eligible to allow us to reach our site specific targets and certainly our overall targets. At the same time, this table illustrates some of the challenges the team faced in enrolling subjects into some of the cohorts: there were few new eligible subjects in the EAC cohort

over the entire enrollment period, particularly in uThungulu and parts of Mopani and Ekurhuleni. This meant that we did not have sufficient numbers of subjects to enroll at several sites as will be shown below and led to the decision not to reach the increased sample size agreed to (discussed below in the section on sample size).

6 ENROLLMENT

6.1 Methods for identifying eligible individuals

To enrol subjects into the study, the team identified patients who met the enrollment criteria for each cohort (described below). The procedures were different depending on whether or not the site was an intervention or control site. In control sites, because the intervention had not been implemented, the team had to find subjects who met the counterfactual definition of a control (i.e. they would have been eligible for the interventions had they gone to an intervention site). These subjects could typically be identified by using TIER.net. At intervention sites, we only included subjects who actually got the interventions. Identifying which patients got the interventions turned out not to always be straightforward. In part, this was because sites didn't always keep good records on who got the interventions for some cohorts (the most striking example being those in the EAC cohort). In other cases, it was because the interventions were not given to those who should have been eligible. This was common with the tracing (TRIC) cohort as in many cases sites chose to apply TRIC to all patients missing appointments, not just those who recently missed them as called for the guidelines. In other cases, it was difficult to identify eligible subjects because sites shifted priorities and moved patients from one intervention to another (e.g. from ACs to DMD) as a result of implementation of the decanting/decongestion strategy. In cases where registers were not sufficient to allow us to identify which patients got the interventions within a site we developed alternative methods to identify the cohorts such as: reviewing DMD script sheets for DMD; checking patient files for evidence of FTIC or EAC counselling and completed Patient Adherence Plans, or AC visits; and collaborating with implementing partners to access their tracing registers where those partners had taken over the responsibility for tracing.

An exception to how we enrolled subjects into the cohorts at control sites was for the DMD and the AC cohorts. To create the counterfactual control group we needed to find patients who were eligible for these interventions. Because the eligibility criteria for these two cohorts were identical, we sought to prevent enrollment of the same subject into two cohorts at a control site. We note, however, that there would not have been bias introduced if we had, we simply did this for logistical reasons to increase the probability that we would get roughly balanced patient characteristics predictive of the outcomes within each cohort. Therefore to enrol into these two cohorts, we identified patients eligible for these two interventions at each control site and allocated them

randomly to one of the two cohorts. This was further complicated by the fact that the DMD analysis was observational as described below.

For certain cohorts at specific sites we were unable to prospectively enrol the required number of patients before closing enrollment on the 16 December 2016 (e.g. EAC and TRIC in Mopani, AC and DMD in Ekurhuleni). For these cohorts we are continuing to review cohort registers and patient files during follow up visits to double check that eligible patients were not missed during the enrollment period. If these patients are identified they will be enrolled retrospectively and followed as part of the cohort.

6.2 Specific Procedures for Intervention Sites

As noted, at intervention sites we sought to identify individuals who were both eligible for and received specific interventions. We note that in some cases, sites did not give all patients eligible for an intervention the intervention and in other cases they gave the interventions to subjects who were not eligible. Accordingly, we required both eligibility for and receipt of the intervention as enrollment criteria. To achieve this, we used one of three approaches described below. Our goal was to spread out enrollment into each cohort over a period of months (June to December). We did this to prevent overenrolling subjects into the cohorts during the early stages of the rollout when sites were still learning how to deliver the interventions. This was not always successful as in some cases site enrollment could be spaced over the enrollment period because rollout of the interventions occurred early and quickly, while in others the interventions were not rolled out early enough for us to enrol over many months.

We identified potentially eligible subjects by first downloading the most recent TIER.Net dispatches from each facility and running STATA code to check for patients who should have received the interventions as described in the AGL for each specific HIV cohort. Prior to each facility visit that the team made, the Data Manager sent lists of eligible patients for each cohort to the Provincial Study Coordinators. A password protected 'Cohort Creation List' was sent along with targets for visit enrollment for each cohort. Then one of three approaches was used at each intervention site:

1. **List to Register Approach.** In cases where intervention specific registers (e.g. FTIC register, AC register, etc.) were kept, our Cohort Creation Lists were compared against each one to identify which of the eligible patients had actually received the intervention. Provincial teams checked each patient on the cohort creation list until the target number of cohort patients to be enrolled was identified.
2. **List to File Approach.** In cases where intervention registers were absent, did not contain enough information to verify a patient got the interventions, or were deemed to be of poor quality and therefore might miss patients who actually got the interventions, files of patients on the Cohort Creation Lists were identified and used to determine whether or not the patient had in fact received the intervention for which they were eligible. Evidence of receiving the intervention varied by cohort (e.g. record of specific AGL counselling sessions, presence of a patient adherence plan, etc.). This approach was used in later rounds of

recruitment mainly to complete enrollment of FTIC and EAC cohorts and predominantly in Ekurhuleni.

3. **Direct from Register Approach**. If patients on the Cohort Creation List could not be found using the List to Register Approach then rather than using the cohort creation lists to identify eligible patients, patients were identified directly from the intervention specific registers and their files found to confirm they were eligible according to the AGL criteria.

Regardless of the method used to identify patients, patient files were reviewed and information extracted using an electronic case report form (CRF) to confirm patients did meet all eligibility criteria for that cohort (including receipt of the intervention).

6.3 Control sites

For controls sites, the Data Manager created Cohort Creation Lists of eligible individuals as described above using TIER.net data and sent each list to the Provincial Study Coordinators. Each list was reviewed and the team pulled files for each patient until the cohort enrollment target was achieved (i.e. all patients enrolled in control cohorts were found using the List to File Approach). Files were then reviewed and information extracted using the electronic CRF to confirm eligibility. We note that many control sites did implement some form of the interventions (e.g. adherence counselling is routinely done at sites even if not enhanced, tracing is often done even if not targeted at those recently missing visits). At control sites, patients were enrolled based on eligibility for the interventions, while receipt of interventions at these control sites was disregarded for enrollment purposes.

6.4 Cohort Specific Enrollment

Below we describe the approach to identifying eligible patients for each of the cohorts. For all cohorts at both intervention and control sites we first produced Cohort Creation Lists from the most recent TIER dispatch for each facility identifying patients who on the date of the site visit by the data team:

- Were active in care (visit within last 124 days and no record that the patient was listed as “died”, “lost to follow up” or “transferred/moved out”)
- Were greater than 18 years of age
- Had their pregnancy status at last visit was not listed as “pregnant”

Cohort lists were refined using TIER.net to select patients who met the general inclusion criteria. We then proceeded differently for intervention and control subjects and followed specific procedures for each cohort as described below.

6.4.1 Cohort 1: Fast Track Initiation Counselling (Patients newly eligible for ART)

- *Control Subjects:* Control subjects were identified and enrolled using the 'List to File' approach. Patient files for eligible patients were found and screened using the electronic CRF to ensure FTIC eligibility criteria were met.
- *Intervention Subjects:* For intervention subjects, we first used a 'List to Register' approach then a 'Direct from Register' then the 'List to File' approach. In some facilities (predominantly in Ekurhuleni) FTIC registers were absent or inadequately completed, hence a 'List to File' approach was used. Eligible files were reviewed for evidence of FTIC counselling sessions recorded on clinical stationery and/or presence of a completed or partially completed AGL Patient Adherence Plan on the patient file.

All selected files were then screened using the electronic CRF to confirm all eligibility criteria that could not be verified through TIER.net (i.e. resident in the facility catchment area, no intention to transfer to another facility, no cryptococcal meningitis diagnosis at ART initiation). Once eligibility had been confirmed an FTIC barcode was assigned and the patient enrolled.

6.4.2 Cohort 2: Adherence Clubs (Patients stable on ART)

AC enrollment was complicated by the fact that DMD was rolled out at some of the control facilities and because at some sites AC patients were shifted to DMD to meet DMD targets, necessitating additional checks.

- *Control Subjects:* Control subjects were identified and enrolled using the 'List to File' approach and patient files screened to ensure all AC eligibility criteria were met. Further checks were made to ensure selected patients were not currently receiving their medication through DMD if it was in use at a control site.
- *Intervention Subjects:* For intervention subjects, first a 'List to Register' approach was used to identify patients recorded on the facility AC register(s). If the sample size could not be achieved using this approach, the 'Direct from Register' approach was used to identify and find AC patient files. A 'List to File' approach was not used for this cohort.

Eligible patient files were screened using the electronic CRF to confirm patients' eligibility (including confirmation of enrollment in an AC for intervention sites), and ensuring that patients had no record of picking up their medications separately from a DMD pick-up-point. All patients who eligible for the AC cohort were assigned an AC barcode.

6.4.3 Cohort 3: Decentralized Medicine delivery (Patients stable on ART)

As noted, DMD was not rolled out at all intervention sites and was rolled out at some control sites (Table 2). Therefore, we had to tailor our approach to enrollment for this cohort. For DMD, cohort lists were developed as described above for the AC cohort, although in the case of DMD we did not have a way to confirm enrollment into DMD using TIER.net as no field captures this information.

- **Control Subjects:** Unlike the other HIV cohorts, because DMD was rolled out in some randomized control sites and not in all randomized intervention sites, control DMD subjects were enrolled from any site that *was not implementing DMD during the enrollment period* (June-December) regardless of whether or not the site was randomized to intervention or control. Control subjects were identified and enrolled using the 'List to File' approach. Given that we did enroll DMD control subjects at some intervention sites, we instituted further checks to ensure that selected cohort patients were not also enrolled in an AC. At control sites where DMD was implemented during the enrollment period, we checked the IDs of all patients enrolled in the AC cohort and replaced any patient in that cohort who received DMD.

- **Intervention Subjects:** For intervention subjects (as noted, enrolled at any site currently implementing DMD irrespective of randomization assignment), the 'List to register' approach was used to identify patients recorded on DMD register(s) as having been decanted to a DMD (CCMDD/CDU) medicine pick up point. The relevant patient file numbers were recorded and those patient files found. If the targeted sample size of DMD patients could not be enrolled at a site, then the 'Direct from register' approach was used and patient files found. As with ACs, a 'List to file' approach was not used for this cohort at DMD intervention sites. At intervention sites that implemented DMD while we were enrolling, any patient in the AC cohort who was transferred to DMD was replaced in the AC cohort.

Patient files were found and then screened using the electronic CRF to confirm patients' eligibility including confirmation that the patient was not also enrolled in an AC. Assuming all criteria were met the patient was enrolled and a DMD barcode assigned.

Table 2 Assumptions and sample sizes for each cohort

Facility	DMD Intervention/ Control Status	Facility	DMD Intervention/ Control Status
gp Motsamai Clinic	DMD Intervention	nw Letlhabile CHC	DMD Intervention
gp Tamaho Clinic	DMD Intervention	nw Wonderkop Clinic	DMD Control
gp Phola Park CHC	DMD Control	nw Hebron Clinic	DMD Intervention
gp Ramokonopi CHC	DMD Control	nw Majakaneng Clinic	DMD Intervention
gp Khumalo Clinic	DMD Control	nw Tlhabane CHC	DMD Intervention
gp Zonkizizwe 1 Clinic	DMD Control	nw Bafokeng CHC	DMD Intervention
lp Grace Mugodeni CHC	DMD Control	kz King Dinizulu Clinic	DMD Intervention
lp Motupa Clinic	DMD Control	kz Nkwalini Clinic	DMD Control
lp Giyani CHC	DMD Control	kz Thokozani Clinic	DMD Intervention
lp Dzumeri	DMD Control	kz Nseleni CHC	DMD Intervention
lp Tzaneen Clinic	DMD Control	kz Buchanana Clinic	DMD Control
lp Nkowankowa CHC	DMD Control	kz Ntambanana Clinic	DMD Control

6.4.4 Cohort 4: Enhanced Adherence Counseling (Patients on ART with poor adherence)

For EAC, cohort lists were first developed using TIER.net.

- *Control Subjects:* Control subjects were identified and enrolled using only the 'List to file' approach.
- *Intervention Subjects:* For intervention subjects, first the facility EAC register(s) were used in a 'List to register' approach. If the targeted sample size for a site for the EAC cohort could not be enrolled, the 'Direct from Register' approach was used. In some intervention facilities where EAC registers were absent or inadequately completed (predominantly Ekurhuleni) the 'List to File' approach was used. Patient files were reviewed for evidence of EAC sessions and/or presence of a completed or updated AGL Patient Adherence Plan.

Once eligibility had been confirmed the patient was enrolled and an EAC barcode assigned.

6.4.5 Cohort 5: Early patient tracing (TRIC)

For TRIC, cohort lists were again refined using TIER.

- **Control Subjects:** Control subjects were identified using just the 'List to File' approach. Eligible files were screened using the electronic CRF to ensure that patients had in fact missed an appointment by 5-90 days as indicated on TIER (occasionally a TIER backlog could result in patients being identified as having missed a visit when in fact they had not).
- **Intervention Subjects:** For intervention subjects, a 'List to Register' approach was used to identify patients from the TRIC registers who needed tracing or who had been traced. The relevant patient files were then found. If the targeted TRIC sample size for a site could not be enrolled, then the 'Direct from Register' approach was used to identify TRIC eligible patients and their patient files.

  In some facilities (e.g. some Mopani and uThungulu clinics), TRIC registers were not held by the facility but by implementing partners or Ward Based Outreach Teams (WBOT) teams and information was not sent back to the facility. This led to delays in enrolling this cohort at some intervention sites. When possible, visits were made to partner offices and meetings with WBOTs were organized in order to gain access to the registers and tracing information. This is similar to the 'Direct from Register' approach. The names and file numbers (if recorded) of patients recorded on these lists were noted and taken back to the facility by the team and these patient files found. The 'List to File' approach was not used at intervention sites for this cohort. Patient files were screened to confirm eligibility (including confirmation that they had missed a scheduled appointment by 5-90 days).

Once eligibility was confirmed a TRIC barcode was assigned.

6.4.6 Cohort 6: Tuberculosis, Hypertension, and Diabetes Cohort (TBHD patients)

TBHD Screening Cohort (Cohort 6A)

At each facility visit the study team reviewed patient files from the previous or current day to exclude patients < 18 years and pregnant women. All remaining patients are then eligible for the TBHD Screening cohort (Group A). Baseline data for these patients is extracted from their files using the electronic CRF. As we require 100 eligible subjects per site for Group A, we continued this process until the targeted sample size was reached.

After the patient information was captured in the CRF, it is reviewed by the research team to determine the status of each patient:

- Not screened or eligible for screening (i.e. not screened for tuberculosis, hypertension or diabetes; no evidence of TB, hypertension or diabetes/no known disease/screened negative; prevalent case of tuberculosis or hypertension (diagnosed more than 1 month ago), prevalent case of diabetes (diagnosed more than 6 months ago), MDR or XDR TB)
- Screened positive for tuberculosis (at last visit)
- Screened positive for hypertension (at last visit)
- Screened positive for diabetes (at last visit)
- Newly diagnosed with tuberculosis (in last month)
- Newly diagnosed with hypertension (in last month)
- Newly diagnosed with diabetes (in last 6 months)

At this point the Data Manager returned a list of file numbers of all patients who had screened positive for tuberculosis, hypertension or diabetes to the Provincial Teams and these files were found and marked with a barcode label to signify enrollment in the *TBHD Screening cohort* to be followed up.

TBHD Diagnosed Cohort (Cohort 6B)

There were three ways in which patients are identified as eligible for and enrolled in the *TBHD Diagnosed cohort*:

1. *Incident cases from the TBHD screening cohort.* Patients from the *TBHD screening cohort* who are diagnosed with tuberculosis, hypertension or diabetes during the TBHD cohort enrollment period (June-December 2016) are eligible for inclusion in the *TBHD diagnosed cohort* (Cohort 6B). These file numbers are confirmed by the Data Manager and then marked with a Cohort 6B (*TBHD diagnosed*) barcode.
2. *Cases identified as recently/newly diagnosed while enrolling the TBHD screening cohort.* Cases of tuberculosis and hypertension diagnosed at their last site visit (June-December

2016), or diabetes cases diagnosed after Jan 2016 that were identified during the creation of the *TBHD Screening cohort* (Cohort 6A) were also eligible. These were identified by the Data Manager from the baseline CRF data previously collected. A list of file numbers is then returned to the provincial teams so that patient files could be marked with a Cohort 6B (*TBHD Diagnosed*) barcode.

3. *Register identified cases*. Tuberculosis patients (diagnosed after May 2016) were identified from the tuberculosis suspect register or the tuberculosis register, and hypertension (diagnosed after May 2016) and diabetes patients (diagnosed after Jan 2016) were identified from the PHC tick register. File numbers were noted and patient files pulled to verify the diagnosis is within the required time period. If eligibility was confirmed files were marked with the Cohort 6B (*TBHD Diagnosed*) barcode label.

6.5 Enrollment process/Identification of cohorts

While enrollment generally went smoothly after initiation of enrollment procedures began on June 20th, 2016 the team did identify some barriers to completing the process, and in some cases, starting the enrollment process. This was often cohort specific, with sites having difficulty enrolling into one or two of the cohorts, while the others were able to enrol without problem. Barriers for each cohort, therefore required different solutions.

The initial barriers to enrollment fell into four general categories: 1) delays in implementation of the interventions at the sites and delays in implementation per the NDOH's Standard Operating Procedures of the AGL; 2) changes in rollout of the intervention due to the pressure to "decant" patients; 3) incomplete or not used registers for the interventions; and 4) delay in enrollment at control sites due to delays in implementation of the interventions at intervention sites. These have each been discussed in the previous enrollment report.

While these challenges were largely solved or the impacts mitigated, some new challenges arose to completing full enrollment. In addition to the barriers reported in the first enrollment report, the team encountered: 1) additional delays in rollout of the interventions; 2) an insufficient number of patients provided with the interventions at some intervention sites; and 3) delays in implementation of the interventions meant we could not continue to enroll subjects and still meet our endpoints within the appropriate time frame. Below we discuss each barrier.

6.5.1 Delays in Implementation or not implemented as per AGL

As with the previous report, we note that the main barrier to enrollment resulted from delays in the implementation of the rollout of some of the interventions in the AGL or failure to implement interventions as specified in the AGL. DMD and ACs were the most likely to be affected and this was largely due to the implementation during the study period of a National Decanting Strategy which sought to decongest clinics. The Decanting Strategy meant that many sites, whether control or intervention, needed to quickly implement DMD, preventing us from achieving a "pure" counterfactual. Because of this, we made the shift to analyse this cohort using methods for

observational research rather than randomized trials. Still, the shift also had the impact of slowing recruitment because we could not be certain that subjects recruited into the AC cohorts were not being decanted to DMD. The issue was most commonly seen in Gauteng and uThungulu.

Reluctance to implement interventions as specified in the AGL SOPs further hampered enrollment as on occasion this meant that those enrolled in the interventions were not eligible or if they were eligible had not been enrolled in sufficient numbers. This issue was most commonly seen in uThungulu, particularly where ACs had previously existed prior to the AGL and had used slightly different enrollment criteria (e.g. only one viral load required). Other examples included EAC in Buchanana, uThungulu where staff in charge had seemingly been enrolling patients who were virally supressed rather than unsuppressed; EAC in Grace Mugodeni in Mopani where clinicians were reluctant to refer patients for EAC; and also TRIC at Grace Mugodeni where a decision had been made to focus tracing on patients who had just missed a visit (i.e. by 1 day) rather than early and late missed appointments. These issues were all escalated to managers and support partners but unfortunately were not rectified quickly enough or are still ongoing.

6.5.2 Incomplete, poorly completed or not used registers for the interventions

While in most cases, our data enhancement plans allowed us to work with sites to ensure improved record keeping and data recording, not all sites had the capacity to use the registers for documenting who got the interventions. This issue occurred most often in Mopani and Ekurhuleni for the Early Adherence Counselling and TRIC interventions and was often the result of implementing partners choosing to keep separate registers for interventions, which were not kept at the sites, or a shortage of staff capacity and some resistance by staff to complete these registers. Poor completion and use of registers and no record of intervention delivery in patient files was why recruitment into the Early Adherence Counselling cohort fell well below target at Khumalo, Tzaneen and Thokozani and the reason we were unable to achieve TRIC target numbers in Tzaneen.

6.5.3 Insufficient numbers of patients enrolled onto the interventions

While the decanting strategy resulted in delays in enrollment, in other sites, some interventions simply did not enrol a sufficient number of patients into the interventions or they enrolled patients without using the AGL inclusion criteria, which meant some subjects who got the interventions were not eligible for enrollment into the evaluation. The most common examples of this were for DMD and EAC.

For example, while DMD numbers at Motsamai in Ekurhuleni were initially encouraging, the number of patients enrolled and picking up their medications at the DMD pick-up-point began to diminish quite quickly after implementation with clients preferring to pick their medications up at the facility. The reluctance by clinicians to refer patients for Early Adherence Counselling at Grace Mugodeni in Mopani resulted in too few patients being enrolled for this intervention.

Delays in Implementation Prevented Enrollment Due to the agreed Endpoint Timeframes

Not all sites that delayed rollout of the interventions (or slow rollout once they began the interventions). However, as the evaluation's timeline has already been shifted several times due to delays in AGL implementation, and the long-term outcomes would take 12 months of cohort follow-up, there was a limit to the timeframe of possible cohort enrollment. The intention was to close HIV cohort enrollment in December 2016 to obtain the data on AGL effectiveness by December 2017. Therefore, it was challenging in some sites to achieve the full sample size for each HIV cohort by December 2016. The most common examples of this were for ACs in Ekurhuleni (Motsamai and Khumalo) in Gauteng.

6.6 Strategies to Overcome Barriers

The team enacted three main strategies to achieve the targeted sample size in the face of the issues described above. Each is described below.

6.6.1 Increasing the duration of enrollment through 16 December 2016

We had initially hoped to complete enrollment by the end of November of 2016. In consultation with the World Bank, we made the decision to extend the enrollment period and only close enrollment on December 16th, 2016. This increased duration allowed us to meet or nearly meet the increased sample size targets in 4 of the 5 cohorts with only Early Adherence Counselling not approximately reaching the targeted sample size. Because not a sufficient number of subjects received EAC and met the eligibility criteria (EAC was often provided to those who did not meet the criteria according to the guidelines), we were not able to achieve our targeted sample size in the required time and the strategies below were also not entirely sufficient to achieve the target.

6.6.2 Overenrolling patients at some sites

While we had initially hoped for a perfectly balanced design in which all sites enrolled the same number of subjects for each intervention, this was not possible at all sites. As we had to under enroll at some sites, we increased enrollment at others where there were sufficient numbers of patients to do so. This was easier to do in control sites than in intervention sites because control site subjects were not required to have actually gotten the intervention, only to have been eligible to do so. This meant more patients could be found who met the inclusion criteria. The most common examples of this were in FTIC, ACs and Early Adherence Counselling although some over enrollment occurred at specific sites for DMD and TRIC as well. The sites where over enrollment occurred can be seen in Table 5 below.

6.6.3 Shifting to including some retrospective enrollment

While we did need to close enrollment as of December 16th 2016 in order to reach the long-term endpoints by end 2017, this did not prevent us from enrolling subjects from sites that we had previously not enrolled all eligible subjects. This retrospective approach to enrollment meant that the site teams were not looking for newly eligible subjects on their visits but rather were looking for subjects who had been eligible but had not already been enrolled. This strategy was used

sparingly as it was not possible at many sites as either all eligible subjects were enrolled or because we didn't want to have a strongly unbalanced design in which we had a large sample size at one site and few at another. The most common examples of this were in EAC, DMD and TRIC.

7 SAMPLE SIZE

In our initial protocol, our total sample size for the study was estimated to be 2,880 subjects in the five intervention cohorts and 4,800 in the TBHD cohort, for a total sample size of 6,680. However, as we noted there was crossover between subjects in the AC and DMD cohorts, in consultation with the co-Principal Investigators we decided to increase the sample size by 20% in each of the HIV cohorts. While this sample size was likely not necessary for most of the cohort, it would give us sufficient power to detect differences even if some subjects needed to be excluded from the final analysis there was no reason not to. The table below shows the sample size that was estimated to be required for each cohort initially and after we increased the target numbers. We determined each sample size to be sufficient to measure the short term outcome for that cohort. For all the cohorts except the TBHD cohort, calculations assumed a site-clustered design with the clinic as the cluster and 24 clusters evenly randomized between intervention and comparison groups. They also assumed a coefficient of variation of 0.1, 80% power; and an alpha of 0.05. In Table 3 below we describe the remaining assumptions behind the sample size for each cohort.

Table 3 Assumptions and sample sizes for each cohort

Cohort	Initial Sample Size	Increased Sample Size	Assumed % with the outcome in control arm	Detection limit
Fast Track ART Initiation Counseling	600 patients (25 per clinic)	720 patients (30 per clinic)	60% of patients will initiate ART	15% change
Adherence Clubs	480 patients (20 per clinic)	576 patients (24 per clinic)	80% of patients will make all medication pickups	15% change
Decentralized Medicine delivery	480 patients (20 per clinic)	576 patients (24 per clinic)	80% of patients will make all medication pickups	15% change
Enhanced Adherence Counseling	840 (35 per clinic)	1008 patients (42 per clinic)	52% of patients with a detectable viral load will re-suppress after one session	15% change
Early tracing of patients lost to follow up	480 patients (20 per clinic)	576 patients (24 per clinic)	30% of patients will be loss to follow up without intervention	15% change
TB, hypertension, and diabetes	4800 patients	4800 patients	Descriptive in nature, no specific sample size calculation was done	No specified change

8 ENROLLMENT

8.1 Timing of cohort initiation

As noted, cohort enrollment began on June 20th, 2016. Table 4 below describes the timing of initiation of site assessments, and data collection for each cohort. The table also shows matched pairs of clinics where the start of cohort enrollment was 2-4 weeks (yellow) or one month or more (red) apart.

Table 4 Timing of cohort initiation by site and cohort

Facility	Site assessment date	Cohort 1 (FTIC): Data collection start date	Cohort 2 (AC): Data collection start date	Cohort 3 (DMD): Data collection start date	Cohort 4 (EAC): Data collection start date	Cohort 5 (TRIC): Data collection start date	Cohort 6 (TBHD): Data collection start date
gp Motsamai Clinic	28-Oct-15	23-Jun-16	*Pending*	23-Jun-16	16-Aug-16	23-Jun-16	23-Jun-16
gp Tamaho Clinic	25-Nov-15	20-Jun-16	31-Aug-16	21-Jun-16	20-Jun-16	20-Jun-16	20-Jun-16
gp Phola Park CHC	10-Nov-15	25-Aug-16	20-Jul-16	20-Jul-16	26-Aug-16	15-Aug-16	20-Jul-16
gp Ramokonopi CHC	23-Nov-15	29-Aug-16	21-Jul-16	30-Aug-16	29-Aug-16	29-Aug-16	20-Jul-16
gp Khumalo Clinic	17-Nov-15	18-Aug-16	29-Jun-16	29-Jun-16	19-Aug-16	19-Aug-16	30-Jun-16
gp Zonkizizwe 1 Clinic	16-Nov-15	05-Aug-16	04-Jul-16	04-Jul-16	05-Aug-16	08-Aug-16	01-Jul-16
lp Grace Mugodeni CHC	16-Nov-15	24-Jun-16	27-Jun-16	27-Jun-16	13-Jul-16	12 Oct-16	27-Jun-16
lp Motupa Clinic	20-Nov-15	28-Jun-16	14-Jul-16	15-Jul-16	28-Jun-16	28-Sep-16	28-Jun-16
lp Giyani CHC	17-Nov-15	30-Jun-16	11-Aug-16	21-Jul-16	30-Jun-16	*Pending*	30-Jun-16
lp Dzumeri Clinic	14-Dec-15	04-Jul-16	11-Aug-16	05-Jul-16	05-Jul-16	04-Oct-16	04-Jul-16
lp Tzaneen Clinic	19-Nov-15	21-Jun-16	06-Jul-16	20-Jun-16	20-Jul-16	06-Oct-16	20-Jun-16
lp Nkowankowa CHC	18-Nov-15	22-Jun-16	22-Jun-16	22-Jun-16	08-Jul-16	23-Sep-16	22-Jun-16
nw Letlhabile CHC	24-Nov-15	28-Jun-16	28-Jun-16	17-Aug-16	29-Jun-16	30-Jun-16	28-Jun-16
nw Wonderkop Clinic	25-Nov-15	27-Jun-16	27-Jun-16	02-Sep-16	28-Jun-16	14-Jul-16	27-Jun-16
nw Hebron Clinic	25-Nov-15	20-Jun-16	21-Jun-16	26-Aug-16	20-Jun-16	10-Aug-16	20-Jun-16
nw Majakaneng Clinic	24-Nov-15	22-Jun-16	22-Jun-16	16-Aug-16	22-Jun-16	15-Jul-16	22-Jun-16
nw Tlhabane CHC	26-Nov-15	25-Jul-16	22-Aug-16	06-Sep-16	08-Aug-16	25-Jul-16	24-Jun-16
nw Bafokeng CHC	26-Nov-15	12-Jul-16	12-Jul-16	29-Aug-16	12-Jul-16	12-Jul-16	23-Jun-16
kz King Dinizulu Clinic	09-Dec-15	28-Jun-16	07-Sep-16	06-Sep-16	28-Jun-16	09-Nov-16	28-Jun-16
kz Nkwalini Clinic	24-Dec-15	30-Jun-16	22-Aug-16	26-Sep-16	21-Jul-16	30-Jun-16	30-Jun-16
kz Thokozani Clinic	27-Nov-15	04-Aug-16	17-Aug-16	17-Aug-16	21-Sep-16	14-Sep-16	04-Aug-16
kz Nseleni CHC	21-Dec-15	25-Aug-16	26-Aug-16	26-Aug-16	25-Aug-16	13-Oct-16	04-Aug-16
kz Buchanana Clinic	11-Dec-15	21-Jun-16	21-Oct-16	21-Jun-16	28-Jul-16	22-Jun-16	20-Jun-16
kz Ntambanana Clinic	10-Dec-15	23-Jun-16	31-Aug-16	23-Jun-16	24-Jun-16	27-Jun-16	23-Jun-16

Note: More than one month between enrollment at control and enrollment at intervention site.

2-4 weeks between enrollment at matched pair.

8.2 Enrollment by cohort

The team has tracked enrollment into each cohort over time to ensure progress towards the sample size targets and to ensure we did not exceed the total sample size allowed. Table 5 below shows the results of that tracking, demonstrating accrual into each cohort at each site through December 16th, 2016. The table is also stratified by evaluation facility and district.

In the control arm alone, all five HIV cohorts reached the target sample size. *In the intervention arm alone*, four HIV cohorts did not reach the full sample size: the DMD cohort attained 96% (231 enrolled/240 target), AC cohort 95% (275/288), EAC cohort 71% (360/504) and TRIC 94% (272/288). Three of these four cohort met their initial sample size before it was increased by 20% (DMD, AC, TRIC) with only EAC falling below the initial sample size.

Table 5 Enrollment by cohort as of October 6th

Facility	Enrolled Cohort 1 (FTIC)	Enrolled Cohort 2 (AC)	Enrolled Cohort 3 (DMD)	Enrolled Cohort 4 (EAC)	Enrolled Cohort 5 (TRIC)	Enrolled Cohort 6a (TBHD)	Enrolled Cohort 6b (TBHD)	Total
Target per facility	**30**	**24**	**24**	**42**	**24**	**100**	**100**	**344**
GAUTENG								
Motsamai Clinic	28	23	8	43	24	100	36	262
Tamaho Clinic	29	24	27	42	24	100	21	267
Phola Park CHC	31	28	24	49	25	100	62	319
Ramokonopi CHC	30	24	25	42	24	100	36	281
Khumalo Clinic	28	8	26	10	24	100	18	214
Zonkizizwe 1 Clinic	30	24	24	41	23	100	16	258
LIMPOPO								
Grace Mugodeni CHC	30	24	24	10	15	100	5	208
Motupa Clinic	35	24	24	42	23	100	3	251
Giyani CHC	30	24	24	37	24	100	2	241
Dzumeri	30	24	24	41	24	100	3	246
Tzaneen Clinic	27	24	24	18	15	100	2	210
Nkowankowa CHC	30	25	24	44	28	100	4	255
NORTH WEST								
Letlhabile CHC	32	24	22	42	26	100	51	297
Wonderkop Clinic	30	24	19	42	25	100	18	258
Hebron Clinic	31	24	25	42	21	100	29	272
Majakaneng Clinic	30	24	24	42	24	100	36	280
Tlhabane CHC	30	24	24	42	24	100	21	265
Bafokeng CHC	30	25	24	42	24	100	14	259
KWAZULU NATAL								
King Dinizulu Clinic	34	24	24	42	24	100	56	304
Nkwalini Clinic	34	27	27	43	28	100	40	299
Thokozani Clinic	37	24	26	15	26	100	30	258
Nseleni CHC	30	25	27	43	29	100	21	275
Buchanana Clinic	31	24	33	10	24	100	28	250
Ntambanana Clinic	30	24	26	43	24	100	25	272

Table 5 Enrollment by cohort as of October 6th (continued)

District	Cohort 1 (FTIC)	Cohort 2 (AC)	Cohort 3 (DMD)	Cohort 4 (EAC)	Cohort 5 (TRIC)	Cohort 6a (TBHD)	Cohort 6b (TBHD)	Total
Ekurhuleni	176	131	134	227	144	600	189	1601
Mopani	182	145	144	192	129	600	19	1411
Bojanala	183	145	138	252	144	600	169	1631
uThungulu	196	148	163	196	155	600	200	1658
Study Total	737	569	579	867	572	2400	577	6301
Study Target	720	576	576	1008	576	2400	2400	8256
Percent of target achieved	102%	99%	101%	86%	99%	100%	24%	76%
Intervention enrollment	369	275	231	360	270	1200	340	3047
Control enrollment	368	294	348	507	302	1200	237	3254

Two factors were mainly responsible for the underachievement of the sample size for DMD: DMD was implemented at only 10 clinics while the remaining 14 sites were control sites. In addition, Motsamai (DMD intervention site) only had 8 patients for enrollment. Other DMD implementation issues also posed enrollment challenges including: a) Accessibility of the DMD registers and the ability to identify patients when they were picking up medicines through DMD; b) cases where DMD was being implemented for hypertension/diabetes but not for patients with HIV; c) Incorrect labelling of medicines and spelling of patient names; and d) Lack of documentation from CCMDD providers to update TIER. The last was perhaps the biggest barrier as we saw very little documentation of DMD in TIER.

The chief reason for not meeting the enrollment target in the EAC cohort was the low number of patients who were eligible for enrollment in the following clinics: Khumalo (GP), Grace Mugodeni (LP), Tzaneen (LP), Thokozani (KZN), and Buchanana (KZN). This occurred because of the following EAC implementation challenges: a) Poor recording on registers and in patient files (difficulty identifying those receiving the EAC intervention); b) Registers not being updated due to absence of Lay Counsellor, or lost registers; and c) Confusion over which patients are eligible for EAC (virally suppressed patients have been receiving EAC but were not meant to be enrolled in the evaluation cohort). The evaluation team has also observed that EAC (as well as FTIC) registers are primarily driven to completion through the request of the Evaluation Team and not for patient management reasons.

Two clinics contributed to under-achievement of the targeted sample size in the TRIC cohort as they had insufficient numbers of eligible patients: Grace Mugodeni and Tzaneen Clinic. The main implementation challenges for TRIC at the intervention clinics were: a) lack of airtime or access to phones within clinics; b) Difficulty linking information between facility, support partner, WBOTs, and CHWs; c) Wrong targeting of TRIC (defaulters, unsuppressed, appointments missed 1 day ago only); d) Absence of Lay Counsellor (delays tracing and completion of registers); and e) incomplete registers.

The AC cohort achieved 95% of its targeted sample size in the intervention cohort. This was mainly due to insufficient numbers of eligible patients for cohort enrollment at Khumalo Clinic. Other sites

under-enrolled by one or two subjects, and this was only because on data cleaning some patients enrolled were found to not have met the inclusion criteria and had to be excluded. Thus, overall this cohort did not experience many issues, though as with the other cohorts, completion of registers was an issue.

8.3 Enrollment over time

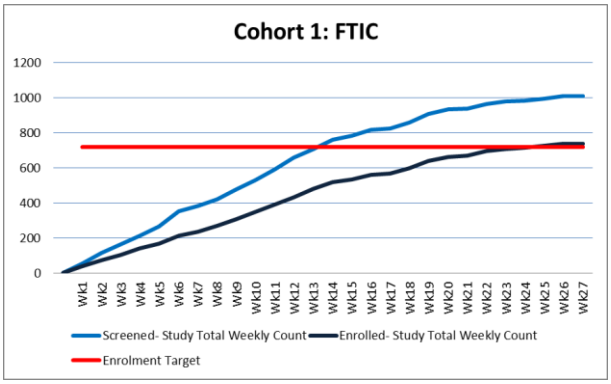
While we initially wanted each site to recruit the same number of subjects per cohort, due to logistical constraints at some sites and, more commonly, due to delays in implementation of the interventions at the sites, enrollment was not evenly distributed across time with some cohorts enrolling faster than others. Figure 1a-g below demonstrate this for the six cohorts.

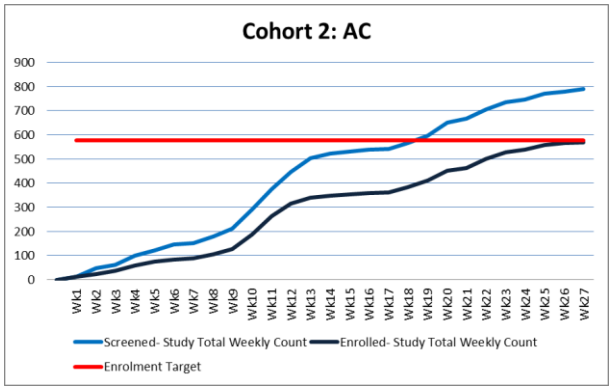
These figures show that the FTIC, ACs and DMD cohorts were the fastest to enrol, reaching targets at some sites in about 16 weeks and at all sites within 24 weeks. While enrollment was largely steady week on week in these cohorts, enrollment accelerated between week 8 and 9 for the Adherence Clubs and DMD cohorts. This acceleration was largely due to enrollment at control sites in pairs where enrollment of the cohort at the intervention site was delayed and resolution of some register issues that had previously delayed enrollment. Each of these cohorts required screening more subjects than we ultimately enrolled. Subjects who were not eligible are described below.

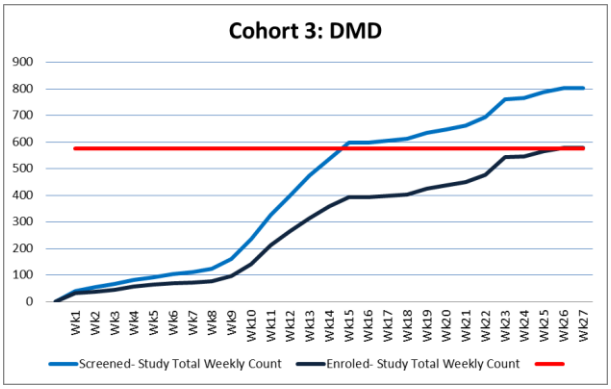
The EAC and TRIC cohorts took longer to enrol (up to 26 weeks) and by the end of enrollment on 16 December 2016 it had not been possible to enrol the full EAC cohort. The most prominent reasons enrollment was slower or incomplete for these cohorts was related to: 1) interventions not being implemented to AGL specifications (e.g. focussing EAC on defaulters rather than unsuppressed patients, or only tracing pre-ART or patients who had defaulted rather than those who had early or late missed appointments); and 2) incomplete or unavailable registers at intervention sites. We also noted that for the TRIC cohort, a larger number of patients who were screened were found to be ineligible compared to other cohorts. This was due in large part to the intervention not being delivered as per the AGL specifications.

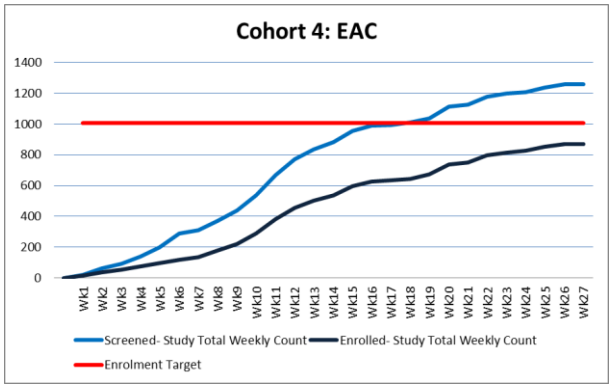
As anticipated, the Tuberculosis, Hypertension and Diabetes cohorts are taking the longest to complete. We have currently identified all 2400 eligible patients for the TBHD Screening cohort and are in the process of identifying those who screen positive who will be followed as part of this cohort. By January 13, 2017, we had also identified 577 (24%) subjects as eligible for enrollment into the TBHD Diagnosed cohort. However as described on page 13, we have not yet initiated cohort enrollment via the third method for the TBHD diagnosed cohort but will be able to do this retrospectively once it is initiated. We anticipate that enrollment of these two cohorts will be completed by March 2017.

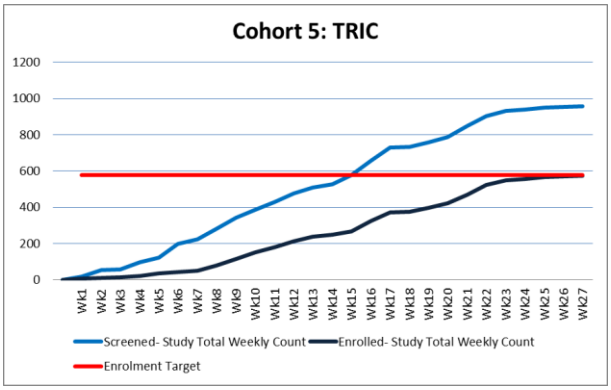
Figure 1 (Cohort 1–6a, 6b) Screening and enrollment by cohort over time compared to the target total through December 16th, 2016

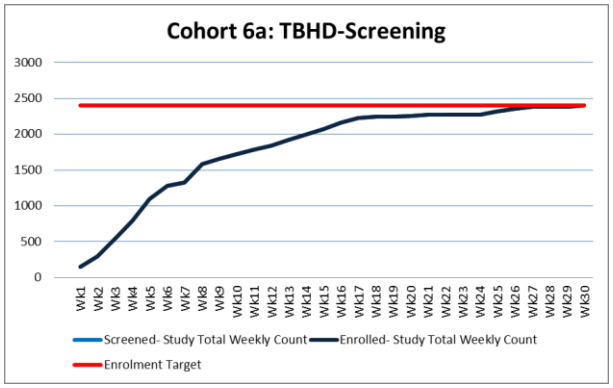


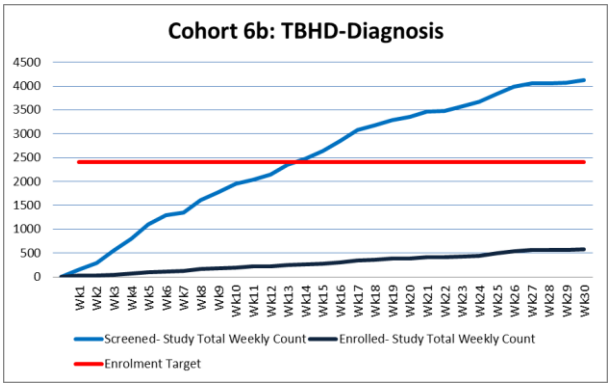












8.4 Enrollment by facility/district

In addition to variation in enrollment over time by cohort, we also encountered variation in enrollment by site and province. While overall all five intervention cohorts have nearly completed (with the possibility of some retrospective enrollment if feasible), Figure 2 shows that enrollment was uneven with facilities in North West province enrolling fastest and Limpopo and KwaZulu Natal taking somewhat longer. This was largely due to delays in being able to enrol for one or more cohorts because of implementation or register issues.

Figure 2a–d Enrollment over time by province and clinic

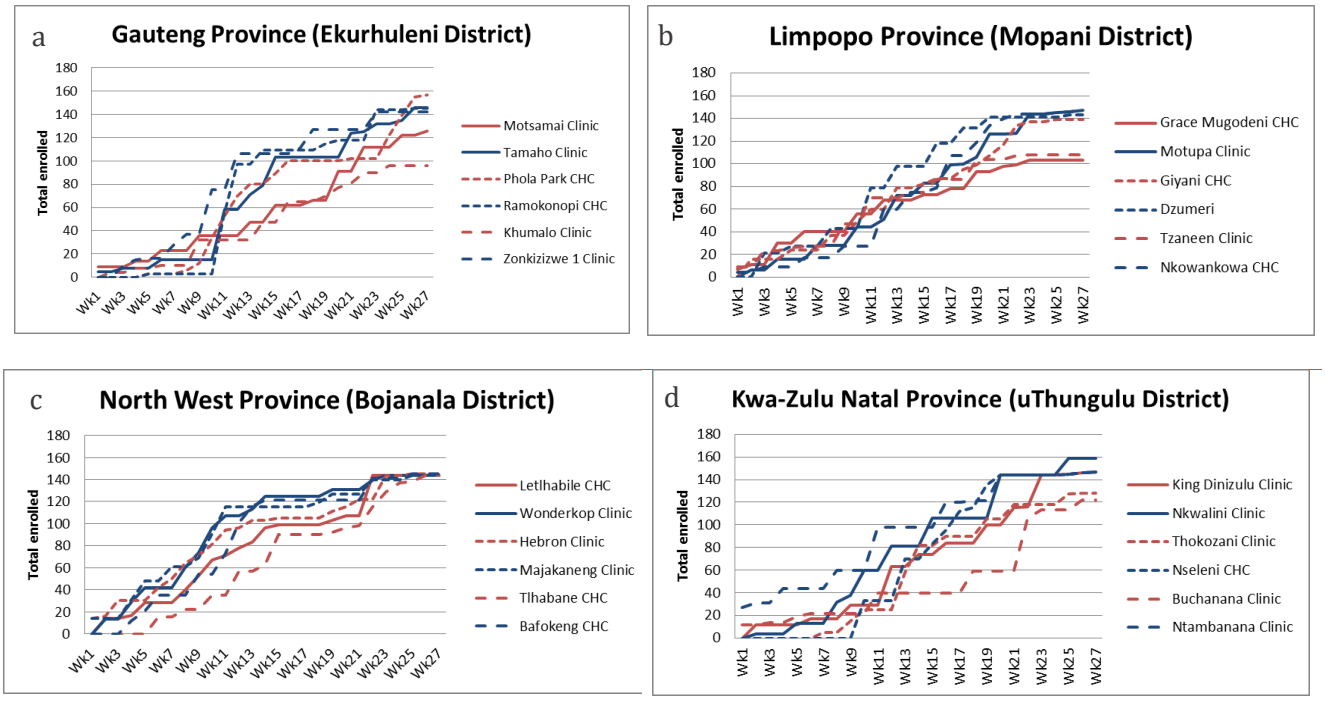
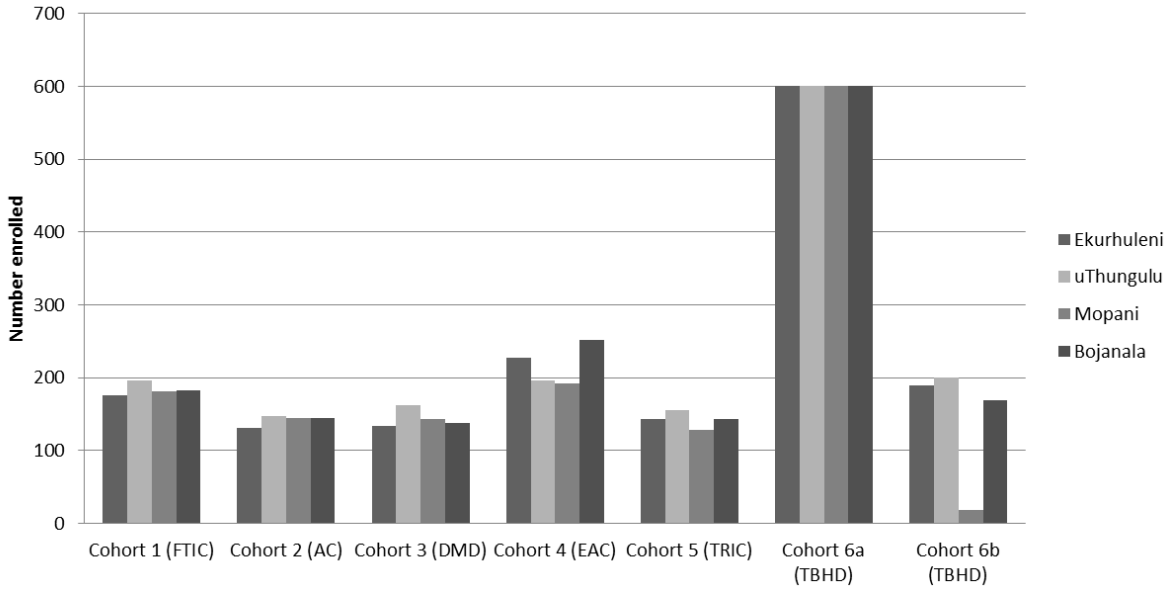


Figure 3 below shows enrollment into each cohort within each district. Note that the large difference between 6A and 6B cohort numbers in Mopani is due to only having screening information for TB patients (for hypertension and diabetes cases, no records are created until patients are diagnosed). Because the third route of detecting the diagnosed patients has not been implemented yet, the number of diagnosed patients in Figure 3 only contains those Mopani patients diagnosed TB positive who were identified from those screened. This will change as we implement the third method of identifying diagnosed patients.

Figure 3 Enrollment by District and Study Cohort



8.5 Ineligible Patients

As part of the enrollment process we have screened subjects for eligibility and identified subjects who were ineligible upon file review. Below in Table 6 we describe the number of ineligible subjects per cohort. We note that for all cohorts except DMD (where the intervention was delivered in control sites) more subjects were screened in the intervention cohorts than the control cohorts. This was expected as interventions subjects had additional eligibility criteria, namely getting the intervention.

The most common reason for not being eligible in the intervention cohorts was a patient not actually receiving the intervention for which they were eligible. This was most common with FTIC where 89 patients (46% of all those excluded) were eligible for FTIC but did not receive it.

For all cohorts, between 4% (Early Adherence Counselling controls) and 15% (FTIC intervention) of files were missing resulting in the need to exclude patients. Not being able to locate a patient file was more common in intervention sites than control sites, but this is largely due to the fact that more files needed to be screened in interventions sites due to the additional screening criteria. Very few patients were found ineligible due to the other general eligibility criteria (e.g. <18 years old, not resident, pregnant) suggesting that TIER.Net data was reasonable for screening patients for eligibility.

Of note, in the TRIC cohort, the numbers screened were similar in the intervention and control arms. This was because many patients were found ineligible in this cohort because TIER.net data was not up to date given the time between the TIER.Net dispatch date and file screening, causing us to think a patient had missed a visit on our initial screen when clinic files confirmed they had not.

While this was more common in control clinics, this was balanced out in the intervention cohort by patients who did not receive the intervention.

Table 6 Ineligible subjects by cohort and reason for exclusion

	Cohort 1: FTIC		Cohort 2: AC		Cohort 3: DMD		Cohort 4: EAC		Cohort 5: TRIC	
Reason not eligible	Control N (%)	Intervention N (%)	Control N (%)	Intervention N (%)	Control N (%)	Intervention N (%)	Control N (%)	Intervention N (%)	Control N (%)	Intervention N (%)
Total screened (eligible + ineligible)	445	564	340	444	441	361	564	689	479	476
STUDY CRITERIA										
File not found	6 (8%)	29 (15%)	4 (9%)	12 (7%)	9 (10%)	15 (12%)	2 (4%)	36 (11%)	12 (7%)	27 (13%)
Not 18yrs	0 (0%)	0 (0%)	1 (2%)	0 (0%)	11 (12%)	0 (0%)	9 (16%)	16 (5%)	6 (3%)	9 (4%)
Not resident	6 (8%)	3 (2%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (2%)	1 (0%)	2 (1%)	0 (0%)
Intention to transfer	5 (6%)	2 (1%)	0 (0%)	2 (1%)	1 (1%)	1 (1%)	5 (9%)	1 (0%)	14 (8%)	4 (2%)
Pregnant	8 (10%)	12 (6%)	2 (4%)	3 (2%)	6 (6%)	0 (0%)	6 (11%)	12 (4%)	11 (6%)	12 (6%)
Unknown	0 (0%)	0 (0%)	2 (4%)	0 (0%)	2 (2%)	0 (0%)	1 (2%)	0 (0%)	2 (1%)	0 (0%)
COHORT-SPECIFIC CRITERIA										
COHORT 1: FTIC										
Not HIV positive	3 (4%)	2 (1%)								
TB Diagnosis	7 (9%)	7 (4%)								
Not eligible in last 30d	28 (36%)	17 (9%)								
Not ART Naïve	14 (18%)	34 (17%)								
Not receiving intervention	0 (0%)	89 (46%)								
COHORT 2: AC & COHORT 3: DMD										
Not 12-36 mos on ART			6 (13%)	32 (19%)	5 (5%)	30 (23%)				
ART change in last 12mos			6 (13%)	7 (4%)	3 (3%)	7 (5%)				
Last 2 VL not suppressed			20 (43%)	41 (24%)	28 (30%)	37 (28%)				
No VL in last 3 mos			3 (7%)	21 (12%)	5 (5%)	9 (7%)				
Not in AC / DMD			2 (4%)	50 (30%)	4 (4%)	30 (23%)				
Receiving other RPS than randomized			0 (0%)	1 (1%)	19 (20%)	0 (0%)				
COHORT 4: EAC										
No ART 3 mos							7 (12%)	14 (4%)		
No VL > 400							18 (32%)	50 (15%)		
Not on EAC register							2 (4%)	192 (58%)		
No VL in last 3 mos							6 (11%)	7 (2%)		
COHORT 5: TRIC							7 (12%)	14 (4%)		
Not ART Initiated									5 (3%)	11 (5%)
Didn't miss last visit*									116 (66%)	63 (31%)
Did not receive tracing									9 (5%)	80 (39%)
Total ineligible	**77**	**195**	**46**	**169**	**93**	**130**	**57**	**329**	**177**	**206**
Total enrolled	**368**	**369**	**294**	**275**	**348**	**231**	**507**	**360**	**302**	**270**

Note: * For this group, often these patients appear on TIER as eligible but by the time we visit the site, clinical data has been updated and/or the patient has returned and so they are no longer eligible.

9 COHORT DESCRIPTIVES

Now that enrollment has been nearly completed (with the possibility of some retrospective enrollment if feasible), we have baseline data on subjects in each of the cohorts. Data come from TIER.net and patient files and have been entered into an electronic database for descriptive analysis

in STATA. Below in Table 7 we describe each of the cohorts in terms of their baseline characteristics, both overall and by intervention arm.

Table 7 Baseline characteristics of the cohorts

COHORT 1: FAST TRACK INITIATION COUNSELLING	FTIC Control	FTIC Intervention	FTIC Total
	N=368	N=369	N=737
Characteristic	*n* (%)	*n* (%)	*n* (%)
Age (n=737)			
18-29	87 (24%)	97 (26%)	184 (25%)
30-39	142 (39%)	150 (41%)	292 (40%)
40-49	84 (23%)	79 (21%)	163 (22%)
50+	55 (15%)	43 (12%)	98 (13%)
Gender (n=737)			
Female	214 (58%)	218 (59%)	432 (59%)
Male	154 (42%)	151 (41%)	305 (41%)
CD4 Count (at ART initiation) (n=714) (median, IQR)	234 (123-357)	210 (108-358)	224 (117-357)
TB status (n=737)			
Current TB diagnosis	0 (0%)	0 (0%)	0 (0%)
No current TB diagnosis	368 (100%)	369 (100%)	737 (100%)

Note: *Totals for individual variables may differ because some observations have been dropped due to missing or out-of-range values. These are undergoing review to determine the correct value.

The FTIC cohort participants are mostly under age 40 (65%). As is typical of a public-sector HIV treatment population, the cohort is more likely to be female (59%) though slightly less than the 66% we typically see (see Egger et al. *Int Journal Epidemiol* 2011; 41: 1256-1264 Table 2 for example). The average CD4 count at ART initiation in this cohort is also barely above the initiation threshold when the ART program started (<200) with an average of 224 cells/ml^3 at ART initiation, suggesting that our population is more immunocompromised than the general population of patients eligible for ART. This is expected as FTIC is likely to be prioritized for sicker patients even if not as per the SOP. Despite being a population that by definition was expected to be sicker than the general population, by design we did not enrol any patients with tuberculosis in this cohort.

For FTIC, the intervention and control cohorts were largely balanced on baseline characteristics with only minor differences between groups, much like what would be expected in a moderate sized individually randomized trial. We did observe some small difference in the CD4 count medians, with higher CD4 counts among those in the control group although only by 24 cells. This is also not surprising as it is not possible to know who in the control group would have gotten the intervention had the intervention been delivered there and likely sites prioritized the sickest. Still, it is reassuring the differences are so small. In addition, we note that there were only 23 subjects (3%) for whom we could not find a baseline CD4 count, far less than we typically see in observational cohorts in South Africa (20% in the IeDEA cohort, Egger et al. 2011).

Table 8 Adherence clubs

Characteristic	AC Control N=294 n (%)	AC Intervention N=275 n (%)	AC Total N=569 n (%)
Age (n=569)			
18-29	61 (21%)	58 (21%)	119 (21%)
30-39	108 (37%)	100 (36%)	208 (37%)
40-49	68 (23%)	72 (26%)	140 (25%)
50+	57 (19%)	45 (16%)	102 (18%)
Gender (n=569)			
Female	204 (69%)	206 (75%)	410 (72%)
Male	90 (31%)	69 (25%)	159 (28%)
CD4 Count (at ART initiation) (n= 263 control; 240 intervention)*	282 (170-411)	255 (146-357)	268 (157-379)
Viral Load (copies/ml) (median, IQR) (n=569)	50 (20-124)	50 (20-124)	50 (20-125)
log10 Viral Load (copies/ml) (median, IQR) (n=569)	1.70 (1.30-2.09)	1.70 (1.30-2.09)	1.70 (1.30-2.09)
TB status (n=569)			
Current TB diagnosis	1 (1%)	0 (0%)	1 (1%)
No current TB diagnosis	293 (99%)	275 (100%)	568 (99%)
Time on ART at enrollment (days) (median, IQR) (n=569)	**577 (472-860)**	**839 (551-1163)**	**714 (506-938)**

Note: * We note that the adherence club cohort is not limited to those who were treatment naïve, so some patients could have been transfer-in patients without a baseline CD4 count. Others may have had a lost file and no record of the baseline CD4 count. The NHLS data we have access to for this study only contains lab results from April 2016 onward, so we are not able to find baseline CD4 counts for those in adherence clubs as we require them to be on ART for more than one year.

For the adherence clubs, a little over half of patients were under age 40 (58%) and just above 70% were female. These patients were somewhat healthier at ART initiation than those in the FTIC cohort at an average of 268 cells, but with a fairly wide range (157-379). We had nearly complete viral load data in this cohort as this was necessary to confirm eligibility for the interventions. Baseline CD4 count was missing from 66 subjects (12%) closer to but still below what we observe in the literature for observational HIV cohorts (again see Egger et al. *Int Journal Epidemiol* 2011; 41: 1256-1264 Table 2 for example). As noted, these cannot be updated using the NHLS data because we only have data from April 2016 onwards and these patients are not new on ART.

The intervention and control cohorts were similar with respect to the demographic variables (age and sex) and with respect to log viral load at time of eligibility, which is by design (patients must be supressed to be eligible for the intervention). We did however observe a difference between the cohorts in terms of CD4 count at treatment initiation with the control cohort being somewhat healthier at ART initiation (282 vs. 255). As with FTIC, the differences were small and unlikely to impact the results. We also saw differences between groups in the duration on treatment at enrollment with the control population on treatment for a shorter period of time than the intervention population. This suggests that the intervention sites were either targeting the ACs towards patients who were on treatment for a longer time than eligibility criteria required or that patients who were on treatment for longer were more interested in this intervention.

Table 9 Decentralized Medicine delivery (DMD)

Characteristic	DMD Control N=348 n (%)	DMD Intervention N=231 n (%)	DMD Total N=579 n (%)
Age (n=579)			
18-29	67 (19%)	38 (16%)	105 (18%)
30-39	117 (34%)	90 (39%)	207 (36%)
40-49	100 (29%)	69 (30%)	169 (29%)
50+	64 (18%)	34 (15%)	98 (17%)
Gender (n=579)			
Female	241 (69%)	168 (73%)	409 (71%)
Male	107 (31%)	63 (27%)	170 (29%)
CD4 Count (at ART initiation) (control n=297, intervention n=218)	**279 (142-387)**	**259 (133-346)**	**269 (139-366)**
Viral Load (copies/ml) (median, IQR) (n=577) **	**42 (20-100)**	**124 (35-124)**	**50 (20-124)**
log10 Viral Load (copies/ml) (median, IQR) (n=577)	**1.62 (1.30-2.22)**	**2.09 (1.54-2.09)**	**1.69 (1.30-2.09)**
TB status at study enrollment (n=574)			
Current TB diagnosis	0 (0%)	1 (1%)	1 (1%)
No current TB diagnosis	343 (100%)	230 (99%)	573 (99%)
Time on ART at enrollment (days) (median, IQR) (n=579)	**756 (488-916)**	**797 (498-951)**	**769 (491-935)**

Note: ** 2 viral loads were not found. As this is an inclusion criteria, we will need to verify if these can be found and if not, they will not be included in the final dataset.

The DMD cohort also had roughly half of the patients below age 40 (54%) and had many more females (71%) than males. As we would expect given the interventions had the same eligibility criteria, the cohort was similar to the Adherence Clubs cohort with respect to ART initiation CD4 count (269 cells), though we note that this is not the CD4 count at the time of enrollment into the cohort. As with Adherence Clubs, we were missing a baseline CD4 count on 64 (11%) of subjects, typical of but lower than, most HIV programs in South Africa. The median viral load at baseline was also very low as would be expected given the eligibility criteria for the intervention (i.e. stable patients).

The intervention and control cohorts were well balanced with respect to sex and age but there were some small imbalances in CD4 count at ART initiation (279 vs. 259) and log viral load at eligibility (1.62 vs 2.09). These don't appear too large, but it is something we will pay attention to when we conduct the analysis. Interestingly, here the time on treatment was very similar between groups, suggesting that unlike Adherence Clubs, DMD was not being targeted towards those on treatment longer or shorter than the eligibility criteria would require. The median time on ART for both groups was also much more similar to the intervention group in the Adherence Club cohorts, suggesting overall that patients who got one of the two interventions were on treatment a fair bit longer than required (a minimum of one year), likely as clinics processed a backlog of eligible patients as part of the Decanting Strategy. In addition, due to the Decanting Strategy some of our DMD control sites were evaluation intervention sites, and as such we would exclude any patient from our DMD group who had been enrolled in an Adherence Club. This likely would have excluded those who had been on ART for shorter periods of time.

Table 10 Enhanced Adherence Counselling (EAC)

Characteristic	EAC Control N=507 *n* (%)	EAC Intervention N=360 *n* (%)	EAC Total N=867 *n* (%)
Age (n=867)			
18-29	56 (11%)	56 (16%)	112 (13%)
30-39	184 (36%)	138 (38%)	322 (37%)
40-49	150 (30%)	103 (29%)	253 (29%)
50+	117 (23%)	63 (18%)	180 (21%)
Gender (n=867)			
Female	310 (61%)	212 (59%)	522 (60%)
Male	197 (39%)	148 (41%)	345 (40%)
CD4 Count (at ART initiation) (n=437 control; 323 intervention)* **	**163 (79-270)**	**146 (79-261)**	**157 (79-269)**
Viral Load (copies/ml) (median, IQR) (n=864) **	**3550 (914-36,000)**	**11712 (2010-67200)**	**5256 (1145-46,300)**
log_{10} Viral Load (copies/ml) (median, IQR) (n=864)	**3.55 (2.96-4.55)**	**4.06 (3.30-4.82)**	**3.72 (3.05-4.67)**
TB status at study enrollment (n=866)			
Current TB diagnosis	2 (1%)	2 (1%)	4 (1%)
No current TB diagnosis	505 (99%)	357 (99%)	862 (99%)
Time between last viral load and enrollment (days) (median, IQR)* (n=867)	**54 (34-77)**	**58 (33-92)**	**55 (34-83)**

Note: * Time between last viral load and enrollment. It is likely patients are only enrolled in EAC at their next visit after becoming eligible through an elevated viral load unless there is a specific intervention at the site to follow up patients with high viral loads (if the patient is only returning every other month to pick up medication then these times seem reasonable, as the EAC SOP says "an EAC identified file should trigger referral for EAC as soon as the patient comes back to the facility"). It is possible that an EAC patient may be contacted in between telling them they need EAC but this is not recorded; ** We note that 3 viral loads were not found. As this is an inclusion criteria, we will need to verify if these can be found and if not, they will not be included in the final dataset; *** We note that the enhanced adherence counselling cohort is not limited to those who were treatment naïve, so some patients could have been transfer-in patients without a baseline CD4 count. Others may have had a lost file and no record of the baseline CD4 count. The NHLS data we have access to for this study only contains lab results from April 2016 onward, so we are not able to find baseline CD4 counts for those in adherence clubs as we require them to be on ART for more than one year.

The EAC cohort was very evenly divided between those below and above 40 (50%) but slightly fewer females (60%) than we typically see in ART cohorts, possibly suggesting that males may be more likely to have elevated viral loads in these cohorts than in the general population. The cohort was quite sick at ART initiation with an average CD4 count below 200 cells/ml^3 (157 cells/ml^3). The cohort was eligible for the intervention for a median of 55 days at enrollment, suggesting a little over a one month delay between eligibility and enrollment. We believe most patients who get EAC only get it after returning to the clinic from a previous visit where a blood draw for viral load monitoring found them to have met the eligibility criteria. As with the previous two interventions we had near complete data on viral load at enrollment as this was necessary to determine eligibility. We were missing CD4 counts at ART initiation for 107 (12.4%) still below the 20% we typically observe in our observational cohorts.

The intervention and control cohorts were well balanced with respect to age and sex and tuberculosis enrollment. There were small differences in CD4 count (163 vs 146 cells/ml^3). Log viral load was also somewhat different and lower in the control cohort (log_{10} 3.55 vs. 4.06). This suggests that despite the eligibility criteria, EAC was being targeted towards those with the highest viral loads while those with lower, but still eligible viral loads are not being given the same priority.

Table 11 Early Tracing (TRIC)

Characteristic	TRIC Control N=302 *n* (%)	TRIC Intervention N=270 *n* (%)	TRIC Total N=572 *n* (%)
Age (n=572)			
18-29	55 (18%)	67 (25%)	122 (21%)
30-39	102 (34%)	111 (41%)	213 (37%)
40-49	82 (27%)	63 (23%)	145 (25%)
50+	63 (21%)	29 (11%)	92 (16%)
Gender (n=572)			
Female	192 (64%)	182 (67%)	374 (65%)
Male	110 (36%)	88 (33%)	198 (35%)
CD4 Count (at ART initiation) (control n=268, intervention n=244)	**209 (124-327)**	**215 (108-335)**	**211 (114-331)**
Last Viral Load (copies/ml) (median, IQR) (control n=232, intervention n=179)	**100 (20-159)**	**100 (20-270)**	**100 (20-200)**
log_{10} last Viral Load (copies/ml) (median, IQR) (control n=232, intervention n=179)	**2.00 (1.30-2.19)**	**2.00 (1.30-2.43)**	**2.00 (1.30-2.30)**
TB status (n=567)			
Current TB diagnosis	2 (1%)	2 (1%)	4 (1%)
No current TB diagnosis	296 (99%)	267 (99%)	563 (99%)
Time between last missed visit and enrollment (days)* (median, IQR) (n=566)	**32 (17-58)**	**85 (29-131)**	**45 (21-99)**

Note: * Most patients are only enrolled at their next visit between last missed visit and enrollment (visit can be missed by up to 90 days). The patients need to be eligible for tracing from May through October. Therefore if someone missed a scheduled visit in February, they would be eligible for tracing through May, and only enrolled in October, resulting in 243 days between missed visit and enrollment.

The TRIC cohort was also roughly divided between those below (58%) and above 40 (42%) and very close to what we expect for percent females at 65% suggesting those that receive TRIC are similar to the general clinic populations. As with previous cohorts the patients were quite sick at ART initiation with an average CD4 count of 211 cells/ml[3], though higher than the EAC cohort. In this cohort 60 (10.4%) patients had a missing CD4 count at ART initiation, lower than what we typically observe in our HIV cohorts. We note here that there was a substantial amount of missing viral load data, but this is explained by the fact that this cohort is not required to have a viral load to be eligible, and many patients in this cohort have left care and are therefore expected to not have had a viral load. In addition, patients may also have not reached the point of needing a viral load (e.g. if they missed an appointment between initiation and 6 months). Overall the last viral load was low in this cohort, suggesting that many of the patients lost and being traced (or eligible to be traced) had not been experiencing an elevated viral load just prior to missing a visit. The cohort was eligible for the intervention for an average of 45 days at enrollment (days between last missed visit and enrollment to the cohort, not time between missed visit and tracing attempt).

The intervention and control cohorts were very well balanced with respect to CD4 at ART initiation and log of last viral load. However they did show some differences, with younger patients in the intervention cohort and the intervention cohort being eligible for the intervention substantially longer than the control cohort (32 vs. 85 days). This likely reflects the fact that we did retrospective enrollment into the cohorts rather than reflecting any meaningful differences.

Table 12 Tuberculosis, Hypertension and Diabetes - Screening Cohort (TBHD)

	HIV Negative N=1385		HIV Positive N=1015		Total TBHD- Screening N=2400	
Characteristic	***n***	**(%)**	***n***	**(%)**	***n***	**(%)**
Age						
18-29	271	(20%)	180	(18%)	451	(19%)
30-39	198	(14%)	326	(32%)	524	(22%)
40-49	218	(16%)	280	(28%)	498	(21%)
50-59	289	(21%)	158	(16%)	447	(19%)
60+	409	(30%)	71	(7%)	480	(20%)
Gender						
Female	895	(65%)	670	(66%)	1565	(65%)
Male	490	(35%)	345	(34%)	835	(35%)
Any TB Screening at last visit						
Yes	292	(21%)	794	(78%)	1086	(45%)
No	1093	(79%)	221	(22%)	1314	(55%)
Any Diabetes screening at last visit						
Yes	51	(4%)	6	(1%)	57	(2%)
No	1334	(96%)	1009	(99%)	2343	(98%)
Any Hypertension screening at last visit						
Yes	117	(8%)	131	(13%)	248	(10%)
No	1268	(92%)	884	(87%)	2152	(90%)
Screening at last visit- combined						
No screening	962	(69%)	183	(18%)	1145	(48%)
TB screening	260	(19%)	697	(69%)	957	(40%)
Diabetes screening	39	(3%)	3	(0%)	42	(2%)
Hypertension screening	89	(6%)	35	(3%)	124	(5%)
TB and Diabetes screening	7	(1%)	1	(0%)	8	(0%)
TB and Hypertension screening	23	(2%)	94	(9%)	117	(5%)
Hypertension and Diabetes screening	3	(0%)	0	(0%)	3	(0%)
TB, Hypertension, and Diabetes screening	2	(0%)	2	(0%)	4	(0%)
Any recent TB diagnosis						
Yes	13	(1%)	17	(2%)	30	(1%)
No	1372	(99%)	998	(98%)	2370	(99%)
Any recent Diabetes diagnosis						
Yes	91	(7%)	3	(0%)	94	(4%)
No	1294	(93%)	1012	(100%)	2306	(96%)
Any recent Hypertension diagnosis						
Yes	182	(13%)	36	(4%)	218	(9%)
No	1203	(87%)	979	(96%)	2182	(91%)
Recent diagnosis- combined (enrolled in cohort 6a and 6b)						
No diagnosis	1151	(83%)	961	(95%)	2112	(88%)
TB diagnosis	13	(1%)	17	(2%)	30	(1%)
Diabetes diagnosis	39	(3%)	1	(1%)	40	(2%)
Hypertension diagnosis	130	(9%)	34	(3%)	164	(7%)
Hypertension and Diabetes diagnosis	52	(4%)	2	(1%)	54	(2%)

Overall, the TBHD cohort was older than the previous cohorts (only 41% under age 39) but their sex distribution looked exactly like an ART cohort, suggesting that ART cohorts are much like the general population of patients seeking care at a PHC. TB screening was common in this cohort (with 45% receiving TB screening at last visit) with only 10% getting hypertension screening and only 2% receiving diabetes screening. This differed strongly by HIV status, however, as would be expected. Those with HIV were much more likely to get TB screening at last visit than those who did not have HIV (78% vs 21%). Overall, those with HIV were much less likely not to receive any screening (18% with HIV vs 69% without did not receive any screening, though again this was

largely driven by TB screening). Still even among hypertension there was some suggestion that screening was better among those with HIV (13%) compared to those without (8%), though the numbers were small overall. The opposite was true for diabetes however, with the HIV cohort receiving almost no screening (4% vs 1%).

Among all patients, 79% had no diagnosed condition at last visit, though this included the 48% of patients who received no screening. Diagnosis of all conditions was rare, with 1% diagnosed with TB, 2% diagnosed with diabetes and 7% diagnosed with hypertension. The HIV negative cohort was less likely to have no condition diagnosed than the HIV positive cohort (83% vs 95%). This might seem counterintuitive, but likely reflects the fact that more patients in the HIV cohort would already have been diagnosed with a condition. The most common condition diagnosed among the HIV negatives was hypertension (9%).

Table 13 Tuberculosis, Hypertension and Diabetes - Diagnosed Cohort

	HIV Negative N=479	HIV Positive N=98	Total TBHD- Diagnosed N=577
Characteristic	***n* (%)**	***n* (%)**	***n* (%)**
Age			
18-29	23 (5%)	11 (11%)	34 (6%)
30-39	50 (10%)	34 (35%)	84 (15%)
40-49	72 (15%)	22 (22%)	94 (16%)
50-59	121 (25%)	21 (21%)	142 (25%)
60+	213 (44%)	10 (10%)	223 (39%)
Gender			
Female	305 (64%)	52 (53%)	357 (62%)
Male	174 (36%)	46 (47%)	220 (38%)
Screening at last visit			
No screening	343 (72%)	55 (56%)	398 (69%)
TB screening	105 (22%)	36 (37%)	141 (24%)
Diabetes screening	12 (3%)	3 (3%)	15 (3%)
Hypertension screening	13 (3%)	4 (4%)	17 (3%)
TB and Hypertension screening	5 (1%)	0 (0%)	5 (1%)
Hypertension and Diabetes screening	1 (0%)	0 (0%)	1 (0%)
Recent diagnosis			
TB diagnosis	33 (7%)	47 (48%)	80 (14%)
Diabetes diagnosis	65 (14%)	1 (1%)	66 (11%)
Hypertension diagnosis	305 (64%)	48 (49%)	353 (61%)
Hypertension and Diabetes diagnosis	76 (16%)	2 (2%)	78 (14%)

The diagnosed cohort is still in recruitment, so it is difficult to interpret the data. However, of the 577 subjects enrolled, very few were young with only 21% being under 40 years of age. This would be consistent with the age distribution of these comorbid conditions. In addition, more males have been diagnosed than females, again consistent with what we know about tuberculosis rates.

10 FOLLOW UP PROCESSES

With the HIV cohorts now nearing completion of enrollment (with only possible retrospective enrollment remaining), we will continue to follow up patients through passive record review while continuing to work with the sites to maintain quality data and to monitor data systems for study outcomes. The short term and long-term outcomes are described in Table 8 below.

Table 14 Study evaluation outcomes for protocol 1

Cohort	Short-term Outcome	Long-term Outcomes
Fast track ART initiation counseling	% who initiate ART within 30 days of becoming ART eligible	% of patients virally suppressed (< 400 copies/ml[3]) within 9 months of ART eligibility
Adherence clubs	% who receive all medications within the first four months after eligibility	% virally suppressed (< 400 copies/ml[3]) at twelve months after club eligibility
Decentralized medicine delivery	% who receive all medications within 3 months	% virally suppressed suppression (< 400 copies/ml[3]) 12 months
Enhanced adherence counseling	% who resuppress their viral load (< 400 copies/ml[3]) within 3 months of eligibility	% who resuppress their viral load (< 400 copies/ml[3]) within 12 months of eligibility
Early tracing of patients lost to follow up	% who return to care within 3 months of eligibility	% who return to care within 12 months of eligibility
TB, hypertension, and diabetes	For each condition, % of patients who have 80% visit compliance in first 3 months after diagnosis	For each condition, % of patients who achieve disease control at the six-month visit after diagnosis

We will continue to monitor TIER.net and work with the sites to collect follow up data for patients enrolled in the study. The Gantt chart below in Figure 4 show the timeline for follow up and completion of data collection for protocol 1.

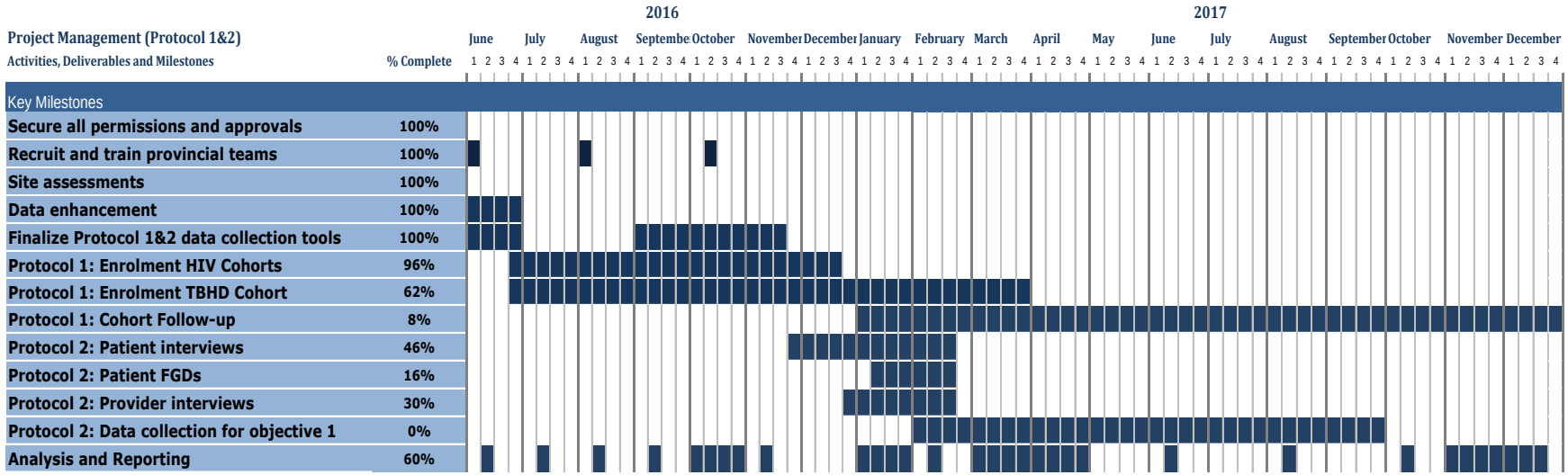
10.1 Data collection for short-term endpoint for Fast Track Initiation Counselling

The short-term outcome for FTIC requires a 30-day follow up for each patient to assess the percentage who initiate ART. FTIC follow up occurs through TIER.net through identification of the initiation visit with verification through patient registers if needed. FTIC follow up has been completed for 81% of patients who have currently been enrolled. All subjects are expected to reach a short-term outcome by February 2017. At that point we will need to verify data against patient files for any subjects with missing data in TIER (e.g. should a backlog occur) with an expected date of having all short-term outcomes by March 2017. Below are outcomes for the patients who have reached a primary short term outcome for FTIC. Currently 84% of patients in intervention sites and 81% of patients in control sites initiated ART within 30 days of eligibility.

Table 15 Short-term outcomes (ART initiation within 30 days) for those eligible for FTIC cohort

INTERVENTION					CONTROL				
Facility	Total	Eligible for outcome	Initiated within 30 days	% initiated	Facility	Total	Eligible for outcome	Initiated within 30 days	% initiated
Motsamai Clinic	28	25	18	72%	Tamaho Clinic	29	14	10	71%
Phola Park CHC	31	8	6	75%	Ramokonopi CHC	30	23	17	74%
Khumalo Clinic	28	26	26	100%	Zonkizizwe 1 Clinic	30	21	11	52%
Grace Mugodeni CHC	30	29	23	79%	Motupa Clinic	35	25	20	80%
Giyani CHC	30	25	22	88%	Dzumeri Clinic	30	28	25	89%
Tzaneen Clinic	27	24	15	63%	Nkowankowa CHC	30	27	19	70%
Letlhabile CHC	32	26	23	88%	Wonderkop Clinic	30	30	25	83%
Hebron Clinic	31	27	23	85%	Majakaneng Clinic	30	30	26	87%
Tlhabane CHC	30	30	26	87%	Bafokeng CHC	30	29	26	90%
King Dinizulu Clinic	34	29	26	90%	Nkwalini Clinic	34	32	29	91%
Thokozani Clinic	37	26	22	85%	Nseleni CHC	30	27	22	81%
Buchanana Clinic	31	16	13	81%	Ntambanana Clinic	30	26	24	92%
Total	**369**	**291**	**243**	**84%**	**Total**	**368**	**312**	**254**	**81%**

Figure 4 Gantt Chart of Timeline for Project



11 CONCLUSIONS

Enrollment into the HIV cohorts has now completed with enrollment into the TBHD cohort expecting completion in March 2017. While there have been challenges to getting the cohort enrolled, including delays in implementation of the interventions and changes to the way the interventions have been implemented, the team has been able to enrol subjects into the cohorts. These challenges have been overcome through a combination of support from the World Bank and NDoH PIs to working with the sites to ensure accurate record keeping and access to registers. The cohorts are now entering the follow up phase for the HIV cohorts and work will shift to a mix of maintaining control over the quality of the cohort data, completing enrollment into the TBHD cohorts and to continue with protocol 2 where we will collect largely qualitative data from patients and providers to better understand how the rollout is occurring and the impacts that it is having.