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Costs and cost-effectiveness of interventions to improve HIV treatment adherence in Cape Town, South Africa

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COSTS AND COST-EFFECTIVENESS OF INTERVENTIONS TO IMPROVE HIV TREATMENT ADHERENCE IN CAPE TOWN, SOUTH AFRICA

by

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DEDICATION

To my grandparents, Stephen and Judith Adler, whose love is always with me.
May their memory be for a blessing.

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COSTS AND COST-EFFECTIVENESS OF INTERVENTIONS TO IMPROVE HIV TREATMENT ADHERENCE IN CAPE TOWN, SOUTH AFRICA

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ABSTRACT

Background: Improving adherence to antiretroviral therapy (ART) is crucial for achieving HIV epidemic control in South Africa. The SUSTAIN trial aims to identify the most cost-effective package of evidence-based strategies for adherence monitoring (pharmacy refill monitoring (PRM), electronic adherence monitoring (EAM), viral load (VL) monitoring) and support (check-in texts (SMS), enhanced adherence counselling (EC)) for patients newly initiating ART. Participants were randomized to receive one of sixteen combinations of interventions using a multi-phase optimization strategy design.

Methods: First, a cost analysis of implementing SUSTAIN interventions for the first cohort (n=260) of participants was conducted from a health system perspective, using a micro-costing approach that employed three data collection methods: self-reported time and cost worksheets, independent staff observation, and discussions with staff during site visits. Second, a cost-effectiveness analysis was conducted using costing and adherence data from SUSTAIN participants to explore costs for achieving >80%, >90%, and >95% adherence for each intervention component. Third, a forward-looking costing model estimated costs for scaling up the interventions in a real-world setting (City of Cape

Town) over a 10-year time horizon. All cost analyses were adjusted for inflation and discounted using an annual rate of 3%.

Results: The costs for one person-year of participation in SUSTAIN were $12 for PRM, $25 for VL monitoring, $162 for EAM, $16 for EC and $42 for SMS. Cost-effectiveness analyses showed PRM was cost-saving versus EAM and VL monitoring for achieving all categories of adherence. For support interventions, EC was cost-saving compared to SMS for achieving all categories of adherence. Estimated per annum future costs per patient ranged from $11–$25 for general program costs, $12–$20 for VL monitoring, $69–$122 for EAM, $3–$5 for PRM, $12–$14 for SMS, and $16–$31 for EC. A cost-effectiveness analysis of future costs found SMS would be more cost-saving than EC; the monitoring interventions remained the same.

Conclusion: EAM was costliest due to high technology costs; however, these will decrease with mass production if scaled up. Pending final cost-effectiveness results from the main SUSTAIN trial, a differentiated approach based on cost and sensitivity of monitoring interventions could be considered for those restarting versus initiating ART. Support options require further investigation.

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ABBREVIATIONS

ART = antiretroviral therapy

CEA = cost-effectiveness analysis

CRW = Community Research Worker

GDP = Gross Domestic Product

HIV = Human Immunodeficiency Virus

ICER = incremental cost-effectiveness ratio

LEAP = Locally-tailored, Evidence-based, And Personalized

MOST = Multi-phase Optimization Strategy

OECD = Organization for Economic Co-operation and Development

PHIV = people with HIV

RCT = randomized controlled trial

SMS = short-message system

SUSTAIN = Supporting Sustained HIV Treatment Adherence after Initiation

USD = United States Dollar

ZAR = South African Rand

CHAPTER ONE: INTRODUCTION

A. Problem Statement

South Africa has the largest population of people with HIV (PHIV) globally (approximately 8.2 million) and the largest antiretroviral therapy (ART) program in the world[1,2]. In South Africa, lifelong adherence to ART remains a major challenge: adherence ranges from 40–75%[3–6], and only 43–58% of all PHIV are virally suppressed[7]. To improve HIV treatment outcomes, clinics must identify non-adherent PHIV as quickly as possible and implement effective interventions to assure ART adherence and retention in care. While evidence-based strategies for optimal ART adherence have been identified[8–13], translation of these strategies into clinical practice is slow. There is thus an urgent need to identify the most effective and feasible intervention or intervention packages to integrate into routine care. To address this, the **Su**pporting **S**ustained HIV **T**reatment **A**dherence after **In**itiation (SUSTAIN) study will test the impact of five interventions in sixteen combinations on treatment outcomes for PHIV newly initiated on ART over two years.

B. Research Questions and Specific Aims

This dissertation is a costing and cost-effectiveness assessment for the first cohort of participants (initial 50% enrolled) in the SUSTAIN study at their midpoint of participation (one year). The primary aims of this dissertation are to:

1. Determine costs of implementing interventions for the first 50% of SUSTAIN participants from the payer (health system) perspective.
2. Assess the cost-effectiveness of interventions on ART adherence after one year of participation.
3. Conduct a forward-looking costing analysis to estimate costs of implementing SUSTAIN activities outside of a research environment at scale, to provide programmatic costs for decision-makers.

C. Study Setting

The Western Cape is one of nine provinces in South Africa, with a population of 7.0 million people. There are an estimated 506,000 PHIV, of which 65.5% are on ART[14]. The SUSTAIN study takes place in three City of Cape Town clinics (Phumlani, Weltevreden Valley, Mzamomhle) in the Klipfontein and Mitchells Plain health districts (with estimated total populations of 414,693 and 635,716, respectively)[15]. These clinics serve a population with a high prevalence of HIV and provide ART services delivered by doctors, clinical nurse practitioners, and registered nurses. Services provided at these clinics also include family planning, vaccinations, antenatal care, and tuberculosis care.

D. Research Translation: Contribution to Public Health Practice

The dissertation will provide several products intended for use by a range of stakeholders in both academic and practice settings.

- *SUSTAIN study costing framework:* A framework for collection of costing data will be developed for use by the study team to cost the entirety of the SUSTAIN study and providing inputs into the final cost-effectiveness analysis.
- *Future-looking SUSTAIN costing framework:* A costing framework for future implementation of SUSTAIN will be prepared for City of Cape Town stakeholders, with costs estimated for implementation outside of a research setting and scaled up to the city level.
- *Dissemination meeting:* A presentation on interim costing and cost-effectiveness results will be given to City of Cape Town stakeholders in April 2024.
- *Peer-reviewed manuscripts:* The results of the costing analysis for SUSTAIN and cost-effectiveness analysis will be prepared for submission to a peer-reviewed journal. The results of the future costing will also be prepared for publication in a peer-reviewed journal.

E. Overview of Dissertation Chapters

Chapter 2 describes the context within which the research is taking place and why it is needed. It describes the current burden of HIV in South Africa and need for enhanced ART adherence support, SUSTAIN methodology, and evidence behind the selected adherence interventions being tested.

Chapter 3 contains a description of the dissertation research aims and the methodology used to investigate them.

Chapter 4 presents the results of dissertation aim one: costs of participation in the SUSTAIN study for the first 50% of participants over one year.

Chapter 5 presents the results of dissertation aims two and three, the cost-effectiveness of SUSTAIN interventions on adherence to ART, a forward-looking costing scenario of SUSTAIN interventions when implemented at scale within City of Cape Town outside of a research setting, and a cost-effectiveness analysis using the future costing estimates.

Chapter 6 details recommendations for public health practice based on the integrated findings from aims one, two and three.

CHAPTER TWO: BACKGROUND

A. Chapter Overview

This chapter describes the context within which the dissertation research takes place and why it is needed, including the burden of HIV in South Africa and the need for enhanced ART adherence support. It also introduces SUSTAIN, the parent study for this dissertation, describing the methodology used in SUSTAIN and the evidence behind the selected adherence interventions which are analysed in this dissertation.

B. The South African Healthcare System

In 2021, South Africa had a reported population of 60,140,000 with a Gross Domestic Product (GDP) of $351.4 billion, GDP per capita of $6,001, and net official development assistance received of $971.5 million. While the country was recently reclassified from middle- to upper-middle income, unemployment hit a record high of 34.4% as a result of the COVID-19 pandemic, which caused a significant decline in the country's economic growth[16]. Current government health expenditure is 9% of GDP (compared to 9.6% in Organization for Economic Cooperation and Development [OECD] countries, on average), and there are 0.8 physicians and 1.3 nurses per 1,000 people (compared to the average of 3.5 and 8.8, respectively, among OECD countries)[17].

Health sector governance in South Africa is centered within the provincial health departments, while funding and policy guidelines are made at the national level[18]. Most of the public health system is funded through a National Revenue Fund, which collects

payments made to local, provincial and federal governments; there is a centralized distribution of funds from federal to local municipalities[19]. Provincial departments are the direct employers of the health workforce, while the National Department of Health is responsible for policy development and coordination[20]. Provincial health departments (for example, the Western Cape Department of Health and Wellness) provide a comprehensive package of health services including clinics, district/provincially aided hospitals, tertiary hospitals, tuberculosis hospitals, psychiatric hospitals and reproductive and other specialized health care facilities[21]. Local government (or municipalities) such as City of Cape Town deliver primary health care to all citizens with no formal health insurance plan for free[19]. Services offered in primary health care facilities include maternal and childcare, immunization, family planning, syndromic treatment of sexually transmitted infections, HIV testing and counseling, and care for chronic diseases. Clinics typically offer services eight to nine hours a day between five and seven days per week[22].

There is immense pressure on the South African healthcare system to provide services: an estimated 84% of South Africans rely on the provision of public healthcare[23] and the country faces a quadruple burden of disease driven by coexisting infectious diseases (HIV, tuberculosis), non-communicable diseases (vascular illness, diabetes, cancer), avertable maternal and child mortality, and high levels of violence and injuries[24–27]. The HIV program alone accounts for more than 10% of all government health sector expenditure with growth outpacing the overall budget for health[28]. There is thus a clear need to identify low-cost and cost-effective interventions for diagnosing and managing disease to meet the demand for responsive healthcare while keeping costs to a minimum.

B. Overview of HIV in South Africa

South Africa bears the greatest HIV burden in the world with nearly 8.2 million PHIV, and HIV remains one of the leading causes of death in the country[29]. HIV prevalence is disproportionately high among Black South Africans compared to other racial and ethnic groups in the country[30], and among the poor and middle class[31]. Prevalence is highest among key populations including female sex workers (approximately 55%) and men who have sex with men (approximately 25%)[14]. Adolescent girls and young women aged 15–24 are also at high risk of HIV acquisition. In 2022, HIV prevalence was twice as high in young women aged 15–19 years (5.7% vs 3.1%) and 20–24 years (8% vs 4%), and three times higher in women aged 25–29 years (19.5% vs 6.3%) than their male peers. By province, prevalence ranges from 8.2% in the Western Cape to 21.8% in KwaZulu-Natal[32] (Table 2.1).

Table 2.1. HIV Prevalence by Province, 2022

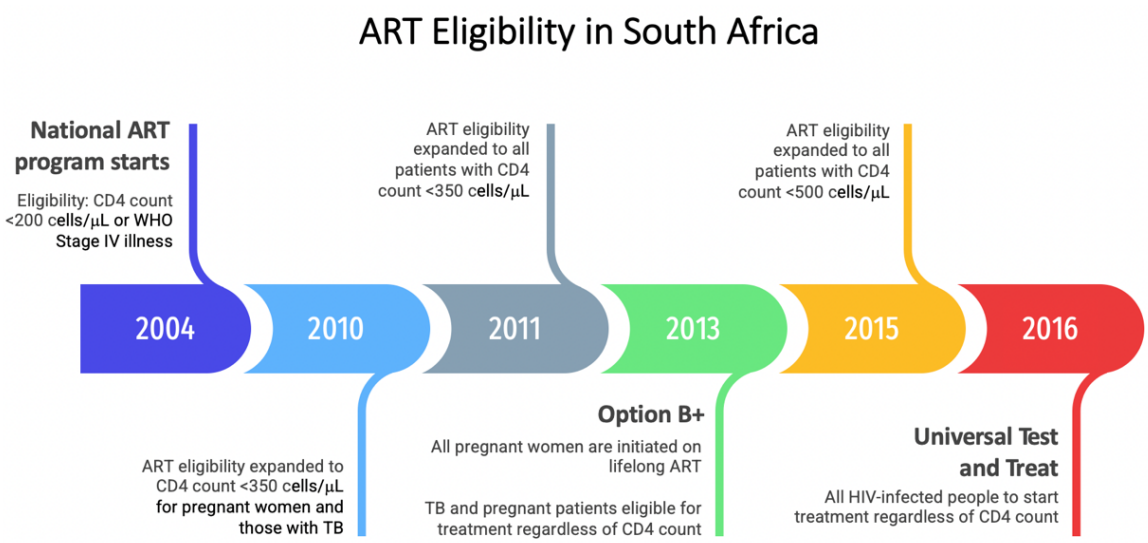
Province	Prevalence (%)
KwaZulu-Natal	21.8
Mpumalanga	20.8
Free State	19.1
Eastern Cape	18.8
North West	16.5
Gauteng	15.0
Limpopo	11.9
Northern Cape	10.0
Western Cape	8.2

Source: SABSSM VI[32]

South Africa has the largest ART program in the world, with more than 5.5 million PHIV receiving treatment[1]. ART first became available in the early 2000's

through pilot projects, and coverage increased after 2004 when ART provision to all PHIV meeting specific clinical criteria became national policy. From 2004–2010, PHIV were eligible for ART with a CD4 cell count of <200 cells/μL or Stage IV illness as classified by the World Health Organization[33]. Eligibility requirements have evolved over time (Figure 2.1), and South Africa adopted universal ART access in 2016 whereby anybody with HIV could start treatment regardless of CD4 count ("universal test and treat")[34].

Figure 2.1. Evolution of ART Eligibility Guidelines in South Africa



UNAIDS laid out the ambitious 95-95-95 targets to end the HIV epidemic by 2025: that 95% of HIV-positive individuals know their status, 95% of people with HIV who know their status are on treatment at any given time, and 95% of people with HIV on treatment are virally suppressed[35]. Despite the advances made in HIV care and treatment in South Africa over the last several decades, weaknesses in the care cascade are evident. It is estimated that only 74% of PHIV overall are on ART, and adherence and

retention in South Africa remain critical challenges: adherence to ART ranges from 40%–75% of doses taken[3,6,36], far below what experts believe is required for successful treatment (typically at least 80%)[37–39]. An estimated 51–86% of people show suppressed virus at 12 months on treatment[3,6,40–42], and approximately 66% of PHIV in South Africa are believed to be virally suppressed.

Achieving the third 95-95-95 goal of viral suppression requires both adherence to treatment and retention in care. Adherence encompasses medication initiation, defined as taking the first dose; dose-taking execution (taking doses as prescribed) throughout treatment; and treatment persistence, meaning continuing therapy without prolonged gaps[10]. Retention in care is defined as a patient's regular engagement with medical care after initial entry into the system[43] and can be evaluated in multiple ways, including missed visits, appointment adherence, and gaps in care using pharmacy, laboratory and clinic data[44,45]. Lower rates of viral suppression are linked to early drop-offs from care: 17% of PHIV who start ART fall out of care by 16 weeks, and >20% are lost in the first year on treatment[4–6]. Patients who miss doses early in treatment are known to exhibit poor outcomes and are disproportionately lost to care[46–48]. Tools to identify those at risk of loss of virologic control as early as possible are needed to improve individual outcomes and to maximize the impact of treatment as prevention[49]. Additionally, higher ART adherence can reduce health care costs, particularly hospitalization costs[50]. While evidence-based strategies for optimal ART adherence have been identified[8–13], translation into clinical practice is slow. Interventions that are successful within controlled research environments are often not implemented in routine real-world care for many reasons,

including poor knowledge of evidence-based interventions, cost, and resource requirements[51]. There is thus an urgent need to quicken the pace of integrating evidence-based interventions into standard care.

C. Use of MOST Methodology to Improve ART Adherence

As of 2020, there were an estimated 506,000 PHIV in South Africa's Western Cape province, of whom 88.73% had been diagnosed with HIV, 65.5% had been initiated on ART, and 52.2% had achieved viral suppression[14]. Cape Town is the largest metropolitan district in the Western Cape and one of the five largest metro areas in South Africa[52]. The SUSTAIN study is part of an ongoing partnership between Boston University and the the University of Cape Town with the City of Cape Town to identify and adopt optimal evidence-based adherence strategies for newly diagnosed PHIV.

The randomized controlled trial (RCT) is considered the gold standard for testing interventions because it minimizes bias when testing effect. However, RCTs are not intended for evaluating the performance of individual intervention components included in a multi-component package. The multi-phase optimization strategy (MOST) approach is an alternative approach to testing interventions which are multi-component. This approach calls for empirically examining the efficacy of each separate intervention component as well as in combinations, along with the relevant resource requirements and costs[53,54]. Inspired by engineering methods, MOST has three phases: preparation, optimization, and evaluation in an RCT. After the preparatory phase, the optimization phase is designed to identify the optimal combination of intervention components before

moving on to devoting the resources and time to testing the effect of the optimized packaged interventions versus the standard of care in a definitive RCT[53,55].

The preparation phase of MOST involves development of a conceptual framework, identification of feasible candidate intervention components, and determining the optimization objective. The optimization objective is a set of pre-specified criteria to guide the process of deciding which intervention components will be included in the multi-component intervention (e.g., the best combination of components that can be carried out within a specific time or for a specific cost). In the optimization phase, the effectiveness of individual components, as well as combinations of components, is assessed using designs such as factorial experiments, sequential multiple-assignment randomized trials, and micro randomized trials. A decision-making process is then carried out where the optimization criteria are applied and modeling analyses are conducted to identify those components (likely 2–3) with the greatest levels of efficacy and cost-effectiveness, while the poorly performing, costly or ineffective components are eliminated[53]. This process is designed to produce a multi-component intervention called the "optimized intervention" or to suggest the need to return to an earlier stage in the MOST framework[55–57]. Finally, in the evaluation phase the optimized intervention package is assessed through an RCT before scale-up.

Following this schema, in the "Preparation" phase for SUSTAIN, the research team conducted formative research through the Locally-tailored, Evidence-based, And Personalized (LEAP) study[58]. In LEAP, local officials and clinical staff in Cape Town were consulted to identify the most effective, acceptable, and feasible HIV adherence

intervention components for patients and providers. These potential components formed the basis for a pilot study which used in-depth interviews with patients and focus group discussions with providers to determine the most preferred intervention components to be used in SUSTAIN. The SUSTAIN study represents the "Optimization" phase of the MOST design, as it seeks to identify the intervention package that is most impactful at supporting PHIV to remain adherent to ART, with viral suppression as the primary outcome. If appropriate, a final "Evaluation" phase will follow SUSTAIN to test the optimized intervention package.

D. ART Adherence Intervention Components and Review of Evidence

The current standard of care for those on ART in the Western Cape is additional adherence support once detected as nonadherent through indication of unsuppressed virus following a standard viral load test comprising up to two structured enhanced adherence counselling session. In the first session, a detailed assessment is completed; if the patient has another viral load test >50 copies/ml three months later, they are referred for a second counselling session. Switching to a second-line treatment may be discussed, and a new adherence plan is developed, including linkage to community-based care and support programs as needed[59]. A number of "Risk of Treatment Failure" clinics have also been established in the Western Cape to provide structured adherence support including a flagging system to identify patients with elevated viral loads, counsellor led adherence support groups, combined clinical and adherence support consultations, and access to ART adherence clubs[60].

SUSTAIN will test the most preferred possible additional or alternative strategies for outreach and adherence support identified in the LEAP pilot study[61]. These include three means of rapidly identifying and reaching out to nonadherent patients: (1) an immediate call to the patient after a standard viral load test showing viremia, (2) pharmacy refill monitoring with a call to the patient after a missed refill, and (3) electronic adherence monitoring with a call to the patient if doses are missed. Two adherence support strategies are also included: weekly check-in texts and individual enhanced adherence counselling sessions using motivational interviewing. These intervention components are all evidence-based, as described below.

Rapidly identifying and reaching out to nonadherent patients

While self-reported adherence remains the most widely used method in real-world settings, it is subject to multiple limitations including social desirability and recall biases[62]. Using objective adherence data instead can enhance clinicians' ability to identify risk of unsuppressed viral load, allowing for more rapid intensification of adherence support, treatment switching, and better triaging of whether resistance testing is needed[63].

Pharmacy refill monitoring

Pharmacy refill monitoring has been shown to be one of the best methods to predict virologic failure and identify patients in need of viral load monitoring[64]. However, nonadherence can only be detected after a missed refill and refilling medication supply does not confirm actual pill dosing[5,65]. Pharmacy refill monitoring represents a low-cost,

easy-to-use tool for prediction of virologic failure[66] that leverages existing clinic infrastructure, but (to our knowledge) there have been no studies evaluating the role of pharmacy refill monitoring coupled with other adherence interventions in sub-Saharan Africa.

Electronic adherence monitoring

Electronic adherence monitoring devices are "smart" pill containers that record a date-and-time stamp with each opening of the container to use as a proxy for taking medication, which is then transmitted to a database via cellular networks[67]. Strengths of electronic adherence monitors include their objectivity and day-to-day records, which allow for analysis of adherence patterns[68]. However, electronic adherence monitors have several potential weaknesses: they are expensive, cannot measure actual drug ingestion[67], and may be susceptible to technical challenges as they rely on battery life and network availability to record and send data[69]. Electronic adherence monitors such as the Wisepill™ (used in SUSTAIN) that track adherence in real time have been shown to be acceptable and feasible in settings including China and Uganda[10,70–74]. Studies conducted in urban South Africa have shown some promising results: a 2015 study in Cape Town found that use of electronic adherence monitoring with text reminders reduced frequency of treatment interruptions[6], and a 2016 study in Johannesburg found use of electronic adherence monitoring had a modest effect on retention and viral suppression (however, the study period was brief – only 6 months)[75]. South African PHIV have also indicated that they found the Wisepill™ devices "acceptable and useful," with no concerns about

stigma, confidentiality or remote monitoring[76].

Phone call notification for elevated viral load

Immediate patient outreach when unsuppressed virus is detected is not done in most low-resource settings, but is feasible and well-liked by patients[77]. A 2017 review found that supporter plus telephone interventions performed better than all interventions except cognitive behavioral therapy[11], but there is limited evidence of the impact of phone call interventions in sub-Saharan Africa (most phone-based interventions have focused on text reminders). However, one study in Cameroon found that compared to the control group receiving no reminders, improvement in attending ART appointments was highest among those receiving a reminder text and phone call; phone calls alone in this study also increased attendance five-fold[78]. Outside of sub-Saharan Africa, phone call reminders have been demonstrated to be effective in improving treatment and adherence outcomes[79,80].

Adherence and retention support strategies

Enhanced counselling using motivational interviewing

Motivation to change is a key component of the behavior change process[81]. One approach to change motivation and subsequent behavior is motivational interviewing, introduced by William Miller in 1983[82]. Motivational interviewing aims to explore and resolve ambivalence that people have about health behavior in favor of change and encourages people to say why and how they might change. Motivational interviewing consists of four

overlapping processes: engaging in a working relationship, focusing on a problem to change, evoking the person's desire to change, and planning change[82].

The use of motivational interviewing in HIV prevention and ART adherence counseling has been widely studied, with evidence that it can be successful in many settings, particularly to improve adherence[83–87]. One review of RCTs using motivational interviewing found that three of five studies showed significant increases in adherence rates, two showed significant decreases in viral load, and one showed an increase in CD4 cell count as a result of participating in the intervention[88]. A number of studies evaluating use of motivational interviewing have shown positive results, including significantly higher adherence to ART[83,85,89], improvements in self-efficacy and HIV knowledge[83], and reductions in sexual risk behavior[84]. Evidence from urban South Africa is limited, but one 2014 study in KwaZulu-Natal found that participants receiving a counseling intervention using motivational interviewing reported significantly greater reduction of HIV risk behaviors compared to those receiving the standard of care[90].

Check-in texts

Multiple systematic reviews have shown text messaging is effective in increasing adherence to ART[92–94]. Short-messaging service (SMS)-based adherence interventions have also been shown to be cost-effective by World Health Organization standards, with an incremental cost-effectiveness ratio (ICER) of $1,037 per quality-adjusted life year. In sub-Saharan Africa, a number of studies using check-in texts have shown positive outcomes: higher adherence to ART[70,92,95–97], increased CD4 count[95], increased viral

suppression[96], and reduced numbers of treatment interruptions[92]. To our knowledge, only one study to date has been conducted in urban South Africa evaluating the use of text message reminders; as mentioned previously this 2015 study in Cape Town found that use of electronic adherence monitoring with text reminders reduced frequency of treatment interruptions[6].

E. SUSTAIN Study Methodology

SUSTAIN enrolled 512 individuals beginning ART in three community clinics in two districts in Cape Town: Klipfontein and Mitchell's Plain. The study assessed five adherence interventions in 16 packages to identify those packages which optimize ART outcomes over a 24-month timeframe. The project also collected implementation-related data, described elsewhere[99]. Cost-effectiveness after 24 months of intervention implementation will be modeled to help identify the optimal package for integration into City of Cape Town clinics following study completion in 2024.

Eligibility criteria

Adults ≥18 years of age and adolescents aged 16–17 years presenting to the clinic for initiation of ART were recruited to participate in SUSTAIN. Study participants must have been willing and able to sign informed consent or, in the case of minors, informed assent with parents willing to sign informed consent. Participants were required to have a working cellphone and be willing to receive study related text messages. They also had to be willing and able to comply with study procedures, including using an electronic

adherence monitor and providing current contact information.

Randomization and intervention assignment

A total of 512 participants (roughly 170 per clinic) were enrolled beginning in March 2022. Participants were randomly assigned to one of 16 study conditions using a permutation allowing for the study conditions to include an equal number of participants (16 * 32 = 512). Table 2.2 below shows each of the experimental conditions where "X" indicates an intervention component is "on" and "O" indicates a component is "off." Four of the five intervention components (M1, M2, M3 & S1) could either be switched "on" (the component was applied) or switched "off" (the component was not applied). The counselling component (S2) could either be basic (standard of care) or enhanced (using motivational interviewing)[99].

The randomization process was run in Stata v.14 using *runiform* and *rank* functions and was concealed from all study staff involved in recruitment and enrollment. Participants were assigned to a study condition using the REDCap electronic database[99].

Table 2.2. Intervention Components and Experimental Conditions in SUSTAIN

	Experimental Conditions															
Intervention Components	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**
Standard of Care: After a viral load test shows unsuppressed virus, patient is alerted at next clinic visit and given a counselling session	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Viral load monitoring: Outreach to patient due to unsuppressed viral load test result	O	O	O	O	O	O	O	O	X	X	X	X	X	X	X	X
Pharmacy refill monitoring: Pharmacy refill monitoring + patient outreach	O	O	O	O	X	X	X	X	O	O	O	O	X	X	X	X
Electronic adherence monitoring: Electronic adherence monitoring + patient outreach	O	O	X	X	O	O	X	X	O	O	X	X	O	O	X	X
Check-in texts: Weekly check-in text messages	O	X	O	X	O	X	O	X	O	X	O	X	O	X	O	X
Counselling: Individual counselling, either basic (B) or enhanced using motivational interviewing (E)	E	B	B	E	B	E	E	B	B	E	E	B	E	B	B	E

Outcomes

This dissertation focused on adherence to ART throughout 12 months of participation as measured by electronic adherence monitors. We measured those who achieved ≥80%, ≥90% and ≥95% of adherence to medication over the first year.

Statistical analysis

Analysis for the SUSTAIN trial was conducted separately from the proposed dissertation research, but outcomes data generated from this analysis were utilised to conduct cost-effectiveness analysis for the dissertation (described in the following chapter). The SUSTAIN trial will adopt an intention to treat approach to estimate treatment effects. For missing adherence data, the most recent month's adherence will be used to estimate single-month adherence; for cumulative calculations, available data over the period will be used. Logistic regression will be used to estimate effects of components on adherence measured as a binary outcome. Linear or Poisson regression will be used to estimate effects of components on outcomes measured as a continuous variable (e.g., mean adherence).

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Ethical approval

Ethical approvals were obtained from Boston University, the University of Cape Town, and the City of Cape Town.

CHAPTER THREE: METHODOLOGY

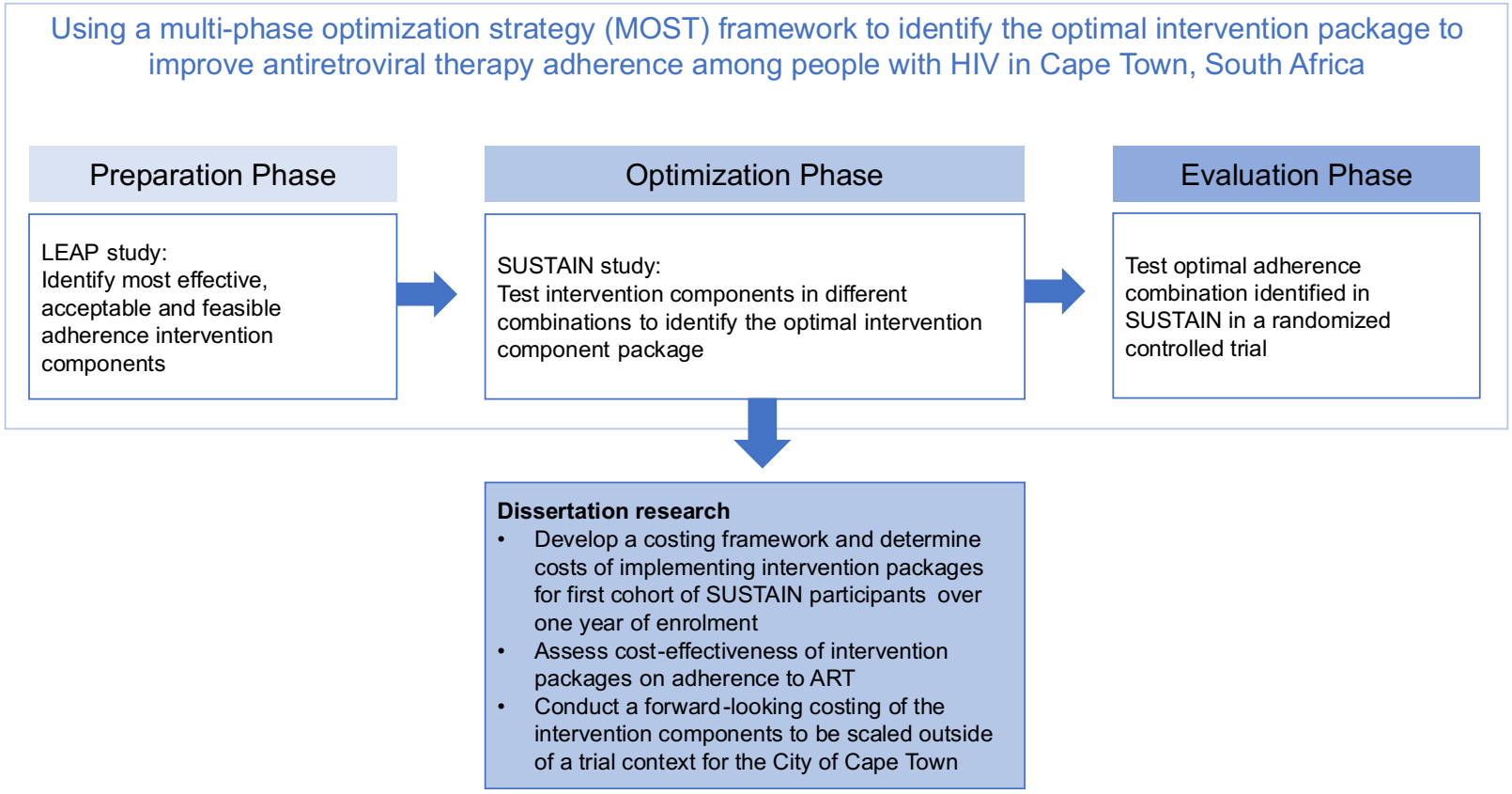
A. Chapter Overview

This chapter contains detailed information on the design and methodology employed to answer the research questions of the dissertation. The chapter contains an overview of the research question and study aims, followed by an in-depth discussion of each aim and the corresponding data collection methods and analysis plan. Finally, limitations of the methodology are discussed.

B. Research Questions

As described in Chapter Two, this dissertation is associated with the parent SUSTAIN study, which uses a MOST framework to identify optimal intervention packages to improve ART adherence among PHIV in Cape Town, South Africa (Figure 3.1). This dissertation analyzed results from a cohort of SUSTAIN participants after twelve months of participation and developed a costing framework to be used for the full study costing.

Figure 3.1. MOST Framework: SUSTAIN Study and Dissertation Research



The primary research questions of this dissertation were:

1. *What are the costs (including start-up and steady state) from the payer perspective to deliver packaged interventions to improve ART adherence for the first 50% of SUSTAIN participants after one year of enrollment?*
2. *What is the cost-effectiveness of interventions to improve ART adherence tested among this group of participants after one year of enrollment?*
    a. *What intervention component is most cost-effective for achieving ≥80% adherence to treatment?*
    b. *What intervention component is most cost-effective for achieving ≥90% adherence to treatment?*
    c. *What intervention component is most cost-effective for achieving ≥95% adherence to treatment?*

The secondary research question of this dissertation were:

3. *What are the estimated costs of implementing SUSTAIN interventions in a real-world setting?*
    a. How can current costs be optimized for delivery in a clinic setting?

C. Study Cohort Details

Demographic details of the cohort of participants studied in this dissertation are shown in tables 3.1a (for Experimental Condition groups 1–8) and 3.1b (for Experimental Condition groups 9–16). In total, n=262 participants were included, with experimental condition groups ranging between n=13–20 individuals. 70.2% of participants in the

cohort were female, with a mean age of 30 years old (SD=8). More than three-quarters (77.5%) of participants had completed between Grades 8–12 of schooling, and more than three-quarters (77.5%) were single. 11.5% of women enrolled were pregnant (n=21). The mean age at which participants had first tested HIV-positive was 29 years old (SD=8). 77.1% of participants were ART-naïve and the mean most recent CD4 count was 337 cells/mm^3 (SD=212). Chi-Square and Kruskal-Wallis tests were run to identify significant differences between percentages and means per each variable across groups. No significant differences were identified between groups except for age (p=0.0488). T-tests were run to identify which groups were statistically significant by age: Groups 2 and 12 were significantly younger (p=.0362 and p=.005, respectively), and Group 8 was significantly older (p<.001).

Table 3.1a. Study Cohort Demographics, Experimental Conditions 1–8

		Experimental Condition							
	Total N	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
	262	20	19	19	13	15	15	17	13
Gender									
Male	78 (29.8%)	7 (35.0%)	2 (10.5%)	8 (42.1%)	3 (23.1%)	5 (33.3%)	3 (20.0%)	3 (17.6%)	5 (38.5%)
Female	184 (70.2%)	13 (65.0%)	17 (89.5%)	11 (57.9%)	10 (76.9%)	10 (66.7%)	12 (80.0%)	14 (82.4%)	8 (61.5%)
Age Mean (SD)	30 (8)	30 (9)	26 (8)	29 (6)	32 (6)	30 (11)	28 (7)	29 (7)	38 (10)
Age First Tested HIV+ Mean (SD)	29 (8)	30 (9)	26 (8)	29 (6)	32 (6)	30 (11)	28 (7)	29 (7)	38 (10)
Education									
Grade 1–7	10 (3.8%)	0 (0.0%)	1 (5.3%)	2 (10.5%)	0 (0.0%)	3 (20.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Grade 8–12	203 (77.5%)	17 (85.0%)	16 (84.2%)	12 (63.2%)	10 (76.9%)	10 (66.7%)	12 (80.0%)	11 (64.7%)	12 (92.3%)
Beyond Grade 12	49 (18.7%)	3 (15.0%)	2 (10.5%)	5 (26.3%)	3 (23.1%)	2 (13.3%)	3 (20.0%)	6 (35.3%)	1 (7.7%)
Marital status									
Single	202 (77.1%)	13 (65.0%)	14 (73.7%)	11 (57.9%)	9 (69.2%)	12 (80.0%)	13 (86.7%)	16 (94.1%)	11 (84.6%)
Married	26 (9.9%)	1 (5.0%)	2 (10.5%)	3 (15.8%)	2 (15.4%)	1 (6.7%)	1 (6.7%)	1 (5.9%)	1 (7.7%)
Divorced/Separated	2 (0.8%)	0 (0.0%)	1 (5.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Living together	32 (12.2%)	6 (30.0%)	2 (10.5%)	5 (26.3%)	2 (15.4%)	2 (13.3%)	1 (6.7%)	0 (0.0%)	1 (7.7%)
Currently pregnant (base=women only)									
No	162 (88.5%)	11 (84.6%)	14 (82.4%)	7 (63.6%)	8 (80.0%)	7 (70.0%)	12 (100.0%)	14 (100.0%)	8 (100.0%)
Yes	21 (11.5%)	2 (15.4%)	3 (17.6%)	4 (36.4%)	2 (20.0%)	3 (30.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Most recent CD4 count Mean (SD)	337 (212)	306 (195)	310 (163)	282 (200)	318 (208)	317 (213)	447 (195)	350 (188)	290 (168)
Taken ART Before									
No	202 (77.1%)	19 (95.0%)	13 (68.4%)	12 (63.2%)	10 (76.9%)	10 (66.7%)	13 (86.7%)	14 (82.4%)	7 (53.8%)
Yes	60 (22.9%)	1 (5.0%)	6 (31.6%)	7 (36.8%)	3 (23.1%)	5 (33.3%)	2 (13.3%)	3 (17.6%)	6 (46.2%)

Table 3.1b. Study Cohort Demographics, Experimental Conditions 9–16

	Experimental Condition								
	9	**10**	**11**	**12**	**13**	**14**	**15**	**16**	
	17	18	14	14	17	17	15	19	p-value
Gender									
Male	5 (29.4%)	4 (22.2%)	6 (42.9%)	4 (28.6%)	7 (41.2%)	6 (35.3%)	6 (40.0%)	4 (21.1%)	0.6696
Female	12 (70.6%)	14 (77.8%)	8 (57.1%)	10 (71.4%)	10 (58.8%)	11 (64.7%)	9 (60.0%)	15 (78.9%)	
Age Mean (SD)	29 (7)	33 (9)	28 (8)	24 (5)	30 (11)	29 (8)	28 (8)	30 (9)	0.0488
Age First Tested HIV+ Mean (SD)	29 (7)	32 (8)	28 (8)	24 (5)	30 (11)	29 (8)	28 (8)	29 (9)	0.0668
Education									
Grade 1–7	0 (0.0%)	2 (11.1%)	0 (0.0%)	0 (0.0%)	1 (5.9%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	0.1234
Grade 8–12	14 (82.4%)	15 (83.3%)	9 (64.3%)	13 (92.9%)	10 (58.8%)	12 (70.6%)	13 (86.7%)	17 (89.5%)	
Beyond G12	3 (17.6%)	1 (5.6%)	5 (35.7%)	1 (7.1%)	6 (35.3%)	4 (23.5%)	2 (13.3%)	2 (10.5%)	
Marital status									
Single	14 (82.4%)	14 (77.8%)	12 (85.7%)	13 (92.9%)	12 (70.6%)	12 (70.6%)	11 (73.3%)	15 (78.9%)	0.7893
Married	2 (11.8%)	1 (5.6%)	1 (7.1%)	1 (7.1%)	3 (17.6%)	2 (11.8%)	3 (20.0%)	1 (5.3%)	
Divorced/Separated	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Living together	1 (5.9%)	3 (16.7%)	1 (7.1%)	0 (0.0%)	1 (5.9%)	3 (17.6%)	1 (6.7%)	3 (15.8%)	

Currently pregnant (base=women only)									
No	11 (91.7%)	12 (85.7%)	7 (87.5%)	10 (100.0%)	9 (90.0%)	9 (90.0%)	8 (88.9%)	15 (100.0%)	0.1895
Yes	1 (8.3%)	2 (14.3%)	1 (12.5%)	0 (0.0%)	1 (10.0%)	1 (10.0%)	1 (11.1%)	0 (0.00%)	
Most recent CD4 count Mean (SD)	306 (238)	279 (216)	376 (237)	404 (210)	345 (186)	267 (170)	371 (246)	444 (293)	0.3692
Taken ART Before									
No	14 (82.4%)	15 (83.3%)	12 (85.7%)	11 (78.6%)	13 (76.5%)	12 (70.6%)	10 (66.7%)	17 (89.5%)	0.3351
Yes	3 (17.6%)	3 (16.7%)	2 (14.3%)	3 (21.4%)	4 (23.5%)	5 (29.4%)	5 (33.3%)	2 (10.5%)	

D. Research Aim 1: Costing

Research aim and rationale

A detailed costing framework was needed to conduct analyses to determine which of the intervention candidate components and/or packages tested in SUSTAIN was most cost-effective at increasing adherence to ART. Aim 1 determined costs of implementing interventions in the SUSTAIN project's community clinic sites for the first 50% of the study population from the payer (health system) perspective. These costs were used to conduct the cost-effectiveness analysis that was the focus of Aim 2.

Kim et al.[100] describe four primary analytic perspectives by which one can conduct cost-effectiveness analyses. Table 3.2 below provides a description of each of these perspectives and associated strengths and weaknesses, which were considered in choosing the analytic perspective to use in this research. Ultimately, the payer perspective, in which only monetary costs incurred by a third-party healthcare payer are considered[100], was chosen for several reasons. First, the results are primarily intended to be used by the City of Cape Town, which would be the payer responsible for implementing the intervention(s) identified as most effective in the SUSTAIN trial; as such a payer perspective analysis would be most useful for them. Using the health sector perspective was considered for this dissertation, however, it was decided upon further discussion that it would pose undue burden to PHIV participating in SUSTAIN to capture these data in accurate manner, and that the information would not provide additional value to the City of Cape Town regarding intervention costs. The limited societal and societal perspectives were not considered for this dissertation due to concerns about

feasibility and scope. This is noted as a limitation to the methodology as it excludes patients' costs.

Table 3.2. CEA Perspectives

Perspective	Description	Strength(s)	Weakness(es)
Healthcare payer	• Includes only monetary costs incurred by a third-party healthcare payer[100]	• Easiest and most straightforward to estimate • Provides clear information to the healthcare system to understand impact of money spent	• Most limited of perspectives as it does not account for costs incurred by the patient and/or wider societal costs and benefit
Healthcare sector	• Accounts for all monetary costs of healthcare, regardless of who bears the cost, including patients' out-of-pocket costs[100]	• More holistic understanding of cost and effectiveness as patients are likely to incur costs related to receiving any healthcare services, so analysis is reflective of both costs to payer and patient	• Healthcare payer may not be interested in cost to the patient in making a decision regarding cost-effectiveness • May be difficult and time-intensive to capture out-of-pocket costs – requires additional burden to the patient
Limited societal	• Accounts for cost components beyond the healthcare sector perspective, including patient time, patient transportation, unpaid caregiver time, and productivity loss. Excludes spillover	• Captures an even broader view of the costs related to a treatment or intervention than healthcare sector perspective • Considers that it is not just the patient who is impacted by having a condition or treatment	• Harder to collect all costs as requires a wide view of an individual's network and the impact or burden of receiving a treatment • Challenging to draw parameters around what information should be captured

	impacts affecting sectors other than healthcare[100]	• May be particularly important to capture for conditions that require support of a caretaker or family member (e.g., acute illness where a patient is incapacitated)	
Societal	• Represents the overall public interest by including all resources that could be used for other purposes. Accounts for cost impacts affecting other sectors outside of healthcare (e.g., environment, education)[100]	• The broadest view of cost and effectiveness • Recognizes that health (or the absence of health) has wide ranging consequences on society and aims to capture them • Can be powerful to show the long-term and far-reaching effects of a health intervention on wider society	• Harder to collect all costs as requires a wide view of a society and the impact or burden of receiving a treatment • Challenging to draw parameters around what information should be captured

Data collection methods

Costs associated with staff time for project start-up and implementation activities were tracked, along with any direct costs using micro-costing, staff observation and staff discussions. Data were collected during five different time periods (Figure 3.2). The interventions costed for were viral load monitoring and outreach, pharmacy refill monitoring and outreach, electronic adherence monitoring and outreach, check-in texts, and enhanced adherence counselling. Intervention activities were conducted by study staff based at the central Gugulethu Research Office (medical officer(s), study coordinator, senior data clerk, data clerk, driver) and community research workers (CRWs) based in the three study clinics (Figure 3.3).

Micro-costing

Micro-costing is used to estimate economic costs (e.g., cost of time as opposed to financial costs), requiring collecting detailed information about the resources required to implement an intervention, and assigning economic unit costs to each component of resource use[101–103]. This dissertation employed a micro-costing approach to determine the cost of SUSTAIN interventions.

Structured costing forms (log sheets) were developed and distributed to SUSTAIN study staff. Study staff completed individual log sheets to record how much time was spent conducting activities related to intervention delivery (Figure 3.3).

Figure 3.2. Data Collection Activities and Timing

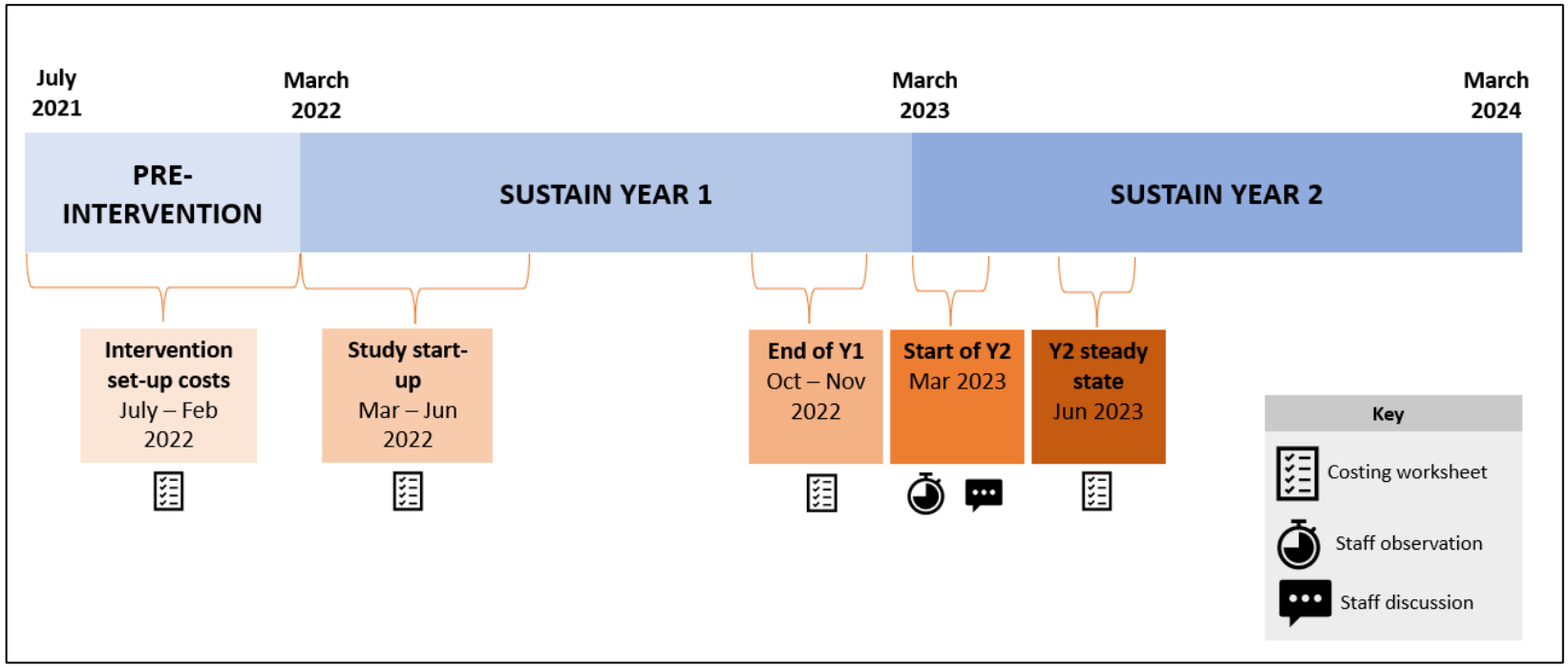
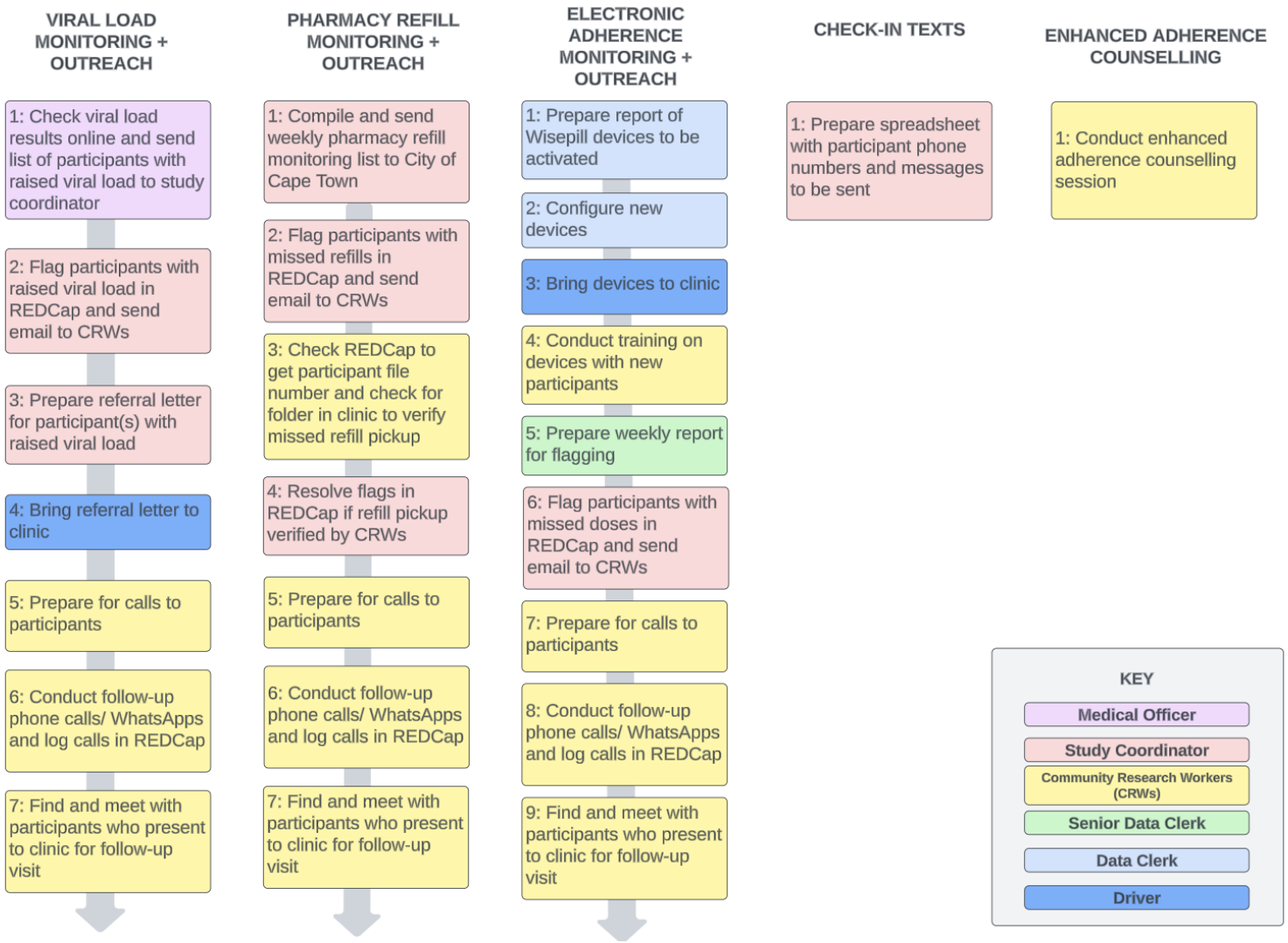


Figure 3.3. Intervention Activities and Staff Time Included in Micro-Costing and Observation



Costs collected included set-up or non-recurrent unit costs (e.g., training staff, purchasing materials and services needed to deliver interventions) and recurrent costs (e.g., staff salaries, fuel, airtime). Costs related to research activities were excluded (e.g., cost of REDCap database set up and maintenance, cost of computers or other materials used by study staff not directly related to intervention implementation, salaries for staff not delivering or directly supporting delivery of an intervention).

Costs were collected in South African Rand (ZAR). Nominal (total costs) were adjusted for inflation using average annual ZAR inflation rates[104] to determine real costs, and then discounted using a 3% annual rate. To present costs in real discounted United States dollars (USD), costs were also converted using average yearly conversion rates from ZAR to USD, adjusted for annual US inflation[105], and discounted using a 3% annual rate.

Staff observation

The recommendations of the panel on cost-effectiveness are to include costs of a health worker's time in the numerator of a CEA, and to evaluate this time by the wage rate in the labor force[106]. Due to the complexity of intervention trials and conducting the other research activities required in the SUSTAIN study, CRWs were employed by the study to deliver the intervention activities to participants in the study clinics rather than clinic staff. To be able to cost the study accurately, as well as understand exactly how much *additional* time would be added for clinical staff to incorporate the interventions into their practices, it was important to generate an estimate of average time needed to

conduct each step related to delivery. These estimates were used in the full costing framework based on number of patients assigned to each intervention and flagged for non-adherence each month.

To achieve this, staff observations were conducted using a modified time-motion study approach, a quantitative method for measuring time to complete a given set of tasks through independent and continuous observation and recording of staff activities and time spent[107]. Based on a review of time-motion studies of HIV service delivery in sub-Saharan Africa over the last ten years[108–112], we determined that four days of staff observation per clinic (or two days per CRW * two CRWs per clinic) would provide a robust sample consistent with the existing literature. Thus for Aim 1, we conducted an external-observer, continuous observation study approach[113] at the three study clinics for a period of four days each to observe the CRWs delivering intervention activities.

During the staff observation period, CRWs were watched throughout their typical workday. Activities were recorded and categorized based on the associated intervention component using a simple paper data collection tool which allowed the observer to record the start and stop time of each activity, and a description of the activity. Activities for which observation data needed to be collected are summarized in Table 3.3 (also shown in Figure 3.1). Data that were not collected or analyzed included those related to non-intervention activities (e.g., conducting interviews related to other study aims, taking a break, eating lunch, personal phone calls or socializing, or any other time in which CRWs were not preparing for or delivering an intervention).

Table 3.3. Intervention Activities Timed During Staff Observation

Intervention Component	Details
Viral Load Monitoring and Outreach	• Prepare for calls to participants • Conduct follow-up phone calls/ WhatsApps and log calls in REDCap • Find and meet with participants who present to clinic for follow-up visit
Pharmacy Refill Monitoring and Outreach	• Check REDCap to get participant file number and check for folder in clinic to verify missed refill pickup • Prepare for calls to participants • Conduct follow-up phone calls/WhatsApps and log calls in REDCap • Find and meet with participants who present to clinic for follow-up visit
Electronic Adherence Monitoring and Outreach	• Conduct training on devices with new participants • Prepare for calls to participants • Conduct follow-up phone calls/WhatsApps and log in REDCap • Find and meet with participants who present to clinic for follow-up visit
Enhanced Adherence Counselling	• Conduct enhanced adherence counselling sessions
Miscellaneous Intervention Prep Time	• Review participant records on tablet • Review call schedule for day/ following day • Make follow-up calls where the intervention component cannot be discerned

Whenever possible, the observer indicated which intervention component the activity was related to (e.g., a phone call was being made regarding viral load test result follow-up) and indicated how many participants had received the intervention activity (e.g., one person received enhanced adherence counselling, or three participants were called about electronic adherence monitoring). Where observers could not identify which intervention component an activity was related to, or if the activity was related to multiple intervention components (e.g., preparing a list of all patients to be followed up

with the following day) the activity was classified under "Miscellaneous Intervention Prep Time." The totals for each type of activity were summed and averaged, to generate an average amount of time per activity[106]. "Miscellaneous Intervention Prep Time" was averaged and applied to all four clinic-based interventions to ensure this preparation time was accounted for in the costing model.

Analysis

Data from the micro-costing and staff observation exercises were used to complete an intervention cost worksheet. Self-reported micro-costing data and observation data were combined to estimate the time required to complete each step associated with intervention delivery. Differences between time required during the beginning of intervention delivery and steady state were identified and accounted for in costing where possible. Time spent to deliver each intervention component per participant was calculated monthly as: (average time spent per activity) * (number of participants receiving each intervention). This formula was used to populate the costing framework so that the costing model was sensitive to changes in participant volume over time (e.g., as more participants were enrolled each month) and assignment to different intervention arms. The final costing model showed costs by study period (preparation, intervention) and was disaggregated by intervention component.

E. Research Aim 2: Cost-Effectiveness Analysis

Research aim and rationale

Assessing the cost-effectiveness of each intervention package on HIV care and treatment outcomes will enable City of Cape Town officials to determine which interventions are worth investment and adoption. Aim 2 assessed the cost-effectiveness of interventions on ART adherence at one year of participation for the first 50% of the study population. Although there are differing opinions regarding what constitutes optimal ART adherence, most experts use between 80 to 95% of prescribed doses[37–39]. Therefore, for the primary outcome of the cost-effectiveness analysis, we examined cost-effectiveness of each intervention component on achieving ≥80%, ≥90 and ≥95% adherence.

Data collection methods

The data used for cost estimates was described in Aim 1. Cost-effectiveness was determined for each intervention package using adherence as the primary outcome. Adherence data were analyzed for the first 50% of SUSTAIN study participants at month 12 of their study participation. Study staff had access to WisePill™ adherence data for all participants.

Analysis

Cost-effectiveness was estimated using the cost data from Aim 1 and patient outcome data from month 12 of study enrollment. The primary outcome of adherence was

measured on a binomial outcome at three different adherence categories: >80%, >90% and >95%.

Monitoring components and support components were compared to each other separately. Cost-effectiveness was estimated using the formula: incremental cost-effectiveness ratio (ICER) = (C1-CC)/(M1-MC), where C1 and CC = total cost per implementing an intervention and M1 and MC = adherence outcomes. In a traditional CEA, C1 and M1 would represent the intervention and CC and MC would represent the control condition. Since there was no control condition, the intervention components were compared in pairs after rank ordering the interventions by adherence outcomes (with the intervention with the best outcomes ranked highest). In analyzing the monitoring components, the highest ranked intervention was used for C1/M1, the second-ranked intervention was used for CC/MC. For the second set of analyses, the second-ranked intervention was used for C1/M1, and the third-ranked intervention was used for CC/MC. For the support components, the intervention with higher outcomes was used for C1/M1 and the second-ranked intervention was used for CC/MC.

Given the different sample sizes across intervention components, costs and adherence outcomes were standardized to a population of 1,000 prior to conducting the cost-effectiveness analysis. For each intervention component, cost per person was calculated and then multiplied by 1,000 to obtain the cost for a population of 1,000 individuals. Outcomes were also multiplied by 1,000 (e.g., 30% of people achieving 80% adherence * 1,000 = 300 people) to generate standardized numbers to use for outcome calculations (M1, MC).

Cost-effectiveness results were then plotted on graphs by ICER and adherence categories, in a style similar to a cost-effectiveness plane in which interventions are plotted according to cost and benefit to identify the most economically dominant (or most cost-effective) intervention components(s)[114,115]. Sensitivity analyses were also conducted to examine the impact of different cost inputs: lower-cost viral load monitoring using different staff, reduced cost of Wisepill™ data and hosting, and reduced cost of the SMS platform.

F. Research Aim 3: Future Costing

Research aim and rationale

It is critical to consider both the costs and costs relative to effects of new HIV support programs for decision-makers to determine if such programs will be feasible to implement in real-world settings[116–118]. The costing exercise in Aim 1 provided a clear depiction of resources and time required to set up and deliver the interventions within the context of a complex trial. Because a clinical trial is inherently more complicated than implementing a clinical program as standard practice, the costing framework developed in Aim 1 would not be relevant for immediate use by the City of Cape Town to inform budget planning and decision-making. Aim 3 of this dissertation was to develop a forward-looking costing framework that projected the cost of scale-up of interventions used in SUSTAIN to all City of Cape Town clinics. The resulting cost framework was designed for implementation in a real-world setting rather than a trial setting.

Data collection methods

The costing framework developed in Aim 1 was used as the basis for the scaled-up model. Costs gathered are described in Table 3.4, and parameters used to develop the framework are described in Table 3.5.

Table 3.4. Costs and Data Sources

Costs	Data Source(s)
Salaries	Salary estimates were found using publicly available data from job postings on the City of Cape Town website. A 6% annual increase was applied to salaries based on 2024 estimates[119].
Phones	Costs for a basic smartphone were used based on SUSTAIN program costs (ZAR 1899). A price reduction of 3.6% per year for phones was applied based on global trends of smartphone costs from 2010–2019[120].
Data for phones	Costs for data were based on SUSTAIN program costs collected for costing the SUSTAIN study. A 5% annual decrease was applied to account for trends the price of data falling over time[121].
Training fees	The training fee for counselling was used based on SUSTAIN program costs collected for costing SUSTAIN. A 6% annual increase was applied to account for the expected increase in salaries.
SMS system	Costs for the SMS system were based on SUSTAIN program costs collected for costing SUSTAIN. A 5% annual decrease was applied to account for trends in cheaper data over time[121].
Wisepill™ devices	A reduced cost estimate based on projections for price reduction in a mass production scenario[122].
Wisepill™ data and hosting	Costs for Wisepill™ data and hosting were based on SUSTAIN program costs. A 5% annual decrease was applied to account for trends in cheaper data over time[121].

Table 3.5. Costing Parameters and Assumptions

Parameters	Assumptions/Formulae
Time frame	Ten-year program, starting in 2024
Exchange rate	A five-year average was used based on historical fluctuation in exchange rates (from 2019–2024[123]) for a more conservative estimate (1 USD = ZAR 16.98) compared to the ten-year average (1USD = ZAR 15.34).
Inflation index	The five year-average (5.24%) and ten-year averages (5.2%) were compared to generate expected inflation rate based on historical inflation[104]. A rate of 5.24% was used.
Discount rate	A 3% discount rate was applied from program year one (2024) per best practice in economic evaluation.[124]
Number of clinics	The model assumed that there were 95 clinics in City of Cape Town, based on the City of Cape Town website.[125]
Number of people initiating ART per year (either newly or re-starting)	As the intervention package(s) will be offered to people initiating ART each year, an estimate was created across City of Cape Town clinics, using the following steps. • The City of Cape Town population estimate for 2023 was used as a starting point (4,890,280). • The estimated number of new HIV infections was calculated using an incidence rate of 0.35%[52] * 4,890,280 to generate an estimate of 17,116 new HIV infections in 2024. • The number of new ART initiations in 2024 was estimated by using the expected % of diagnosed PLHIV initiating ART: 61.4%[52] * 17,116 new infections = 10,509 new ART initiations. • Between 2010–2018, reduction in HIV incidence was 36% or an average 4.5% per year.[52] An estimate of 4.5% reduction in HIV incidence was applied each year after 2024 to reflect incidence should continue to drop over time, to create estimates of HIV incidence over the program.
Number of people flagged for follow-up	Estimates include the average percent flagged for follow-up on viral load monitoring, electronic adherence monitoring, and pharmacy refill monitoring captured during the SUSTAIN study. • Based on SUSTAIN year 1 data, it was estimated that 37% of patients would be flagged through electronic adherence monitoring each year; 14% of patients would be flagged through pharmacy refill monitoring, and 2% of patients would be flagged through viral load monitoring.

	• These estimates were then applied to the number of ART initiates each year to estimate how many patients would be flagged through each intervention monitoring component. • For example, in 2024, 10,509 ART initiations * 37% flagged on electronic adherence monitoring = 3,888 patients flagged on electronic adherence monitoring.

Time per role was also calculated to understand the time burden that implementing the scaled-up program would have upon staff if it were to be added to an existing clinic's operations. Assumptions for this calculation are shown in Table 3.6.

Table 3.6. Time Per Operational Role Assumptions

Assumptions	Notes
• 2 data clerks per clinic to implement the program	
• 2 counsellors per clinic to implement the program	
• Used an average number of patients per clinic to estimate time required	• Number of patients was calculated as: Number of new ART initiations / 95 clinics in City of Cape Town
• Time to conduct role based on estimates of how many patients would be flagged through each monitoring intervention	• Assume that 37% of patients are flagged on electronic adherence monitoring, 2% are flagged on viral load monitoring, 13% are flagged on pharmacy refill monitoring
• Anyone flagged via any monitoring intervention receives 3 enhanced counselling sessions per year	
• 7 hours in a working day	

Analysis

The forward-looking costing model was developed to include all interventions tested in SUSTAIN, although not all will ultimately be scaled. Future costs were

estimated using current ZAR, adjusted for expected inflation, and discounted using a 3% rate to provide discounted real costs (expected present value). Nominal costs (total cost in current ZAR, including expected inflation) were also shown. To provide comparisons in USD, an exchange rate of 16.98 was applied (using the five year-average between 2024 and 2019[123]). Preliminary future costing outcomes were presented to City of Cape Town stakeholders at a dissemination meeting at the end of study year three (April 2024).

A cost-effectiveness analysis was also conducted using the future program costs at years 1 and 10, using adherence outcomes from the SUSTAIN trial. As with the cost-effectiveness analysis of SUSTAIN results, monitoring components and support components were compared to each other separately. Cost-effectiveness was estimated using the formula: incremental cost-effectiveness ratio (ICER) = (C1-CC)/(M1-MC), where C1 and CC = total cost per implementing an intervention and M1 and MC = adherence outcomes. As described previously, the intervention components were compared in pairs after rank ordering the interventions by adherence outcomes (with the intervention with the best outcomes being ranked highest).

G. Limitations

There are several limitations to the methods in this dissertation which should be addressed. First, while this study sought to identify feasible and effective interventions that could be scaled up in City of Cape Town clinics, it was not feasible to test these interventions involving clinic staff. As a result, SUSTAIN used study staff to implement all intervention components. All data collected therefore approximate how these

interventions would be implemented, and do not measure the true feasibility of implementing each component by clinic staff. Secondly, SUSTAIN intervention activities were conducted in the context of a trial which may have incurred time and resource costs that would not be required should the interventions be adopted in a real-world setting. To counter this limitation, we included the Aim 3 forward-looking costing exercise to attempt to approximate the costs of implementing these intervention packages in a real-world setting. Third, micro-costing data could not be collected daily throughout implementation given the additional workload posed to study staff, so some estimation was needed. However, to counter this limitation, we collected staff observation data to refine estimates of time required to implement each intervention component based on in-person observation using a robust sample of four days of observation per clinic. Another limitation is that the limited societal and societal perspectives were not considered for this dissertation due to concerns about feasibility and scope, which excludes patients' costs and therefore does not provide a complete understanding of costs from the patient perspective. Finally, while the clinics and clinic population represented in our sample are generalizable to Cape Town and Western Cape, results should be interpreted with caution regarding other provinces in South Africa which are less resourced.

CHAPTER FOUR: COSTING

Title: Preliminary Cost Evaluation of Interventions to Improve HIV Treatment Adherence in the SUSTAIN Trial in Cape Town, South Africa

Suggested running head: Preliminary Cost Analysis of SUSTAIN Study to Improve ART Adherence

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Code availability: not applicable.

Authors' contributions: CO, LLS, NH, AG, and JH conceptualized the research. RLW led data collection with support from LJ and TM. RLW led data analysis and interpretation. RLW led writing of the manuscript, and all authors contributed edits and feedback.

Abstract

Identifying strategies to improve adherence to antiretroviral therapy among people living with HIV in South Africa is critical to achieving epidemic control. The SUSTAIN trial aimed to identify the most cost-effective intervention package for achieving viral suppression and treatment adherence from a set of evidence-based strategies for monitoring (pharmacy refill monitoring, electronic adherence monitoring, viral load monitoring) and supporting (check-in texts, enhanced adherence counselling) patients. A cost analysis of implementing SUSTAIN interventions for the first cohort of participants enrolled during study year one was conducted (March 2022 – February 2023, n=262). All direct costs, including staff time for project start-up, implementation, and sustainment activities, were tracked using micro-costing and staff observation as well as discussions with staff during site visits. The costs for delivering each monitoring component for one person-year of participation were $11.63 for pharmacy refill monitoring, $25.25 for viral load monitoring, and $162.08 for electronic adherence monitoring. The costs for delivering each support element for one person-year of participation were $15.75 for enhanced adherence counselling and $42.21 for check-in texts. These data will be used to conduct a subsequent cost-effectiveness analysis and forward-looking costing model to bring the cost-effective intervention package(s) to scale across the City of Cape Town.

A. Introduction

South Africa has the largest population of people with HIV (PHIV) globally (approximately 8.2 million) and the largest antiretroviral therapy (ART) program in the world[1,2]. In South Africa, lifelong adherence to ART and retention in care remain major challenges. Adherence ranges from 40%–75%[3,6,36], far below what experts believe is required for successful treatment (at least 80% doses taken)[37–39]. Cape Town is the largest metropolitan district in the Western Cape and one of the five largest metro areas in South Africa. Around 38% of South Africa's total population and 36% of all PHIV live in one of these metropolitan areas[52]. Initiatives such as UNAIDS' Fast-Track cities have highlighted the need for increased focus on HIV testing and treatment programs in metropolitan centers given the rapid urbanization occurring in many African countries[126].

Patients who miss doses early in treatment exhibit poor outcomes and are disproportionately lost to care[46–48]. The Supporting Sustained HIV Treatment Adherence after Initiation (SUSTAIN) study is part of an ongoing partnership with the City of Cape Town to identify and adopt optimal evidence-based adherence strategies for newly diagnosed PHIV. SUSTAIN was conducted as part of the "optimization" phase of a multi-phase optimization strategy (MOST) approach for testing multi-component interventions. SUSTAIN tests the most preferred possible additional or alternative strategies for outreach and adherence support identified in a prior pilot study[61] (the "preparation" phase of MOST). These include three methods of rapidly identifying and reaching out to nonadherent patients: (1) immediate call to the patient after a standard viral load test showing elevated virus, (2) patient pharmacy refill monitoring with a call

to the patient after a missed refill, and (3) real-time electronic adherence monitoring with a call to the patient if doses are missed. Two adherence support strategies were also included: weekly check-in texts and enhanced adherence counselling using motivational interviewing. If an optimal intervention is ultimately identified through the SUSTAIN package, a final "evaluation" phase may follow to test the intervention/intervention package in a randomized controlled trial.

In addition to identifying which intervention package(s) were most impactful in supporting PHIV to achieving viral suppression and adherence to ART, a detailed costing assessment is needed to determine which of the intervention candidate components and/or packages is most cost-effective. This is of critical importance to ensure feasibility and scalability as the cost of the national public-sector ART program, which has risen steadily since its inception in 2004, is one of the major challenges confronting the South African government[127]. While a full costing and cost-assessment analysis will be conducted following completion of the full two-year SUSTAIN trial, this preliminary study provides an interim costing analysis for the first 50% of the study population from the payer (health system) perspective, in which monetary costs incurred by a third-party healthcare payer are considered[100].

B. Methods

Study summary

Starting in March 2022, SUSTAIN will enroll 512 adults ≥18 years of age and adolescents aged 16–17 years who presented for ART initiation over a two-year period at three community clinics in two districts in Cape Town: Klipfontein and Mitchells Plain. The SUSTAIN study will assess five adherence interventions in 16 packages to identify those which optimize ART outcomes over a 24-month timeframe. Table 4.1 shows each of the experimental conditions where "X" indicates an intervention component is "on" and "O" indicates a component is "off." Three monitoring components (viral load monitoring, pharmacy refill monitoring and electronic adherence monitoring) are used to track adherence. When a participant is "flagged" or identified as being non-adherent through one of the monitoring methods (e.g., elevated viral load test result, missed prescription refill pickup, or electronic adherence monitoring captures ≥4 doses or any three consecutive doses in a two-week period), participants will be contacted by study staff. Those receiving check-in texts will receive them weekly regardless of adherence, and participants will receive either basic or enhanced adherence counselling when they present to the clinic based on their experimental condition.

Table 4.1. Intervention Components and Experimental Conditions in SUSTAIN

	Experimental Conditions															
Intervention Components	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**
Standard of Care: After a viral load test shows unsuppressed virus, patient is alerted at next clinic and given a counselling session	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Viral load monitoring: Outreach to patient due to unsuppressed viral load test result	O	O	O	O	O	O	O	O	X	X	X	X	X	X	X	X
Pharmacy refill monitoring: Pharmacy refill monitoring + patient outreach	O	O	O	O	X	X	X	X	O	O	O	O	X	X	X	X
Electronic adherence monitoring: Electronic adherence monitoring + patient outreach	O	O	X	X	O	O	X	X	O	O	X	X	O	O	X	X
Check-in texts: Weekly check-in text messages	O	X	O	X	O	X	O	X	O	X	O	X	O	X	O	X
Counselling: Individual counselling, either basic (B) or enhanced using motivational interviewing (E)	E	B	B	E	B	E	E	B	B	E	E	B	E	B	B	E

Viral suppression after 24 months is the primary trial outcome; secondary outcomes include viral suppression at Month 12, changes in viral load, adherence, and time to nonadherence detection. Cost-effectiveness after 24 months of intervention implementation will be modelled to help identify the optimal package for integration into City of Cape Town clinics. Additional details of the study and planned analyses have been published[99].

Ethical approvals for this research were obtained from Boston University, the University of Cape Town, and the City of Cape Town.

Data collection methods

Costs for delivering the intervention packages to the first half of the SUSTAIN participant cohort were examined in this one-year analysis (those enrolled during between March 1, 2022 – February 28, 2023, n=262). Costs associated with staff time for project start-up, implementation, and sustainment activities were tracked, along with all direct costs, using micro-costing methodology and staff observation as well as discussions with staff during site visits.

Micro-costing

Micro-costing is used to estimate the economic costs of an intervention (as opposed to financial costs), which involves collecting detailed information about the resources required to implement an intervention, and assigning economic unit costs to each

component of resource use[101–103]. For the present study, structured costing forms (log sheets) were developed and distributed to SUSTAIN study staff to collect data during multiple time periods: pre-study start to collect intervention set-up costs (July 2021 – February 2022), the first four months of study start to capture start-up time and costs (March – June 2022), toward the end of study year one (October – November 2022) and in early year two (June 2023) to capture steady state costs. Methods used for estimating unit costs are shown in Table 4.2.

Table 4.2. Methods for Estimating Unit Costs

Resource	Data sources	Methods for estimating costs
Staff time for intervention-specific activities	Time log completed by SUSTAIN staff Staff observation Discussion with staff	SUSTAIN staff time was defined as any time spent preparing to conduct or conducting one of the interventions. We multiplied the estimated time spent on each SUSTAIN-specific service by total labor cost per hour for each staff member to calculate the unit cost per hour. 1) <u>Time spent during prep period:</u> Time spent setting up SUSTAIN interventions was collected from July–February 2021 using log sheets completed by study staff. Staff were asked to indicate which intervention the activity was related to; activities related to general set-up (e.g., communication with the City of Cape Town) were split across interventions. Some assumptions were made when exact time was not recorded but the activity conducted was: a. 5 minutes to send one e-mail b. 1 minute to send one WhatsApp or text message 2) <u>Total labor cost per working hour:</u> For each staff member, monthly costs were divided by total working hours per month to calculate a total hourly cost for each cadre. As the analysis covers multiple years, salaries were provided for intervention Year 1

		and adjusted for cost-of-living increases in Year 2 using a 7% increase provided through salary records. Cost per working hour also included staff attending Basic Counselling and Life Steps training during the preparation period.
Training	Expense reports	Costs for training (excluding study staff labor cost) were identified using expense reports, and included printing, catering and training fees.
Supplies	Expense reports	Costs for supplies were identified using expense reports and allocated to the corresponding intervention where possible. Costs included: 1) Prep period a. Wisepill™ device refurbishment for those assigned to an electronic adherence monitoring component: this cost was allocated to the electronic adherence monitoring intervention and was calculated as a variable cost (e.g., cost per device) i. Electronic adherence monitoring costs for research purposes only were excluded from this analysis 2) Intervention a. Hosting and data for Wisepill™ devices for those assigned to an electronic adherence monitoring component: this cost was allocated to the electronic adherence monitoring intervention and was calculated as a variable cost (e.g., cost per device per month) i. Electronic adherence monitoring costs for research purposes only were excluded from this analysis b. Phones and airtime across all monitoring interventions c. SMS platform device monthly messaging

Costs collected included set-up or fixed unit costs (e.g., training, purchasing materials and services needed to deliver interventions) and recurrent costs (e.g., personnel salaries, airtime, costs for delivering interventions such as SMS platform subscriptions

and Wisepill™ device hosting). Costs related to research activities were excluded (e.g., cost of REDCap database set up and maintenance, cost of computers or other materials used by study staff that were not directly related to intervention implementation, salaries for staff who are were delivering or directly supporting delivery of an intervention, and data collection for other SUSTAIN study elements).

Staff observation

One of the recommendations of the panel on cost-effectiveness is to include costs of a health worker's time in the numerator of a CEA, and to evaluate this time by the wage rate in the labor force[106]. Due to the complexity of intervention trials and conducting the other research activities required as part of the SUSTAIN study, Community Research Workers (CRW) rather than clinic staff were employed to deliver the intervention activities to participants in study clinics. To be able to cost the study accurately, as well as understand exactly how much additional time would be added to clinic staff's days to incorporate these interventions into their workload, we aimed to generate an estimate of average time to conduct each step related to delivery of each intervention. These estimates were then used in the full costing framework based on the number of patients assigned to each intervention and flagged for non-adherence (which would then trigger follow-up activities) each month.

To achieve this, staff observations were conducted using a modified time-motion study approach to measure the time to complete a given set of tasks through independent and continuous observation and recording activities[107]. Based on a review of time-motion

studies of HIV service delivery in sub-Saharan Africa over the last ten years[108–112], we determined that four days of staff observation per clinic (or two days per CRW * two CRW per clinic) would provide a robust sample in line with the existing literature. Thus, we aimed to conduct an external-observer, continuous observation study[113] at the three study clinics for a period of four days each to observe the CRW delivering intervention activities. CRW activities were recorded and categorized based on the associated intervention component using a simple paper data collection tool which allowed the observer to record the start and stop time of each activity, along with a description of the activity. Data not recorded were related to non-intervention activities (e.g., conducting interviews related to other study aims, taking a break, eating lunch, personal phone calls or socializing, or any other time in which CRWs are not preparing for or delivering an intervention).

Whenever possible, observers were instructed to indicate which intervention component was associated with the activity (e.g., a phone call was being made regarding viral load monitoring follow-up) and indicate how many participants received the intervention activity (e.g., one person received enhanced adherence counselling, or three participants were called about being flagged on Wisepill™). Where observers could not identify which intervention component was aligned with a given activity, or if the activity was related to multiple intervention components (e.g., CRWs preparing a list of all patients to be called the following day) the activity was classified under “Miscellaneous Intervention Prep Time.”

Average time spent on each activity per participant was calculated as follows: first, average time spent on intervention component over the observation period was determined, and then multiplied by 21 (average number of working days in a month) to create average time spent per month. The monthly figure was then divided by the number of participants who would have received that intervention step in a month (e.g., number of participants flagged on Wisepill in March 2023) to generate an average time per participant (Appendix 3).

Cost analyses

The total times for each type of activity conducted related to intervention delivery were summed and averaged, for an average amount of time required per activity[106]. "Miscellaneous Intervention Prep Time" was averaged and applied to all monitoring interventions to ensure this preparation time was also accounted for in the costing model. Data from the micro-costing and staff observation exercises were used to complete an intervention cost worksheet to estimate the time required to complete each step associated with set-up and intervention delivery. Differences between time required during the beginning of intervention delivery and steady state were identified and accounted for in the costing model where possible. Time spent to deliver each intervention component per participant was calculated monthly by multiplying (average time spent per activity) * (number of participants receiving each intervention). This was used to populate the costing framework so that the costing model was sensitive to changes in participant volume over time (e.g., as more participants are enrolled each month, or differing

numbers of participants were flagged for monitoring per month) and assignment to different intervention arms.

All costs were collected in South African Rand (ZAR) and converted to derive totals in United States Dollars (USD) using the average exchange rate per period[123]: prep period (July–February 2021, 15.11 ZAR/1 USD), implementation year one (March 2022–February 2023, 16.72 ZAR/1 USD), and implementation year two (March 2023–February 2024, 18.63 ZAR/1 USD). Current USD costs were then adjusted for inflation using the annual inflation rate[105] with 2021 as the index year to derive costs in real (constant) USD; inflation rates were 8% in 2022, 4.1% in 2023, and 3.2% in 2024. Finally, costs were discounted using a 3% discount per year after 2021 per best practice in economic evaluation[124].

C. Results

Staff observation

Eleven days of observation were completed; one planned day of observation could not be completed in Clinic B as the clinic was closed due to an all-day staff meeting, and for two days of observation no intervention activities took place (only research activities were conducted, such as enrolling participants or conducting interviews). Appendix 1 provides a detailed staff observation log. A total of 306 minutes of activity were logged (5.1 hours). 15 unique types of activities were logged across 28 instances of activities; the most common was conducting follow-up calls and logging notes (12/28, 43% of activity logged). Half of recorded observations were classified as “cross-intervention” because

they covered multiple intervention types (e.g., 10 minutes of follow-up calls to participants receiving multiple interventions). For CRWs, the most time-intensive intervention component was enhanced adherence counselling (67.5 minutes per participant receiving counselling), followed by electronic adherence monitoring and outreach (46.65 minutes per participant per month). Viral load monitoring and outreach was the least time-intensive intervention for CRWs to implement (8.9 minutes per participant, per month).

Micro-costing

Appendix 2 shows the results of personnel time required for the set-up period. Table 4.3 shows the steps to deliver each intervention component that were costed in the final model, along with the method of estimation and unit used for costing analyses. Time was converted to hours to enable calculation by hourly salary. In study year 1, the most time-intensive intervention was electronic adherence monitoring and outreach (1.73 hours per participant per month), but it was much less time-intensive in year 2 as no new participants were enrolled and time for Wisepill™ set-up and training was not required. The second most time-intensive intervention was viral load monitoring and outreach (1.25 hours per participant, per month) across both years 1 and 2. By far the least time-intensive intervention was check-in texts, which required only 0.05 hours (3 minutes) per participant, per month.

Table 4.3. Intervention Steps: Method of Estimation and Units Used in Costing

Staff Member	Intervention Delivery Step	Method of Estimation	Unit (per month)	Hours/ month Y1	Hours/ month Y2
	Pharmacy Refill Monitoring				
Senior Medical Officer/ Study Coordinator	Send pharmacy refill monitoring list to City of Cape Town data center	Time logging worksheet	Hours	0.17	0.25
Study Coordinator	Flag missed pick-ups in REDCap and send to Community Research Workers	Time logging worksheet	Hours per participant flagged	0.08	0.08
Community Research Worker	Check clinic folders to ensure missed medication pick-up	Staff observation	Hours per participant flagged	0.17	0.17
Study Coordinator	Remove flag in REDCap if prescription picked up	Discussion	Hours per participant flagged	0.17	0.17
Community Research Worker	Prep, conduct and log follow-up calls	Staff observation	Hours per participant flagged	0.09	0.09
Community Research Worker	Find and meet with participants who come for follow-up visit	Staff observation, discussion	Hours per 40% of participants flagged[1]	0.17	0.17
Community Research Worker	Miscellaneous prep time	Staff observation	Hours per participant flagged	0.09	0.09
Total hours per month (fixed)				***0.17***	***0.25***
Total hours per participant, per month				***0.77***	***0.77***
	Viral Load Monitoring				
Medical Officer	Check viral load results online and send those with raised viral load to Study Coordinator	Time logging worksheet	Hours per participant assigned to viral load monitoring	0.07	0.08
Study Coordinator	Flag participants with unsuppressed virus in REDCap and send to Community Research Workers	Time logging worksheet	Hours per participant flagged	0.08	0.08

Study Coordinator	Prepare referral letters for participants with elevated viral load	Time logging worksheet	Hours per participant flagged	0.25	0.25
Driver	Bring referral letters to clinic	Discussion	Hours per participant flagged	0.50	0.50
Community Research Worker	Prep, conduct and log follow-up calls	Staff observation	Hours per participant flagged	0.09	0.09
Community Research Worker	Find and meet with participants who come for follow-up visit	Staff observation, discussion	Hours per 40% of participant flagged	0.17	0.17
Community Research Worker	Miscellaneous prep time	Staff observation	Hours per participant flagged	0.09	0.09
Total hours per participant, per month				***1.25***	***1.26***
	Electronic Adherence Monitoring				
Data Clerk	Prepare list of Wisepill™ devices to be activated (Year 1 only)	Time logging worksheet	Hours per participant newly assigned to electronic adherence monitoring	0.06	0.00
Data Clerk	Configure Wisepill™ devices (Year 1 only)	Time logging worksheet	Hours per participant newly assigned to electronic adherence monitoring	0.04	0.00
Driver	Bring Wisepill™ devices to clinic (Year 1 only)	Discussion	Hours (Fixed)	0.50	0.00
Community Research Worker	Train participants on Wisepill™ (Year 1 only)	Staff observation	Hours per participant newly assigned to electronic adherence monitoring	0.57	0.00
Senior Data Clerk	Prepare Wisepill™ report for flagging	Time logging worksheet	Hours per participant assigned to electronic	0.04	0.04

			adherence monitoring		
Community Research Worker	Prep, conduct and log follow-up calls	Staff observation	Hours per participant flagged	0.15	0.15
Community Research Worker	Find and meet with participants who come for follow-up visit	Staff observation, discussion	Hours per 40% of participant flagged	0.17	0.17
Community Research Worker	Miscellaneous prep time	Staff observation	Hours per participant flagged	0.20	0.20
Total hours per month (Fixed)				***0.50***	***0.00***
Total hours per participant, per month				***1.25***	***0.56***
	Check-in Texts				
Study Coordinator	Prepare spreadsheet with phone numbers for SMS push	Time logging worksheet	Hours per participant assigned to check-in texts	0.05	0.05
Total hours per participant, per month				***0.05***	***0.05***
	Enhanced Adherence Counselling				
Community Research Worker	Conduct enhanced adherence counselling	Staff observation	Hours per participant receiving counselling	1.13	1.13
Total hours per participant, per month				***1.13***	***1.13***

[1] Estimated that only approximately 40% participants return to clinic for follow-up visit after being called.
[2] Assumed one drop-off per month.

Costs by intervention

Tables 4.4 and 4.5 show final intervention costs of participation for the first cohort of SUSTAIN participants in USD and ZAR, respectively. In discounted real USD, the total program cost to provide intervention activities for the first 50% participants for one year (including start-up) was $30,756.97 (ZAR 504,844.53). In discounted real USD, the total cost per intervention ranged from $1,489.14 (pharmacy refill monitoring) to $18,607.28 (electronic adherence monitoring). Pharmacy refill monitoring had one of the lowest set-up costs as well as personnel costs, as most activities were carried out by lower cadre staff. The same costs for airtime and phones were applied across all monitoring interventions. The second lowest-cost intervention was enhanced adherence counselling ($2,079.96), which was slightly higher due to training costs during the set-up period. Viral load monitoring costs ($3,307.79) were driven by personnel costs as a Medical Officer, paid at a high hourly rate was used to review viral load test results. The second most expensive intervention, check-in texts ($5,403.03), was driven by the monthly SMS platform costs, as personnel costs were minimal and there were no airtime or phone costs. Electronic adherence monitoring was more than twelve times as expensive as check-in texts; costs were driven by monthly hosting and data costs for the Wisepill™ devices and refurbishment of the Wisepill™ devices during the prep period.

Table 4.4. Costs by Intervention (USD)

Intervention	Cost Type	Set-Up	Year 1	Year 2
Pharmacy Refill Monitoring	**Personnel salaries**	$54.31	$509.68	$561.67
	Supplies			
	Airtime	$0	$155.51	$267.61
	Phones	$0	$61.45	$40.72
	Total, Current USD	**$1,650.95**		
	Total, Constant (Real) USD	**$1,567.05**		
	Total, Discounted Real USD	***$1,489.14***		
Enhanced Counselling	**Personnel salaries**	$1,007.28	$196.98	$164.51
	Training costs	$759.32		
	Total, Current USD	**$2,164.09**		
	Total, Constant (Real) USD	**$2,116.57**		
	Total, Discounted Real USD	***$2,079.96***		
Viral Load Monitoring	**Personnel salaries**	$15.61	$1,357.91	$1,768.22
	Supplies			
	Airtime		$155.51	$267.61
	Phones		$61.45	$40.72
	Total, Current USD	**$3,667.03**		
	Total, Constant (Real) USD	**$3,486.18**		
	Total, Discounted Real USD	***$3,307.79***		
Check-In Texts	**Personnel salaries**	$210.90	$613.23	$648.66
	Other Direct Costs			
	SMS platform set-up	$208.77		
	SMS Platform monthly		$2,264.85	$2,032.96
	Total, Current USD	**$5,979.37**		
	Total, Constant (Real) USD	**$5,661.94**		
	Total, Discounted Real USD	***$5,403.03***		
Electronic Adherence Monitoring	**Personnel salaries**	$53.90	$1,356.41	$984.11
	Supplies			
	Wisepill™ device refurbishment	$3,489.03		
	Airtime		$155.51	$267.51
	Phones		$61.45	$40.72
	Other Direct Costs			
	Hosting and data for Wisepill™ devices	$12,351.40		
	Total, Current USD	**$18,760.15**		
	Total, Constant (Real) USD	**$18,607.28**		
	Total, Discounted Real USD	***$18,477.35***		

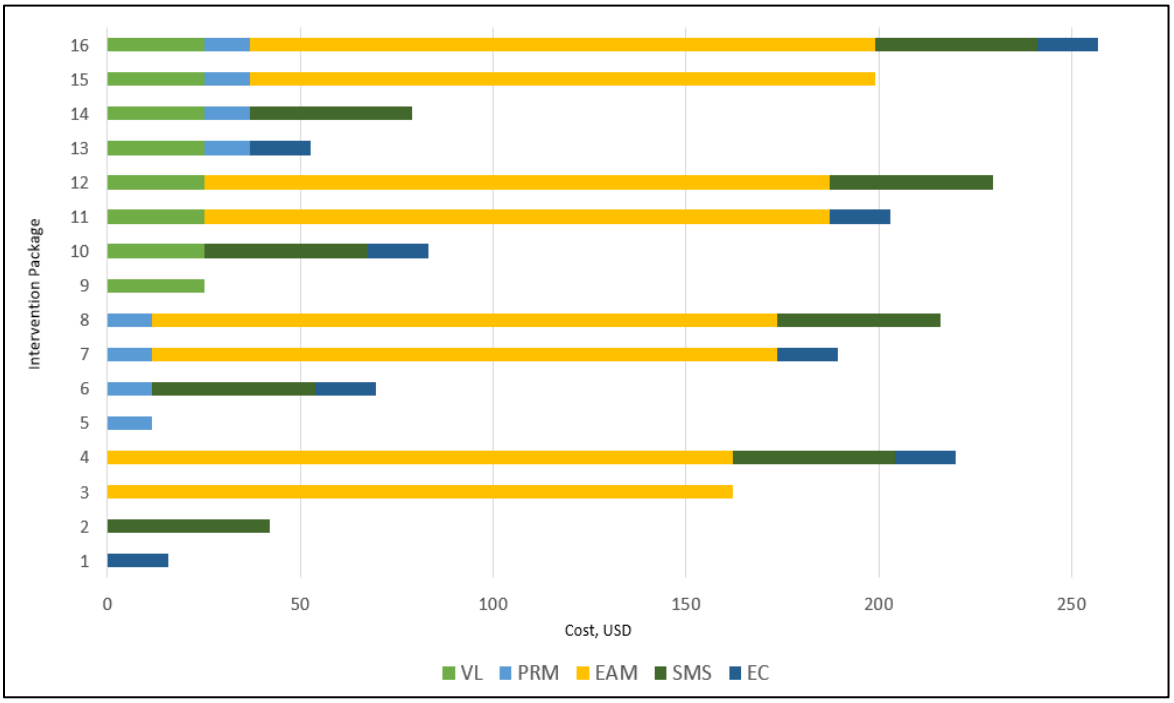
Table 4.5 Costs by Intervention (ZAR)

Intervention	Cost Type	Set-Up	Y1	Y2
Pharmacy Refill Monitoring	**Personnel salaries**	820.87	8,523.53	10,464.45
	Supplies			
	Airtime	0	2,600.64	4,985.92
	Phones	0	1,027.67	758.67
	Total, Current ZAR	**29,181.74**		
	Total, Constant (Real) ZAR	**28,491.10**		
	Total, Discounted Real ZAR	***27,121.03***		
Enhanced Counselling	**Personnel salaries**	15,224.80	3,294.13	3,064.97
	Training costs	12,021.00		
	Total, Current ZAR	**33,604.91**		
	Total, Constant (Real) ZAR	**33,289.66**		
	Total, Discounted Real ZAR	***32,845.75***		
Viral Load Monitoring	**Personnel salaries**	235.96	22,708.85	32,943.63
	Supplies			
	Airtime		2,600.64	4,985.92
	Phones		1,027.67	758.67
	Total, Current ZAR	**65,261.34**		
	Total, Constant (Real) ZAR	**63,746.53**		
	Total, Discounted Real ZAR	***60,587.71***		
Check-In Texts	**Personnel salaries**	3,187.68	10,255.26	12,085.18
	Other Direct Costs			
	SMS platform set-up	3,155.50		
	SMS Platform monthly		37,876.0	37,876.00
	Total, Current ZAR	**104,435.63**		
	Total, Constant (Real) ZAR	**101,812.81**		
	Total, Discounted Real ZAR	***97,136.46***		
Electronic Adherence Monitoring	**Personnel salaries**	814.75	22,683.66	18,335.04
	Supplies			
	Wisepill™ device refurbishment	52,735.64		
	Airtime		2,600.64	4,985.92
	Phones		1,027.67	758.67
	Other Direct Costs			
	Hosting and data for Wisepill™ devices	186,687.75		
	Total, Current ZAR	**290,629.74**		
	Total, Constant (Real) ZAR	**289,438.14**		
	Total, Discounted Real ZAR	***287,153.63***		

Intervention cost per person

Total intervention component costs were divided by the number of participants assigned to that intervention to create a unit cost per participant. The least expensive intervention per participant was pharmacy refill monitoring ($11.63 or ZAR 211.88), followed by enhanced adherence counselling ($15.76 or ZAR 248.83), and viral load monitoring ($25.25 or ZAR 462.50). Check-in texts were $42.21 or ZAR 758.88 per person. The most expensive intervention component was electronic adherence monitoring at $162.08 or ZAR 2518.89 per person. The cost of each intervention package per person is shown in Figure 4.1. The package containing all intervention components (Group 16) was $256.93 or ZAR 4200.99 per person, nearly 20 times the cost of the least expensive intervention (pharmacy refill monitoring only, Group 5). The most expensive intervention assignment that did not include electronic adherence monitoring was viral load monitoring, check-in texts and enhanced adherence counselling (Group 10) at $83.22 or ZAR 1470.21 per participant.

Figure 4.1. Intervention Package Costs per Person (USD)



VL = viral load monitoring, PRM = pharmacy refill monitoring, EAM = electronic adherence monitoring, SMS = check-in texts, EC = enhanced adherence counselling

D. Discussion

This costing analysis of participation in SUSTAIN for the first cohort of participants provides an indication of financial investment required to establish and maintain individual and packaged interventions for PHIV initiating ART. This analysis provides information which will be used to conduct future analyses: a cost-effectiveness analysis using adherence outcome data from SUSTAIN, and a forward-looking costing exercise to consider how each intervention component and/or package(s) could be adapted for use outside of a trial setting and implemented in a clinical setting if proven to be cost-effective.

The costing analysis is useful in showing the cost of each intervention package in the SUSTAIN study per person, ranging from $11.63 (pharmacy refill monitoring) to $162.08 (electronic adherence monitoring). Viral load monitoring, which cost $25.25 per person in this study, was less expensive than in a previous study in Zimbabwe which estimated a per person cost of $62 each year, although this also included an adherence intervention once a patient had been identified as needing support[128]. Provision of enhanced adherence counselling was notably less expensive in SUSTAIN than in another South African trial which estimated providing cognitive behavioral therapy to all people with depression and virologic failure would cost $6,670 per person[129]. However, this difference is likely because a cognitive behavioral therapy regimen would require more counselling sessions and administration by a specialist provider than the counselling administered in the SUSTAIN study.

These figures are especially important when put in context with the cost per patient per year on ART in South Africa (for example, first line treatment is approximately $249.15, per 2017/2018 NACM costs)[127]; showing that the addition of electronic adherence monitoring on its own in the SUSTAIN study would account for nearly two-thirds the cost of first-line ART. Such a significant investment would require compelling evidence of cost-effectiveness, which will be explored in analyses following completion of the trial.

Differences in cost drivers were observed across each intervention. Fixed costs related to set-up of pharmacy refill monitoring, enhanced adherence counselling, and viral load monitoring were all low. Check-in text intervention costs were driven by the

fixed cost of the SMS platform. Electronic adherence monitoring intervention costs were driven by the fixed cost of the Wisepill™ device refurbishments, and monthly costs of device hosting and data. Across the other interventions, personnel costs were generally low. The exception was viral load monitoring, which had higher personnel costs due to having a more expensive cadre of staff (Medical Officer) review records, compared to the other interventions which were implemented by less expensive staff. However, this practice is reflective of viral load monitoring in a clinic setting as clinical officers are required to review lab results.

An important next step for this research is understanding which costs can be reduced and/or how efficiencies could be achieved through redesign of the intervention components for implementation outside of a trial setting. For example, in all monitoring interventions, time is currently spent having a Study Coordinator monitor various databases for participants who have been flagged; these are compiled into lists which must then be emailed to CRWs who prepare and monitor their own list and email back updates to the Study Coordinator who must then resolve flags in the database. Having one or two designated people per clinic in charge of all these tasks could reduce personnel time simply through streamlining communication. Additionally, steps like logging follow-up calls which are used for quality control and monitoring in a study environment may not be considered necessary or worth the time required in a clinic setting, again reducing time and personnel cost.

Considerations for cost-savings and efficiencies that could be made for each intervention component are described in turn below.

Viral load monitoring and outreach: This intervention requires no set-up time as it is already part of the standard of care, making easiest to bring to scale. In SUSTAIN, for this intervention a Medical Officer reviews the system for elevated results; for those with elevated viral load, a referral letter must be prepared and delivered to the clinic, which accounts for more than half of personnel time currently. Within a clinic setting in the City of Cape Town this would be greatly simplified: a nurse would review test results online and could then either make a follow-up call or refer the call to another staff member at lower cost, with no referral letter preparation or delivery necessary as required within a study setting.

Pharmacy refill monitoring and outreach: This intervention is inexpensive and primarily requires personnel cost, with minimal set-up time. It could be the most natural fit to transfer to the role of a data or file clerk, as a large part of what is required is time spent checking clinic records in the filing room. A file clerk could be designated to check records for missed pick-ups and could then make a follow-up call or designate the calls to another support staff; they would not need to conduct any follow-up visits. This intervention also may be easier to scale particularly if clinics already have access to the City of Cape Town pharmacy refill monitoring database; they could then cut down time study staff currently spend compiling lists and sending them to City of Cape Town.

Enhanced adherence counselling and outreach: This is one of the most time-intensive interventions, however, in the context of SUSTAIN it was low-cost as it was primarily comprised of personnel time. It would be worth exploring if this intervention could be taken on by counsellors already employed/working in clinics (e.g., ANOVA

counsellors or those hired by other district support partners). However, it is important to note that this intervention requires space and privacy to conduct counselling sessions, which is already limited (in one SUSTAIN study clinic, counselling sessions were being conducted in a room actively being used as both a printing and break room). There are also up-front and ongoing refresher training costs associated with this intervention.

Check-in texts: While there are currently no obvious changes that could be made, it will be very compelling if this component is shown to increase adherence as it is by far the least time-intensive, requiring about three minutes a month per person to update the database of participants to receive the SMS. This intervention is one of the more expensive options due to actual SMS system cost, but it could achieve an economy of scale as monthly costs do not appear to be sensitive to participant numbers. However, savings in the product and/or data plan could potentially be achieved through government negotiation with the service provider to bring down costs.

Electronic adherence monitoring: This intervention may require the most investigation to understand cost versus benefit. This study found that it required up to 1.73 hours to administer to a participant each month, although it was typically less (closer to 0.5 hours per month) once the participant was registered and trained to use their Wisepill™ device. However, as this intervention is the most sensitive to flagging, it required more time for monitoring flagging and conducting follow-ups, and would require consideration about who could take on such a role if it were scaled up. It is also by far the most expensive due to the cost of device refurbishment (in SUSTAIN this was fixed as costs were paid at set-up) along with monthly data hosting costs. Because of this

high cost and higher sensitivity, it may be pertinent to consider use only for those who have viremia after their first viral load test rather than providing them at time of initiation on ART. Costs could also be reduced if devices were produced and implemented at scale, and if devices were used more than once, for example, given to another person after the first year in care.

There are limitations to this study which should be addressed. Micro-costing data could not be collected daily throughout implementation given the additional workload posed to study staff, so some interpolation was needed (e.g., using the value reported in Month A to represent time spent in Months B and C for which no time was recorded). In addition, recounting time spent (particularly during the preparation period) may be subject to recall bias. However, to counter this limitation, we collected staff observation data to refine our estimates of timing required to implement each intervention component based on in-person observation using a robust sample. While this ideally would have done the observation for all staff members implementing activities, we felt it was most important to conduct for the CRWs who were implementing clinic-based, patient-facing steps of each intervention, and thus most likely to remain in adaptation of the interventions. It is also possible that CRWs may have behaved differently during the observation period (e.g., the Hawthorne effect[130]) because of being watched. However, we have confidence in the time estimates used in the costing model due to our ability to triangulate multiple data sources used in the micro-costing exercise (for example, comparing self-reported time spent on an activity to observation data).

E. Conclusion

This study provides information on the costs of providing adherence monitoring and support interventions to a cohort of PHIV initiating ART during their participation in the SUSTAIN trial. These costs will be used for future analyses exploring cost-effectiveness of the intervention packages as well as to conduct a forward-looking analysis transposing the interventions from a trial setting to a real-world clinic setting.

Acknowledgements

The authors thank the SUSTAIN study staff and participants for their time and efforts to contribute to this research. Special gratitude is given to Alienah Gelem and Zoleka Xaba for their support.

CHAPTER FIVE: COST-EFFECTIVENESS ANALYSIS AND FUTURE COSTING

A. Chapter Overview

This chapter presents the results of aims 2 (cost-effectiveness analysis) and 3 (future costing) together as the discussion and recommendations are closely linked. First, we describe the findings of the cost-effectiveness analysis of the SUSTAIN trial intervention components for the first 50% enrolled after one year of participation. Second, we describe the results of the future costing exercise to adapt the SUSTAIN interventions for scale up in the City of Cape Town. Results of a cost-effectiveness analysis using the future costs are also described. Finally, an integrated discussion is presented.

B. Cost – Effectiveness Analysis Results

Adherence outcomes

Adherence outcomes for the first 50% of SUSTAIN participants after one year of enrollment are shown by intervention component in Figure 5.1. Adherence outcomes were examined across each of the five interventions (rather than intervention packages), e.g., adherence outcomes for anyone receiving viral load monitoring compared to anyone receiving electronic adherence monitoring. The proportion of participants achieving >80% adherence was generally low by all interventions, with steep further declines from 80% to 90%, and 90% to 95%. Of the monitoring interventions, the proportion achieving >80% adherence was highest on electronic adherence monitoring: 55.6% compared to

45% receiving pharmacy refill monitoring and 30.5% receiving viral load monitoring. Adherence outcomes by support intervention were similar at all categories of adherence, with 57% of participants receiving enhanced adherence counselling >80% adherent, and 56% of participants receiving check-in texts >80% adherent.

Figure 5.1. Adherence Outcomes by Intervention Component

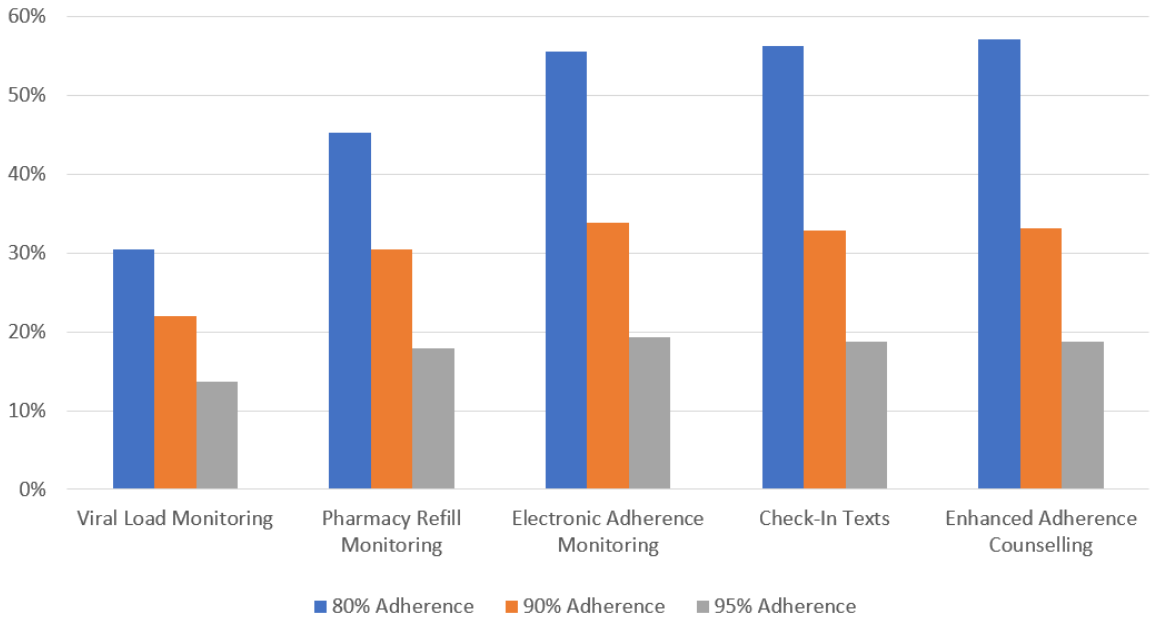


Table 5.1. Costs and Outcomes by Intervention Component

Intervention Component	Total Cost Per Person (USD)	Total n Assigned	80% Adherence		90% Adherence		95% Adherence	
			n	%	n	%	n	%
Viral Load Monitoring	3307.8	131	40	30.5%	29	22.1%	18	13.7%
Pharmacy Refill Monitoring	1489.1	128	58	45.3%	39	30.5%	23	18.0%
Electronic Adherence Monitoring	18477.4	124	69	55.6%	42	33.9%	24	19.4%
Check-In Texts	5403.0	128	72	56.3%	42	32.8%	24	18.8%
Enhanced Adherence Counselling	2079.9	133	76	57.1%	44	33.1%	25	18.8%

Cost-effectiveness analysis

A cost-effectiveness analysis was conducted across intervention components. Incremental cost-effectiveness ratios (ICERs) for the base case scenario were calculated by intervention component at each adherence category (>80%, >90%, >95%) using the SUSTAIN intervention costs. Monitoring components and support components were compared to each other separately. ICERs for monitoring components are shown in Figure 5.2, and in Figure 5.3 for support components.

The ICER for achieving >80% adherence receiving electronic adherence monitoring compared to pharmacy refill monitoring was 1329.5 (e.g., it costs $1,329.5 more per person to achieve adherence using electronic adherence monitoring compared to pharmacy refill monitoring), and up to 9911.1 for achieving 95% adherence. By

comparison the ICER for achieving >80% on pharmacy refill monitoring compared to viral load monitoring was -92.1 and was therefore cost-saving. Compared to viral load monitoring, there was a savings of up to $213.2 for one patient to achieve 95% adherence on pharmacy refill monitoring.

In the cost-effectiveness analysis of the support interventions, enhanced adherence counselling was cost-saving at all three adherence categories compared to check-in texts. The ICER for achieving >80% adherence receiving enhanced adherence counselling compared to check-in texts was -2976.1, with a cost savings of up to $56,546.0 per person achieving >95% adherence.

Figure 5.2. Base Case CEA, Monitoring Components

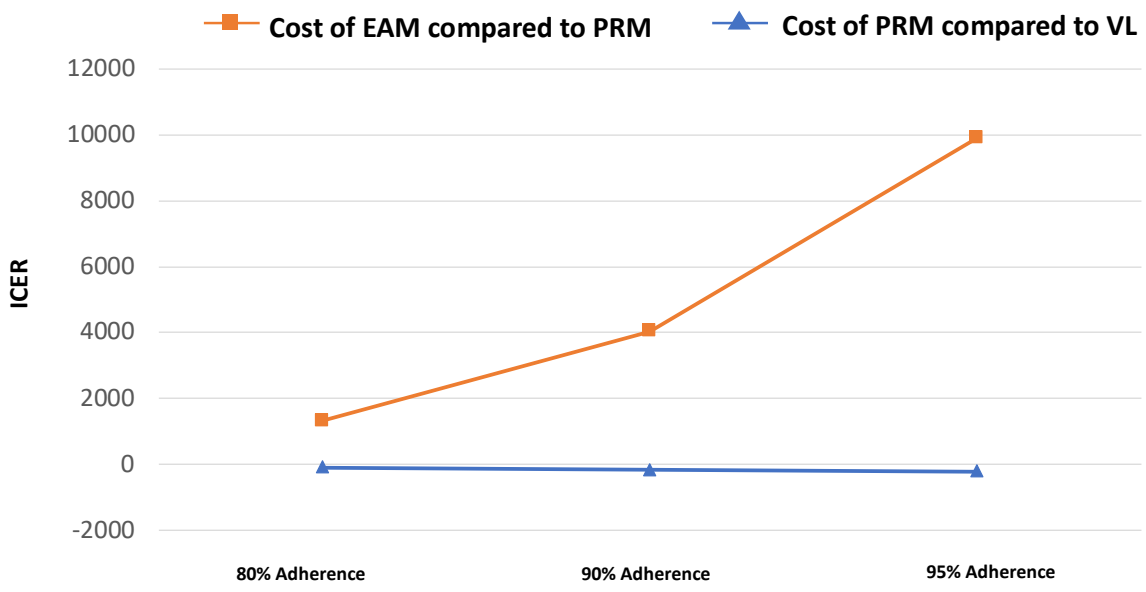
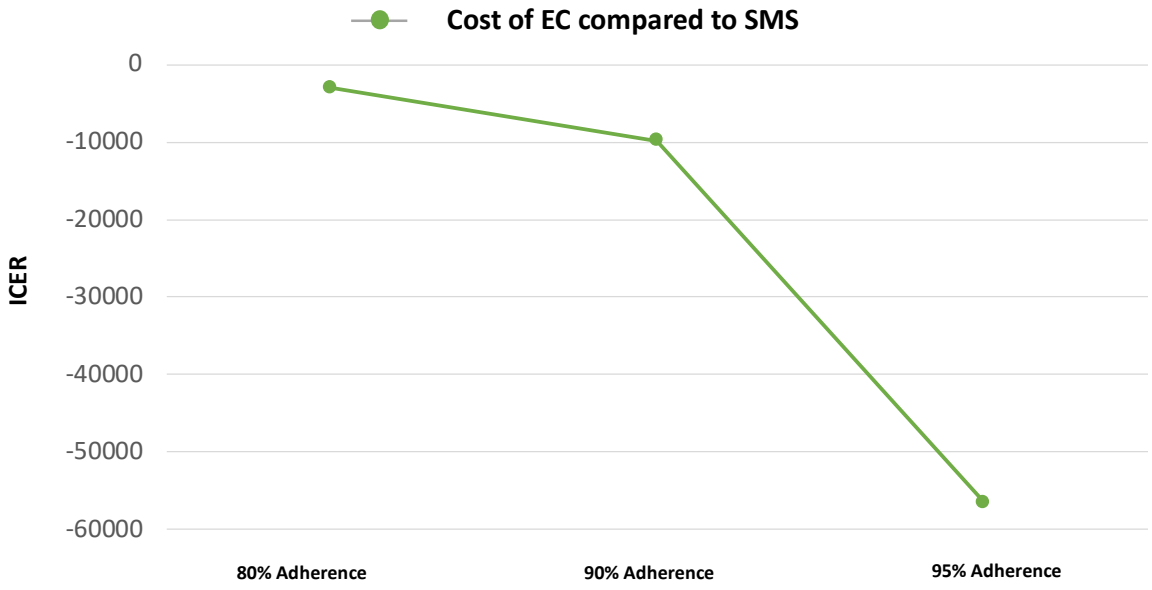


Figure 5.3. Base Case CEA, Support Components



Sensitivity analyses

Sensitivity analyses were conducted by intervention component and compared to the base case, described below and shown in Table 5.2.

In alternative 1, the cost of viral load monitoring was lowered as the tasks conducted by the Medical Officer employed by the SUSTAIN study were changed to be performed by a Study Coordinator (lower salary which may be more in line with City of Cape Town salaries for nurses). Lowering the cost of viral load monitoring, which was used as the baseline comparator, thus decreased the magnitude by which pharmacy refill monitoring was cost saving. However, it was still cost saving at all adherence categories compared to viral load monitoring.

In alternative 2, the cost of data and hosting the Wisepill™ devices was reduced by half assuming a hypothetical scenario in which reduced costs could be negotiated with

the manufacturer. In this scenario, the cost of achieving >80% adherence per patient on electronic adherence monitoring was reduced by $487.6 ($1329.5–841.9) compared to the base case scenario; and electronic adherence monitoring was less expensive at all adherence categories compared to the base case scenario. However, even with significantly reduced costs of hosting the Wisepill™ devices, this intervention remained the costliest.

In alternative 3, the cost of the SMS platform was reduced by $60 (from $160 to $100), assuming an exploratory hypothetical scenario in which reduced costs could be negotiated with the service provider. In this scenario, the cost of achieving >80% adherence per patient on check-in texts was reduced by nearly half ($1,384.2, $2976.1 – 1,591.8) compared to the base case.

Table 5.2. CEA Results and Sensitivity Analyses (USD)

Scenario	Comparison	ICER - 80% Adherence	ICER - 90% Adherence	ICER - 95% Adherence
Base case	EAM[1] to PRM	1329.5	4037.9	9911.1
	PRM to VL	-92.1	-163.4	-213.2
	EC to SMS	-2976.1	-9834.1	-56546.0
Alternative 1: Lower cost VL	EAM to PRM	1329.5	4037.9	9911.1
	PRM to VL	-43.8	-77.7	-173.4
	EC to SMS	-2976.1	-9834.1	-56546.0
Alternative 2: Reduced cost of Wisepill(TM) data + hosting	EAM to PRM	841.9	2556.9	6276.0
	PRM to VL	-92.1	-163.4	-213.2
	EC to SMS	-2976.1	-9834.1	-56546.0
Alternative 3: Reduced cost of SMS platform	EAM to PRM	1329.5	4037.9	9911.1
	PRM to VL	-92.1	-163.4	-213.2
	EC to SMS	-1591.8	-5259.9	-30244.9

[1]EAM: electronic adherence monitoring, PRM: pharmacy refill monitoring, VL: viral load monitoring, EC: enhanced adherence counselling, SMS: Check-in texts

C. Future Costing Results

Changes made to the SUSTAIN program

The costing framework was adjusted to identify efficiencies in program delivery and increase future sustainability using the SUSTAIN study as a starting point. Guiding factors underlying the development of the framework were: a) removing any costs and/or steps related to study activities that would not be carried over outside of a study setting and b) task-shifting to less expensive staff when appropriate. The changes made to the program are outlined in Table 5.3. It was assumed that the program would be delivered by data clerks, nurses, and counsellors.

Table 5.3. Program Scale-Up Changes and Assumptions

Intervention Component	Change
All (PRM, EAM, VL, SMS, EC[1])	• "General Training on Program" cost added for each year to train staff on intervention
	• "General Supplies" cost category added for provision of phones to conduct follow-up calls for all monitoring interventions[2]
All Monitoring (PRM, EAM, VL)	• Removed time and cost for monitoring the SUSTAIN study database (e.g., emailing study coordinator to resolve flags)
	• Removed step to find and meet participants who were flagged as this was related to SUSTAIN study activity
	• Removed miscellaneous prep time related to preparing for SUSTAIN intervention activities
PRM	• Removed Medical Officer from personnel time as this person was originally part of the SUSTAIN study team and would not be involved in scale-up across City of Cape Town
EAM	• Removed data clerk prepping report of Wisepill™ devices to activate; this was specific to SUSTAIN which already owned electronic adherence monitoring devices and needed to monitor inventory

	• Replaced driver bringing devices to clinics from research office with data clerk to pick up and deliver electronic adherence monitors from a central distribution point
	• Added cost of purchasing new Wisepill™ devices required by program scale-up
VL	• Removed sending viral load results to study coordinator, preparing referral letters, and bringing letters to clinic, which were all specific to the SUSTAIN study
	• Replaced Study Coordinator flagging elevated viral loads in REDCap and sending to CRW with nurse checking viral load ahead of visits and data clerk making follow-up calls
SMS	• Replaced Study Coordinator preparing weekly spreadsheet for message push with data clerk
EC	• Replaced CRW conducting enhanced counselling sessions

[1] EAM: electronic adherence monitoring, PRM: pharmacy refill monitoring, VL: viral load monitoring, EC: enhanced adherence counselling, SMS: Check-in texts
[2] Cost would be removed if all monitoring components are removed from final recommended program

Time per operational role in scaled-up program

To estimate the additional burden placed on clinic staff by implementing the scaled-up SUSTAIN intervention components, time per operational role was calculated using an estimated average number of PHIV initiating ART per clinic per year (Table 5.4). If all interventions were brought to scale, it is estimated that up to an additional 382 hours per year (or 55 working days) of extra work would be required from a data clerk. This could also be spread across multiple data clerks; in the costing framework it was assumed that there would be two data clerks per clinic to implement the program resulting in up to an additional 257 hours of work per person each year. If enhanced counselling were brought to scale, it would require an estimated additional 237.5 hours of work per year (34 workdays) in total. The costing model also assumed two counsellors per clinic, resulting in an additional 136 hours of work or 20 working days per counsellor. For checking of

viral load results in real-time (ahead of appointments) an additional 132 hours of work would be added, or 19 work days, which could be shared across several nurses per clinic. Training costs for two nurse champions per year for the program were added to the costing framework.

Table 5.6. Time (Annual Hours) Per Operational Role

Role	Activity	Total Hours
Data clerk	Program training	21.0
	Send pharmacy refill monitoring list to City of Cape Town	0.8
	Pick up and deliver electronic adherence monitors	14.0
	Check clinic folders for pharmacy refill monitoring results	29.3
	Follow-up calls for patients flagged on pharmacy refill monitoring	15.5
	Follow-up calls for patients flagged on viral load monitoring	3.6
	Configure electronic adherence monitors	4.4
	Flag missed electronic adherence monitoring doses	47.7
	Prepare electronic adherence monitoring report for flagging	53.3
	Train patients on electronic adherence monitors	47.7
	Follow-up calls for patients flagged on electronic adherence monitors	45.4
	Prep SMS spreadsheet	106.6
	Total hours	***382.1***
	Total work days	***54.6***
Counsellor	Program training	21.0
	Enhanced counselling training	14.0
	Enhanced counselling	202.5
	Total hours	***237.5***
	Total work days	***33.9***
Nurse	Program training	***21.0***
	Check viral load results online	***132.0***
	Total hours	***111.0***
	Total work days	***18.9***

Future program cost

The final scale-up program cost inputs are shown in Table 5.5. Fixed costs refer to those which do not vary by patient volume; variable costs change according to patient volume. The intervention components costed were the same as those in the SUSTAIN study, but with steps simplified to conducted within a clinic setting. Assumptions and projected costs were reviewed with SUSTAIN program staff based in South Africa to confirm accuracy.

Table 5.5. Program Cost Inputs (Per Year)

	Unit	Value	Notes/assumptions
Fixed Costs			
General Training on New Program			
Data Clerks	Hours per year	42	• Assume 21 hours per clinic (3 days) per year to allow for new staff training and refresher • 2 data clerks per clinic
Counsellors	Hours per year	42	• Assume 21 hours per clinic (3 days) per year to allow for new staff training and refresher • 2 counsellors per clinic
General Supplies			
Phones	Cost per phone (ZAR)	1899	• Assume 2 phones per clinic per year (mid-range smartphones)
PRM			
Personnel			
Data Clerk	Hours per year	10.08	• Time per month for sending PRM weekly list to City of Cape Town
EAM			
Personnel			
Data Clerk	Hours per year	14	• Assume 2 days per year per clinic for picking up and delivering devices
Supplies			
Wisepill	Cost per unit (ZAR)	377.16	• Per discussion with supplier, assume lower cost due to mass

			production (equivalent to 20 USD per device)
Enhanced Counselling			
Personnel			
Counsellors	Hours per year	28	• Time to attend Life Steps training (2 days), 2 counsellors per clinic
Training			
Life Steps Training Fees	Cost per training (ZAR)	2000	• 2 counsellors per clinic per year • Assume 6% salary increase per year
Check-in Texts			
Supplies			
SMS Program	Cost per year (ZAR)	12600	• Multiply by 95 clinics
Variable Costs			
PRM			
Personnel			
Data Clerk	Hours per participant flagged/year	2.04	• Check clinic folders to verify prescriptions missed
Data Clerk	Hours per participant flagged/year	1.08	• Prep, conduct and log follow-up calls
Supplies			
Airtime	Cost per participant flagged/year (ZAR)	32.44	• Multiply by estimated number of participants flagged by pharmacy refill monitoring
Viral Load			
Personnel			
Nurse	Hours per participant assigned/year	1	• Check and annotate files for results
Data Clerk	Hours per participant flagged/year	1.08	• Prep, conduct and log follow-up calls
Supplies			
Airtime	Cost per participant flagged/year (ZAR)	32.44	• Multiply by estimated number of participants flagged by viral load monitoring
EAM			
Personnel			
Data Clerk	Hours per participant assigned/year	0.04	• Configure Wisepill™
Data Clerk	Hours per participant assigned/year	0.48	• Configure Wisepill™ report for flagging
Data Clerk	Hours per participant assigned/year	0.43	• Train participants on Wisepill™

Data Clerk	Hours per participant assigned/year	0.96	• Flag missed doses on Wisepill™
Data Clerk	Hours per participant flagged/year	1.08	• Prep, conduct and log follow-up calls
Supplies			
Wisepill device cost	Cost per participant assigned/year (ZAR)	3454	• All new year in year 1 • Assume 10% must be replaced in subsequent years
Wisepill hosting and data	Cost per participant assigned/year (ZAR)	1517	
Airtime	Cost per participant flagged/year (ZAR)	32.44	• Multiply by estimated number of participants flagged by electronic adherence monitoring
Check-In Texts			
Personnel			
Data Clerk	Hours per participant assigned/year	0.96	• Prep spreadsheet with phone numbers to be sent
Enhanced Counselling			
Personnel			
Counsellor	Hours per participant flagged/year	13.56	• Assume three counselling sessions per year for anyone flagged

Costs for the scaled-up program are shown below. Three types of costs are provided: total cost, cost per clinic, and cost per patient. Costs are provided as both nominal cost in 2024 ZAR/USD to provide information for current budget planning and decision-making, and in real discounted ZAR/USD to provide a comprehensive economic analysis. Costs are provided by each intervention component so that costs can easily be amended should one or more components be dropped from the program based on the results of the cost-effectiveness analysis following study completion.

To scale up the SUSTAIN program, including all five intervention components to all City of Cape Town clinics over a ten-year period, it is estimated that this would have up to a total nominal cost of between $1,141,724.1 and $1,853,465.6 million annually

(ZAR 19,339,444.4 – 31,476,665.2) (Table 5.6). In year 1, electronic adherence monitoring accounts for 69% of costs, followed by enhanced adherence counselling (9%), check-in texts (7%), viral load monitoring (7%), general costs (6%), and pharmacy refill monitoring (1%). By year 10, electronic adherence monitoring and enhanced adherence counselling are still the most expensive interventions, but electronic adherence monitoring decreases to 45% of costs and enhanced adherence counselling increases to 20% costs. The change in electronic adherence monitoring costs is due to lower amount of device purchasing required after Year 1 (e.g., all new devices required in Year 1, only 10% replacement devices in subsequent years). The increase in enhanced adherence counselling costs is due to the expected 6% salary increase per year and associated training fees, as enhanced counselling is by far the most time-intensive intervention for staff to deliver. In real 2024 terms, which are adjusted for expected inflation and discounted at a rate of 3% annually, total costs for the ten-year program range from $795,077.1 to $1,853,465.6 annually (Appendix 4).

The total estimated nominal cost per clinic over the ten-year period for scaling up all interventions ranges between $19,510.2 (Year 1) and $12,018.1 (Year 10) (Table 5.7); the total real cost in 2024 USD ranges from $19,510.2 (Year 1) to $8,369.2 (Year 10) (Appendix 5). This calculation assumes 95 clinics in the City of Cape Town.

The total estimated nominal cost per patient for scaling up all interventions ranging between $176.4 (Year 1) to $164.4 (Year 10) (Table 5.8). The total real cost per patient in 2024 USD ranges from $176.4 (Year 1) to $114.5 (Year 10) (Appendix 6). The cost per patient calculations in the future costing framework assume that HIV incidence

will decrease each year, and thus there will be fewer new patients enrolling into the program. However, this does not account for those who may be re-starting ART, so the cost per patient may be lower than this estimate. This estimate also does not account for in-migration of PHIV to Cape Town or changes in initiations due to increased access to HIV testing.

When examining annual cost per person by intervention component (see Tables 5.8 or 5.9), in Year 1 electronic adherence monitoring costs ZAR 2,071.8 or $122.0 per person, followed by enhanced adherence counselling (ZAR 277.4/$16.3), viral load monitoring (ZAR 207.9/$12.2), check-in texts (ZAR 199.7/$11.8), general program costs (ZAR 189.7/$11.2), and pharmacy refill monitoring (ZAR 48.6/$2.9). By Year 10, electronic adherence monitoring is still the costliest per person at ZAR 1,168.4 ($68.8), followed by enhanced adherence counselling (ZAR 517.3/$30.5), general program costs (ZAR 432.4/$25.5), viral load monitoring (ZAR 350, $20.6), check-in texts (ZAR 239.8/$14.1), and pharmacy refill monitoring (ZAR 84.4/$5.0).

Table 5.6. Total Nominal Costs For 10-Year Program, All CoCT Clinics, 2024 USD/ZAR

Category	Currency	2024	2025	2026	2027	2028
Total	ZAR	31,476,665.2	26,565,779.0	25,333,457.9	24,204,700.6	23,177,544.4
	USD	1,853,465.6	1,564,294.0	1,491,730.2	1,425,264.7	1,364,781.9
General	ZAR	1,993,452.8	2,078,422.2	2,169,269.1	2,266,346.2	2,370,027.3
	USD	117,382.1	122,385.4	127,734.8	133,451.1	139,556.2
Viral Load Monitoring	ZAR	2,184,562.3	2,210,358.0	2,236,547.4	2,263,130.4	2,290,107.7
	USD	128,635.3	130,154.3	131,696.4	133,261.7	134,850.2
Pharmacy Refill Monitoring	ZAR	510,997.1	516,710.2	523,069.3	530,076.8	537,737.0
	USD	30,089.5	30,425.9	30,800.3	31,212.9	31,664.0
Electronic Adherence Monitoring	ZAR	21,773,318.5	16,726,049.3	15,348,727.0	14,066,264.2	12,875,923.8
	USD	1,282,095.7	984,893.3	903,791.4	828,275.1	758,183.3
Check-in Texts	ZAR	2,098,937.7	2,050,181.6	2,001,561.9	1,953,080.3	1,904,738.5
	USD	123,593.4	120,722.5	117,859.6	115,004.8	112,158.2
Enhanced Adherence Counselling	ZAR	2,915,396.7	2,984,057.8	3,054,283.3	3,125,802.8	3,199,010.1
	USD	171,669.6	175,712.7	179,847.8	184,059.1	188,369.9

Table 5.6. (Cont.) Total Nominal Costs For 10-Year Program, All CoCT Clinics, 2024 USD/ZAR

Category	Currency	2029	2030	2031	2032	2033
Total	ZAR	22,246,719.3	21,405,730.6	20,653,059.8	19,981,336.4	19,389,444.4
	USD	1,309,971.3	1,260,450.7	1,216,130.6	1,176,577.0	1,141,724.1
General	ZAR	2,480,708.5	2,598,810.0	2,724,777.0	2,859,081.3	3,002,223.2
	USD	146,073.5	153,027.8	160,445.2	168,353.6	176,782.3
Viral Load Monitoring	ZAR	2,317,479.9	2,345,247.8	2,373,412.6	2,401,975.8	2,430,939.0
	USD	136,462.0	138,097.1	139,755.6	141,437.5	143,142.9
Pharmacy Refill Monitoring	ZAR	546,056.4	555,043.5	564,709.2	575,066.2	586,129.7
	USD	32,153.9	32,683.1	33,252.2	33,862.1	34,513.5
Electronic Adherence Monitoring	ZAR	11,771,958.5	10,747,588.8	9,800,372.1	8,922,845.3	8,112,887.2
	USD	693,177.6	632,858.9	577,083.1	525,411.0	477,717.6
Check-in Texts	ZAR	1,856,538.3	1,808,481.4	1,760,569.6	1,712,804.6	1,665,188.2
	USD	109,320.0	106,490.3	103,669.0	100,856.4	98,052.6
Enhanced Adherence Counselling	ZAR	3,273,977.7	3,350,559.0	3,429,219.3	3,509,563.1	3,592,077.2
	USD	192,784.2	197,293.6	201,925.5	206,656.4	211,515.1

Table 5.7. Total Nominal Cost per Clinic For 10-Year Program, 2024 USD/ZAR

Category	Currency	2024	2025	2026	2027	2028
Total	ZAR	331,333.3	279,639.8	266,668.0	254,786.3	243,974.2
	USD	19,510.2	16,466.3	15,702.4	15,002.8	14,366.1
General	ZAR	20,983.7	21,878.1	22,834.4	23,856.3	24,947.7
	USD	1,235.6	1,288.3	1,344.6	1,404.7	1,469.0
Viral Load Monitoring	ZAR	22,995.4	23,266.9	23,542.6	23,822.4	24,106.4
	USD	1,354.1	1,370.0	1,386.3	1,402.8	1,419.5
Pharmacy Refill Monitoring	ZAR	5,378.9	5,439.1	5,506.0	5,579.8	5,660.4
	USD	316.7	320.3	324.2	328.6	333.3
Electronic Adherence Monitoring	ZAR	229,192.8	176,063.7	161,565.5	148,065.9	135,536.0
	USD	13,495.7	10,367.3	9,513.6	8,718.7	7,980.9
Check-in Texts	ZAR	22,094.1	21,580.9	21,069.1	20,558.7	20,049.9
	USD	1,301.0	1,270.8	1,240.6	1,210.6	1,180.6
Enhanced Adherence Counselling	ZAR	30,688.4	31,411.1	32,150.4	32,903.2	33,673.8
	USD	1,807.0	1,849.6	1,893.1	1,937.5	1,982.8

Table 5.7. (Cont.) Total Nominal Cost per Clinic For 10-Year Program, 2024 USD/ZAR

Category	Currency	2029	2030	2031	2032	2033
Total	ZAR	234,176.0	225,323.5	217,400.6	210,329.9	204,099.4
	USD	13,789.2	13,267.9	12,801.4	12,385.0	12,018.1
General	ZAR	26,112.7	27,355.9	28,681.9	30,095.6	31,602.3
	USD	1,537.6	1,610.8	1,688.9	1,772.1	1,860.9
Viral Load Monitoring	ZAR	24,394.5	24,686.8	24,983.3	25,284.0	25,588.8
	USD	1,436.4	1,453.7	1,471.1	1,488.8	1,506.8
Pharmacy Refill Monitoring	ZAR	5,748.0	5,842.6	5,944.3	6,053.3	6,169.8
	USD	338.5	344.0	350.0	356.4	363.3
Electronic Adherence Monitoring	ZAR	123,915.4	113,132.5	103,161.8	93,924.7	85,398.8
	USD	7,296.6	6,661.7	6,074.6	5,530.6	5,028.6
Check-in Texts	ZAR	19,542.5	19,036.6	18,532.3	18,029.5	17,528.3
	USD	1,150.7	1,121.0	1,091.3	1,061.6	1,032.1
Enhanced Adherence Counselling	ZAR	34,462.9	35,269.0	36,097.0	36,942.8	37,811.3
	USD	2,029.3	2,076.8	2,125.5	2,175.3	2,226.5

Table 5.8. Total Nominal Cost per Patient for 10-Year Program, 2024 USD/ZAR

Category	Currency	2024	2025	2026	2027	2028
Total	ZAR	2,995.1	2,647.0	2,643.1	2,644.4	2,651.5
	USD	176.4	155.9	155.6	155.7	156.1
General	ZAR	189.7	207.1	226.3	247.6	271.1
	USD	11.2	12.2	13.3	14.6	16.0
Viral Load Monitoring	ZAR	207.9	220.2	233.3	247.2	262.0
	USD	12.2	13.0	13.7	14.6	15.4
Pharmacy Refill Monitoring	ZAR	48.6	51.5	54.6	57.9	61.5
	USD	2.9	3.0	3.2	3.4	3.6
Electronic Adherence Monitoring	ZAR	2,071.8	1,666.6	1,601.4	1,536.7	1,473.0
	USD	122.0	98.1	94.3	90.5	86.7
Check-in Texts	ZAR	199.7	204.3	208.8	213.4	217.9
	USD	11.8	12.0	12.3	12.6	12.8
Enhanced Adherence Counselling	ZAR	277.4	297.3	318.7	341.5	366.0
	USD	16.3	17.5	18.8	20.1	21.5

Table 5.8. (Cont.) Total Nominal Cost per Patient for 10-Year Program, 2024 USD/ZAR

Category	Currency	2029	2030	2031	2032	2033
Total	ZAR	2,664.9	2,685.0	2,712.6	2,748.1	2,792.3
	USD	156.9	158.1	159.7	161.8	164.4
General	ZAR	297.2	326.0	357.9	393.2	432.4
	USD	17.5	19.2	21.1	23.2	25.5
Viral Load Monitoring	ZAR	277.6	294.2	311.7	330.3	350.1
	USD	16.3	17.3	18.4	19.5	20.6
Pharmacy Refill Monitoring	ZAR	65.4	69.6	74.2	79.1	84.4
	USD	3.9	4.1	4.4	4.7	5.0
Electronic Adherence Monitoring	ZAR	1,410.1	1,348.1	1,287.2	1,227.2	1,168.4
	USD	83.0	79.4	75.8	72.3	68.8
Check-in Texts	ZAR	222.4	226.8	231.2	235.6	239.8
	USD	13.1	13.4	13.6	13.9	14.1
Enhanced Adherence Counselling	ZAR	392.2	420.3	450.4	482.7	517.3
	USD	23.1	24.7	26.5	28.4	30.5

Table 5.9. Summary: Cost Per Patient (Presented at City of Cape Town Stakeholders Meeting, April 2024)

		Year 1 (2024)	Year 10 (2033)
	Est. patients (ART initiates)	10,509	6,944
Cost per patient	General program costs	ZAR 189.7 USD 11.2	ZAR 432.4 USD 25.5
	Electronic adherence monitoring	ZAR 2,071.8 USD 122.0	ZAR 1,168.4 USD 68.8
	Viral load monitoring	ZAR 207.9 USD 12.2	ZAR 350.1. USD 20.6
	Pharmacy refill monitoring	ZAR 48.6 USD 2.9	ZAR 84.4 USD 5.0
	Enhanced adherence counselling	ZAR 277.4 USD 16.3	ZAR 517.3 USD 30.5
	Weekly check-in text	ZAR 199.7 USD 11.8	ZAR 239.8 USD 14.1

Future cost-effectiveness analysis

A future cost-effectiveness analysis was conducted using the expected total nominal costs to implement each intervention, assuming the same adherence outcomes as observed in the SUSTAIN study. The SUSTAIN base case results were used to compare the ICERs calculated in two future scenarios: cost-effectiveness for scaled-up program in Year 1 (2024) and in Year 10 (2033). The results are shown in Table 5.12.

Comparing monitoring interventions, the ICER for electronic adherence monitoring compared to pharmacy refill monitoring in achieving >80% adherence in Program Year 1 was 1153.1 (e.g., an additional $1,153 to achieve this adherence category through electronic adherence monitoring compared to pharmacy refill). By Program Year 10, while the price of electronic adherence monitoring had dropped, the ICER was much lower for all adherence categories compared to Year 1, but still costlier than pharmacy refill monitoring.

Compared to viral load monitoring, pharmacy refill monitoring was cost-saving at all adherence categories in Programs Year 1 and 10. The ICER to achieve >80% adherence for pharmacy refill monitoring compared to viral load monitoring in Year 1 was -63.5 (e.g., a savings of $63.5. to achieve >80% adherence on pharmacy refill monitoring), with savings up to $221.8 per patient to achieve >95% adherence compared to viral load monitoring. By Program Year 10, pharmacy refill monitoring was even more cost saving, with an ICER of -105.9 for achieving >80% adherence, to -369.9 for achieving >95% adherence compared to viral load monitoring.

When comparing the support interventions, there was a large difference from the

base case scenario, where enhanced adherence counselling was cost-saving. In the future costing however, counselling was no longer cost saving compared to check-in texts, and instead was very expensive, (e.g., an ICER of 1829.9 for achieving >80% adherence on counselling compared to check-in texts). This was due to the changes made in the scaled-up version of the program: in SUSTAIN, enhanced adherence counselling was not used by many participants and therefore had a low cost, while in the scaled-up program it was assumed that any participant flagged through any mechanism would receive three sessions of enhanced counselling per year. This higher intervention cost thus impacted the CEA outcomes in the future costing scenario. The cost of check-in texts was also lower in the future costing exercise due to achieving an economy of scale through the fixed cost of hosting the platform across a larger number of patients. This would keep costs low compared to the high amounts of staff time related to delivering enhanced adherence counselling and rising salaries.

Table 5.10. Future CEA Results

Scenario	Comparison	ICER – 80% Adherence	ICER – 90% Adherence	ICER – 95% Adherence
Base case (SUSTAIN, 2021–2024)	EAM[1] to PRM	1329.5	4037.9	9911.1
	PRM to VL	-92.1	-163.4	-213.2
	EC to SMS	-2976.1	-9834.1	-56546.0
Program Year 1 (2024)	EAM to PRM	1153.1	3501.8	8595.7
	PRM to VL	-63.5	-112.5	-221.8
	EC to SMS	512.3	1693.1	9733.5
Program Year 10 (2033)	EAM to PRM	617.7	968.9	2378.2
	PRM to VL	-105.9	-187.8	-369.9
	EC to SMS	1829.9	10382.4	59687.8

[1] EAM: electronic adherence monitoring, PRM: pharmacy refill monitoring, VL: viral load monitoring, EC: enhanced adherence counselling, SMS: Check-in texts

E. Discussion

SUSTAIN Cost-effectiveness analysis

Aim 2 of this dissertation sought to assess the cost-effectiveness of interventions on treatment adherence after one year of participation in the SUSTAIN study. Electronic adherence monitoring was much more expensive for achieving adherence compared to the next best intervention, pharmacy refill monitoring, and pharmacy refill monitoring was cost-saving compared to the poorest intervention for achieving adherence (viral load monitoring with outreach). As such pharmacy refill monitoring with outreach appears to be the dominant monitoring intervention in this analysis. Of the support interventions, enhanced adherence counselling was cost-saving at all adherence categories compared to check-in texts.

Aside from CEA results, there are some notable differences in adherence outcomes thus far. Of the monitoring interventions, attainment of >80% adherence was highest among participants receiving electronic adherence monitoring (55.6%) compared to those receiving pharmacy refill and viral load monitoring. Adherence was lowest at all categories for participants receiving viral load monitoring. Since electronic adherence monitoring is the most sensitive to detecting non-adherence, it follows that those participants with many more opportunities to be flagged and contacted would have higher levels of adherence. However, it is important to interpret these results with caution as the aim of SUSTAIN is to identify which intervention components work most effectively together in packages, and this analysis did not explore the effect of interactions between components. For example, for a patient who was receiving both electronic adherence and

viral load monitoring, it was not possible to test the interaction of these two components in this analysis to understand the nuances of the packages (e.g., were they picked up by Wisepill™ or viral load monitoring first? Was this flagging followed by enhanced counseling or text messages, none, or both?) In addition, a participant receiving monitoring via Wisepill™ along with any other monitoring strategy would almost certainly be flagged first by electronic adherence monitoring rather than by another strategy, so a "yes" for monitoring by the other two strategies does not preclude flagging via electronic adherence monitoring.

For the reasons discussed above, we also urge caution in interpreting data showing that outcomes of the two support interventions were very similar (56% achieving 80% adherence on check-in texts compared to 57% on enhanced adherence counselling). In this analysis we cannot identify the interactions between the two support interventions and different combinations of monitoring interventions.

Sensitivity analyses were used to explore the impacts of reducing high costs related to electronic adherence monitoring and SMS technology. Significantly reducing the cost of Wisepill™ data and hosting still did not make electronic adherence monitoring cost-saving compared to the next best adherence monitoring intervention (pharmacy refill). While lowering the cost of the SMS platform reduced the magnitude by which enhanced adherence counselling was cost saving, there was still a clear difference in costs. It is also important to note that in the SUSTAIN study costing (which influences cost-effectiveness results), the actual price of Wisepill™ devices was not included, as the study site already owned the devices and instead had to pay for refurbishment. If the cost

of purchasing new Wisepill™ devices had been included, this intervention would have been even more costly. There are currently several electronic adherence monitoring devices on the market ranging from around $20–$200 depending on functionality, with Wisepill™ at the upper end (approximately $160). Wisepill™ was chosen for SUSTAIN for practical reasons, as it was large enough to hold ART tablets, allows for real-time monitoring, and has more robust data systems. However, cost of these devices is expected to drop and in conversations with the manufacturer, they have indicated that in a mass production scenario the devices could be produced for approximately $20 per unit. This lower expected price for the Wisepill™ has been incorporated into the future costing framework.

While there is limited information on the cost-effectiveness of the intervention strategies used in this study, there are several comparison studies which should be noted. One modeling study in Zimbabwe in 2016 found that in the presence of viral load monitoring, an outreach intervention was cost-effective to achieve viral suppression at $23–$32 per person, per year[128]. The cost of this program is similar to the viral load monitoring program in SUSTAIN, which was costed at $25.25 per person. Additionally, enhanced adherence counselling in the SUSTAIN study ($15.76 per person) was cost-saving, showing better financial outcomes than a 2023 study in South Africa which found that implementing cognitive behavioral therapy for patients with depression and virologic failure would be cost-effective at a cost of $6670 per person[129]. However, this is not a like-for-like comparison, as cognitive behavioral therapy requires repeated, more intensive sessions and implementation by a trained nurse, whose salary would be higher

than a CRW delivering counselling in SUSTAIN.

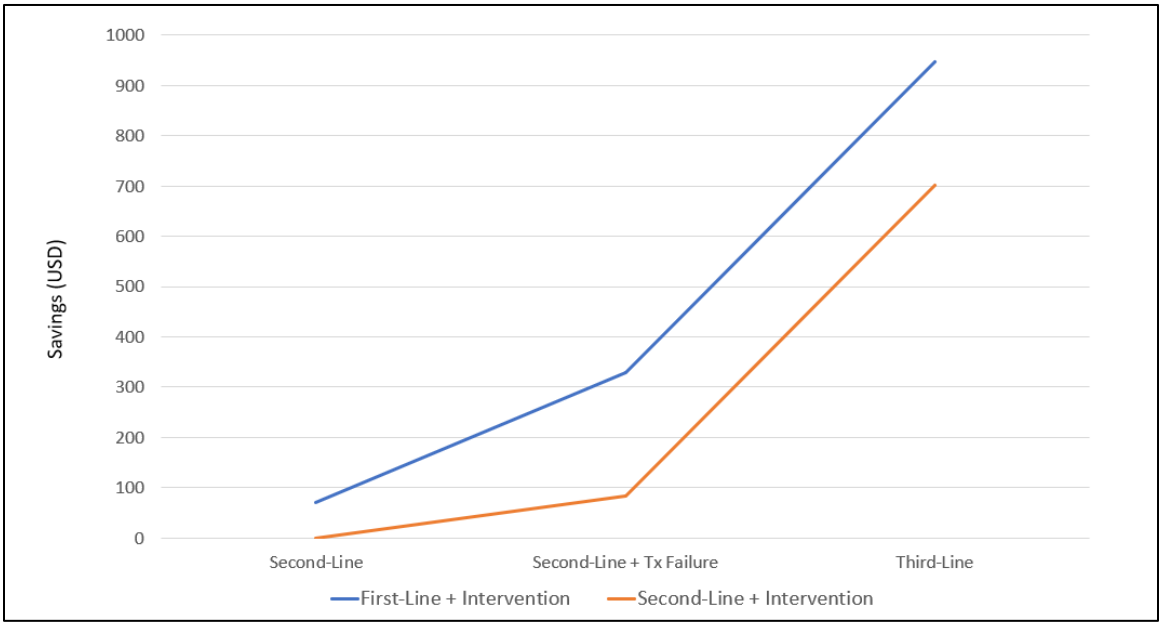
Future costing and cost-effectiveness

Aim 3 of this dissertation was to develop a future costing framework providing costs for the interventions tested in SUSTAIN, to provide the City of Cape Town and other public health decision-makers with a best estimate of the cost of scale-up. Following completion of the SUSTAIN study, a full economic analysis will be conducted to ascertain cost-effectiveness of each of the sixteen intervention conditions and their component parts to identify the most effective and cost-effective intervention or package. However, the research conducted for this dissertation provides interim results on costs and cost-effectiveness to begin considering which intervention components may be worth investing in bringing to scale.

It is important to understand the scaled-up program costs in context of the national ART program. To our knowledge, the most up-to-date published estimates of the cost of providing ART per annum in South Africa are $248 per person for first-line treatment and treatment failure, $495 for second-line treatment, $754 for second-line treatment failure, and $1,372 for third-line treatment[127]. In the full scaled-up program, if all interventions were taken forward (which they likely would not be) the *maximum* cost per patient ranges between $153.0 – $176.4. This represents an investment that could be cost-saving in averting second-line or third-line treatment. For example, first-line treatment plus the scaled-up program would total $424.4, a savings of $70.6 per person compared to second-line treatment; compared to third-line treatment, a savings of $947.6

could be achieved by providing the adherence intervention at first-line treatment (Figure 5.4).

Figure 5.4. Cost Savings Per Patient of Treatment + Interventions Compared to Treatment Options Alone (USD)



We can also compare costs to the City of Cape Town HIV budget based on publicly available budget documents specifying the ART budget[131] in terms of operating transfers and grant receipts for 2023/24 – 2025/26. Table 5.11 shows the estimated costs of the City of Cape Town ART program for the next two years, and how the scaled-up SUSTAIN program would compare to the overall program budget. For example, in Year 1 (2024), the full scaled-up program would account for 9.6% of the City of Cape Town ART budget; if electronic adherence monitoring were removed from the program but all other components maintained, this would account for 2.9% of the budget.

Table 5.11. City of Cape Town ART Budget Compared to Scaled-Up Program Costs (ZAR)

	2024/25	2025/26
Budget value	327,422,000	342,090,000
Full scaled-up program cost	31,476,665.2	26,565,779.0
Full program % of budget	9.6%	7.7%
Program without electronic adherence monitoring cost	9,703,346.6	9,839,729.7
Program without electronic adherence monitoring % of budget	2.9%	2.8

Understanding the cost drivers of the scaled-up program is also important for decision-makers. Even with the reduced cost of $20 per Wisepill™ device, electronic adherence monitoring remains the most expensive intervention component, accounting for 69% of costs in Program Year 1 when new devices would need to be purchased. However, this is a fixed cost, and in subsequent years the cost of the electronic adherence monitoring intervention would decline sharply. In the costing model we budgeted for 10% of devices to be replaced each year due to possibility of being broken, lost, or not returned, but the model also assumes fewer devices would need to be purchased each year as the incidence of HIV decreases and fewer patients start ART. As a result, by Year 10 of the program, electronic adherence monitoring accounts for 42% of program costs. The threshold by which decision-makers determine cost-effectiveness will be an important factor in determining whether electronic adherence monitoring is worth the investment.

Aside from electronic adherence monitors, cost of technology such as the SMS platform, phones, and data are also important to consider. We estimated that the cost of

phones and data would continue to decrease based on past trends, however, negotiating a lower cost for data could reduce costs of all monitoring interventions.

Considerations in decline of technology costs partly led to the biggest change in cost-effectiveness between the SUSTAIN program and a future scaled-up program: in SUSTAIN, enhanced adherence counselling was cost-saving compared to check-in texts, while in the future program, enhanced counselling was no longer cost-saving. This is partly because the cost of the SMS platform is fixed and thus less expensive per person with more patients receiving it. Negotiating a lower price for using this program over a long period (e.g., 10 years of scale up) would further increase savings. Another cost driver was staff salaries in the enhanced adherence counselling intervention. In our model, it was assumed that patients flagged through any device would receive three enhanced adherence counselling sessions in a year, which last for slightly over an hour per session. This was by far the most time-intensive intervention and thus very sensitive to increases in salary, which we assumed would be 6% annually based on 2024 estimates[119]. Adherence counselling training fees were also included annually, and assumed to increase at the same rate to account for salary increases. As a result, the cost per patient to deliver enhanced adherence counselling increased over time, from $16.3 (10% of program costs) to $30.5 (22% of program costs). It should be noted, however, that additional sensitivity analyses or changes to service delivery could be conducted, such as considering reducing the expected annual increase of salaries/training fees or reducing the number of sessions provided to patients from three to two per year (which also accounts for the fact that many patients will attend all sessions they are entitled to).

The time required to implement an intervention is another important consideration when recommending integration into an existing program. In the future costing exercise, we estimated the average time required to implement these interventions per year, and assumed the implementation would be split across four staff per clinic (two data clerks to conduct monitoring interventions and check-in texts, and two counsellors to conduct enhanced adherence counselling). Based on these calculations, we estimated that the monitoring interventions and check-in texts would take up 257 hours or 36.7 additional workdays for two data clerks, and enhanced adherence counselling would take up to 136.25 hours or 19.5 additional workdays for two counsellors[1]. This amount of work would suggest that new staff members may not need to be hired to deliver the interventions. Assuming there are approximately 257 workdays in a year (21.4 workdays per month * 12 months), this would equal 1 additional hour per day per data clerk to implement monitoring and check-in texts, and 20 additional minutes per day per counsellor to provide enhanced counselling. Similarly, real-time viral load monitoring would require approximately 132 additional hours of work per clinic; this work could be split across any number of nurses working in the clinic but using the same assumption of two nurses per clinic, this would similarly equal approximately an additional 20 minutes of work per day.

[1] These are estimates for a "standard clinic" developed for this exercise using an average number of patients; in practice, the time required per clinic will vary based on having more or fewer patients than the estimates used in the model. However, this estimate provides a good baseline understanding of the time required to administer the scaled-up program.

Another important consideration which has not yet been addressed in discussing the scale-up of interventions is examining what is offered for PHIV who are restarting ART compared to those who are ART-naïve and initiating treatment for the first time. The reality of HIV as a chronic disease is that most people cycle in and out of care throughout their lives[132,133], with estimates that up to 25% of PHIV in South Africa experience a treatment interruption of six months or longer during a two-year period[134]. It is in both the patient's and health system's best interest to identify those with treatment interruptions early, as ART interruption is associated with increased risk of opportunistic infections, onward transmission, and mortality[135,136]. In fact, treatment interruptions and visit attendance (e.g., late versus on-time visits) have been shown to be more important in predicting future missed visits than baseline demographic and clinical features[137]. Treatment interruptions and/or disengagement from care can also lead to treatment resistance, necessitating switches to more costly regimens for the health system, and ART regimens with higher pill burden and lower tolerability for PHIV[135,138].

Given the costs of scaling up additional interventions, it is worth considering taking a differentiated approach that prioritizes more intensive support to those who are returning to care compared to those who are newly starting ART. To account for this in the costing framework, estimates would need to be made regarding the number of PHIV re-initiating ART. A 2022 systematic review estimated that between 20–50% of patients initiating HIV treatment are re-initiators, most likely at least 30%[139]. Using these estimates, it would be possible to create a costing framework for a differentiated care program which provides one set of interventions for those re-initiating care versus those

newly initiating care.

An additional point to consider when interpreting the findings from this research is that the limited societal and societal perspectives[100] were not considered for this dissertation due to concerns about feasibility and scope, as well as the decision that the healthcare payer perspective was most relevant for the City of Cape Town when considering costs of scale-up. However, this excludes patients' costs and thus therefore may not provide a full view of the economic and financial costs of implementing these interventions. The limited social perspective accounts for cost components beyond the healthcare sector, including patient time and costs[100]. If this study were to have been conducted using a limited societal perspective, additional time and/or costs to include would be patient time to travel to and attend appointments, cost of travel to appointments, any productivity lost as a result of attending appointments and/or speaking to clinic staff regarding monitoring interventions, and cost of keeping devices and phones charged in order to use the Wisepill™ and receive the check-in text intervention. Societal perspectives are recognized as being challenging to cost for rigorously. To do so, we would have included financial and/or economic costs related to spillover costs affecting other sectors outside of healthcare such as education, housing, or the environment[100]. On balance, this was deemed beyond the scope of this dissertation.

Finally, the results of the cost-effectiveness analysis using future costs should be considered in deciding which interventions should be brought to scale. Again, the full results of the SUSTAIN trial are needed to make an informed decision regarding the most effective intervention or intervention package, but these interim results provide a starting

point for thinking about costs and effectiveness. As in the base case cost-effectiveness analysis using the SUSTAIN costs and interim adherence outcomes, in the findings of the future cost-effectiveness analysis, the dominant monitoring component was pharmacy refill monitoring as it was cost-saving compared to viral load monitoring at all categories of adherence (80%, 90%, 95%), and electronic adherence monitoring was very costly compared to pharmacy refill monitoring. In the future costing scenario, enhanced adherence counselling was clearly dominated by check-in texts in terms of cost-savings; a large difference from the SUSTAIN base case scenario.

Limitations

There are limitations to this research that are important to acknowledge. The most important is that the cost-effectiveness analysis results examine each intervention component *across* all intervention conditions due to small sample by condition in this patient cohort. While a cost-effectiveness analysis was attempted using adherence outcomes by condition, the base sizes were too small to conduct a meaningful analysis. As such, while the cost-effectiveness analysis conducted in this dissertation can provide insights into potential cost-effectiveness of the interventions, it is not able to provide any information on the interactions between intervention components which is a key aim of SUSTAIN. Second, the cost-effectiveness analysis using SUSTAIN costs and outcomes is not representative of these interventions being conducted in a real-world setting, as we were costing using inputs such as expensive labor (e.g., a highly trained medical officer reviewing viral load results). However, this was the benefit and one of the strengths of

conducting a future costing and cost-effectiveness analysis, as adjustments to the delivery of the interventions could be made to more accurately reflect delivery outside of a trial. As previously mentioned, this analysis did not consider societal perspectives (e.g., costs to patients or wider society) and as such may not wholly reflect the total societal cost of each intervention. Another limitation of this analysis is that it does not consider future care costs for PHIV – it only accounts for the first year of care or re-initiation onto treatment. Another limitation is the challenge of identifying what measure to use to analyze cost effectiveness related to adherence. This has been noted in other studies trying to measure cost-effectiveness of adherence monitoring interventions as the net health benefit is difficult to measure (e.g., % adherence compared to traditional measures such as disability-adjusted life-years or quality-adjusted life-years)[128]. For this analysis, the proportion of patients achieving >80%, >90% and >95% adherence were used as at least 80% is considered the threshold for "good" adherence[37–39].

F. Conclusion

This analysis provides information for decision-makers regarding the potential costs and cost-effectiveness of the SUSTAIN interventions if adapted for scale-up at City of Cape Town clinics. Using interim outcomes from the SUSTAIN trial, pharmacy refill monitoring was cost-saving compared to electronic adherence monitoring and viral load monitoring. It is estimated that to adapt and scale the SUSTAIN program to the City of Cape Town, a total annual investment of ranging between ZAR 19,389,444 – 31,476,665 or $1,141,724.1 – $1,853,465.6 would be required (if all interventions were brought to

scale). This represents between 7.7 – 9.6% of the City of Cape Town's annual ART budget, or between ZAR 2,972.3 ($164.4) – ZAR 2,995.1 ($176.4) per patient per year. A cost-effectiveness analysis of the future program estimates that pharmacy refill monitoring would again be cost-saving compared to electronic adherence and viral load monitoring, and check-in texts would be cost-saving compared to enhanced adherence counselling. The future costing and cost-effectiveness analysis exercises identified additional considerations for decision-makers regarding scale-up, such as time required for enhanced counselling, negotiating lower prices of technology, and using a differentiated approach for PHIV restarting ART compared to those who are treatment-naïve.

CHAPTER SIX: PRACTICE RECOMMENDATIONS AND CONCLUSION

A. Chapter Overview

This dissertation research comprises a costing and cost-effectiveness assessment for the first cohort of SUSTAIN participants after one year of participation. To support translation of the intervention(s) identified as most cost-effective, a forward-looking costing framework was also developed to estimate costs of scale up in City of Cape Town clinics.

It is important to note that this dissertation research was conducted on a sub-sample of the SUSTAIN cohort participants and using interim rather than final outcomes data. Following completion of the SUSTAIN study, a cost-effectiveness analysis will be conducted to determine effectiveness of each intervention package on the full study sample. However, the interim adherence outcomes and cost-effectiveness data can provide direction for the City of Cape Town. The practice recommendations in this chapter will therefore discuss implementation of interventions in the future which considers ways to minimize cost and maximize value to City of Cape Town.

In this chapter, we discuss the rationale and benefit of considering a differentiated care approach for PHIV restarting ART versus those newly starting treatment. Then, we discuss the monitoring and support interventions and how these might be adjusted based on the results of the future costing and CEA exercises, and with a differentiated care approach in mind.

B. Considering a Differentiated Approach for ART-Naïve and Returning Patients

In a world with limited resources, given the costs of scaling up the SUSTAIN program it is worth considering adopting a differentiated approach for those re-initiating care compared to those newly starting ART. Previous research demonstrates that differentiated adherence monitoring is most cost-effective[128], as those with high adherence can be triaged to have reduced visit frequency or more standard care, while those with lower adherence can be prioritized to receive more intensive support.

Research has established that first-time ART initiates in South Africa may be vulnerable to poor adherence due to a variety of challenges such as psychosocial issues (e.g., coping with their diagnosis, lack of developed support networks), logistical barriers (e.g., travel or cost of travel), behavioral challenges (e.g., substance use), as well as time since diagnosis[140]; and it is well-established that the first year of care is the most critical for retention in treatment[4–6]. A 2024 observational cohort study from Western Cape identified that substantial disengagement care was evident at every point in the care cascade, with early treatment as a period of higher risk of disengagement[133]; patients who are cyclically engaged in treatment in treatment months 0–6 are nearly twice as likely to disengage in months 7–12[141]. Another study in South Africa showed that likelihood to experience treatment interruptions was highest among repeat interrupters and patients returning to care after previously defaulting on ART[142]. For this reason, while it is clear that PHIV in South Africa require adherence support, we suggest that there may be differing levels of adherence support needed for different patients. For example, Level A: "Basic Support" for those newly initiating ART, Level B: "Enhanced Support" for those

re-initiating or returning to care, and Level C: “Further Enhanced Support” for anyone identified as non-adherent throughout their first year in care. A proposed differentiated care program is shown in Table 6.1, with detailed descriptions of the changes to each of the interventions described in the following narrative.

Table 6.1. Example Differentiated Care Program

	Level A Basic Support	Level B Enhanced Support	Level C Further Enhanced Support
Eligibility	Newly initiating ART	Re-initiating or returning to care	Anyone flagged as nonadherent during year 1
Estimated number of patients – Program Year 1	10,509 * .7 = 7,356.3	10,509 * .30 = 3,152	10,509 * .54 = 5,675
Estimated number of patients – Program Year 10	6,944 *.7 = 4,860.8	6,944 *.3 = 2,083	6,944 * .54 = 3,480
Monitoring Intervention(s) Detail	• Enrollment onto pharmacy refill monitoring • Viral load monitoring and outreach	• Enrollment onto pharmacy refill monitoring • Viral load monitoring and outreach • Provision of electronic adherence monitor	• Provision of electronic adherence monitor (if not already received through Level B)
Support Intervention(s) Detail	• Enrollment onto weekly check-in texts	• Enrollment onto weekly check-in texts • 1 enhanced adherence counselling session upon reinitiation	• 1 enhanced adherence counselling session upon return visit to clinic

Pharmacy refill monitoring: As the results of the future costing and CEA have demonstrated, thus far pharmacy refill monitoring appears to be a low-cost and cost-saving approach to monitoring treatment adherence, requiring minimal start-up costs and low direct costs to administer. While not as sensitive as electronic adherence monitors, pharmacy refill monitoring can flag patients for non-adherence up to eight times per year. As a cost-saving tool in both the SUSTAIN study and future costing CEA we would recommend enrolling all patients into a pharmacy refill monitoring program regardless of treatment experience. There could be an argument for only enrolling new patients in pharmacy refill monitoring as part of "Basic Support" if re-initiates are to receive electronic adherence monitors immediately to save more money up front, however, again due to its cost savings we would recommend implementing it for all program participants. This would also act as a safety net for re-initiates with electronic adherence monitors who were not able to use them successfully, particularly if they had difficulty keeping their batteries charged as noted in previous research with Wisepill™[143].

Viral load monitoring: In the SUSTAIN study and future costing scaled-up program, real-time viral load monitoring plus outreach was included as an intervention on top of standard-of-care viral load test result review when patients return for a follow-up visit. In the SUSTAIN and future costing analyses it appears to be the least effective monitoring intervention, and at a non-negligible price. The cost of additional (e.g., real-time viral load monitoring as results are available online) is important to consider in a scale-up scenario. In the SUSTAIN study, a Medical Officer reviewed lab results and then notified CRWs to contact patients through a process of printing and delivering

referral letters to the clinics and having CRWs make outreach calls. In the future costing scenario, it was assumed that a nurse would review online lab results as they are returned in real time and make outreach calls to patients with elevated viral load (or delegate to someone else to make calls, like a data clerk). While this process was slightly simplified from the SUSTAIN study approach, it was still costly in the future costing exercise given the higher salary of nurses and annual salary increases. A consideration to decrease the cost of this intervention could be to train data clerks to review lab results online and contact patients, however, this is not current approved practice for City of Cape Town.

The value of adding real-time viral load monitoring and outreach, in addition to the standard of care approach (reviewing results in an appointment) will need to be determined following the results of the final SUSTAIN study. Viral load monitoring is the least sensitive intervention as patients can only be flagged up to twice a year given frequency of testing. It is important to note that viral load testing and monitoring is the gold standard for assessing ART outcomes and we do not recommend removing this from any ART program. We suggest instead that based on current findings, the addition of real-time viral load monitoring and outreach on its own would not be enough to significantly improve adherence and should be included in combination with another intervention that is more sensitive.

Electronic adherence monitoring: Given the high cost of these devices (particularly Wisepill™), there is the strongest argument for either removing electronic adherence monitoring from the menu of intervention options to bring to scale, or to reconsider how it is deployed. Electronic adherence monitoring is extremely sensitive in

detecting non-adherence – in the SUSTAIN study anyone who missed three doses in a row or up to four doses in a two-week period could be flagged for treatment non-adherence, providing invaluable real-time feedback. As it has the highest sensitivity and most opportunities to flag patients as non-adherent, it is a valuable tool albeit one that comes at high price. In a differentiated care scenario, it could make sense to provide these devices to patients who are known to be at highest need of adherence support – e.g., those reinitiating care and thus at risk for multi-drug resistance. Additional criteria could also be applied to supply specific groups at high risk of nonadherence with electronic adherence monitors, for example, adolescents or individuals with known substance use disorder. As such in our imagined differentiated care scenario, anyone re-initiating ART would be provided with an electronic adherence monitor upon ART re-start as part of "Enhanced Support" or Care Level B. Subsequently, anyone flagged during the program through either of the alternative monitoring components (viral load or pharmacy refill monitoring) would be given an electronic adherence monitor for the duration of the program as part of "Further Enhanced Support" or Care Level C, unless they already had a device in their possession.

There is of course a major downside of this approach, particularly for relying on viral load monitoring for identifying non-adherent patients, as by the time someone is flagged through laboratory testing, they will have already been experiencing challenges with adherence for several months. It would be ideal to find more rapid ways to identify individuals who are nonadherent. However, in a resource-limited setting, the addition of real-time viral load monitoring and outreach may be seen as a more feasible approach for

focusing more costly and intensive resources to patients who have demonstrated a need for such stepped-up adherence support.

Check-in texts: It is challenging to make a value judgment about the benefits of check-in texts compared to enhanced adherence counselling, given they had almost identical effects using data from one year of participant engagement in the trial. However, while it was not cost-saving in the SUSTAIN study CEA, in the scaled-up future program check-in texts appear to be cost-saving compared to the enhanced adherence counselling support intervention. As previously discussed, this is likely driven by several factors: first, the fixed cost of the platform which made it cheaper per person as it achieved economies of scale through use with larger patient numbers (e.g., in a scaled-up setting). Second, we assumed that a lower cost of the platform could be achieved through negotiations with the supplier in a scale-up setting, as well as assuming technology would decrease in price over time based on historical trends. Third, it has a very low personnel cost, which makes it less sensitive to salary increases and inflation. As a result, if were to make a recommendation today, in a differentiated care scenario given its low cost and high effectiveness, we would recommend providing this support as an option to all patients as part of "Basic Support." However, the results of the SUSTAIN trial will provide important information on the actual utility of this support intervention and whether it should be brought to scale going forward.

Enhanced adherence counselling: The case of enhanced adherence counseling versus check-in texts is an interesting one in thinking about where the costs of person-time supersede the costs of technology, and whether face-to-face or digital interactions

are more impactful. While enhanced counselling was cost-saving in the SUSTAIN setting when it was delivered to all participants, in the scaled-up program scenario it became extremely costly with limited evidence that this cost was worthwhile, given the interim data showed similar adherence outcomes between participants receiving counselling and check-in texts. However, motivational interviewing and counselling for adherence supports are important tools that can assist PHIV to think through and identify ways to overcome barriers to adherence[144]. Until the results of the full SUSTAIN trial are available and can conclusively point to the value of check-in texts over counselling, we would recommend using a differentiated approach to enhanced adherence counselling. This would include providing one enhanced counselling session for all PHIV re-initiating treatment as part of "Enhanced Support" or Care Level B, and then providing another session to anyone flagged as nonadherent as part of "Further Enhanced Support" or Care Level C. This would reduce the number of enhanced counselling sessions compared to the previous iteration of the scaled-up program where it was assumed that anyone flagged for non-adherence would receive up to three sessions per year, while ensuring that those who are most in need of counseling receive it at least once throughout their first year in care (or back on ART).

Using the future costing framework, we estimated the cost of this differentiated care program (Table 6.2), demonstrating that a differentiated approach could achieve around 45% savings annually for electronic adherence monitoring, and 22% of costs annually for enhanced adherence counselling. The City of Cape Town faces very real budget constraints, with many people to serve – at the time of this writing, their budget

had just been cut by 5%. As a result, it is critical to maximize how money is spent and to ensure this expenditure will provide maximum return on investment. While we cannot conclude which interventions should be taken to scale until the SUSTAIN trial has ended, based on analyses conducted for this dissertation we recommend considering a differentiated approach which targets use of the most costly and sensitive approaches for those with demonstrated adherence challenges.

Table 6.2. Costs of Example Differentiated Care Program (USD)

Program Component	Program Year 1			Program Year 2		
	Old	Y1	Change	Old	Y10	Change
General	117,382.1	117,382.1	0%	176,782.3	176,782.3	0%
Electronic adherence monitoring	1,282,095.7	695,566.2	-45.7%	477,717.6	263,403.4	-44.8%
Viral load monitoring	128,635.3	128,635.3	0%	143,142.9	143,142.9	0%
Pharmacy refill monitoring	30,089.5	30,089.5	0%	34,513.5	34,513.5	0%
Enhanced adherence counselling	171,669.6	130,788.6	-23.8%	211,515.1	165,875.2	-21.6%
Check-in texts	123,593.4	123,593.4	0%	98,052.6	98,052.6	0%

C. Conclusion

Maintaining lifelong adherence to ART remains a major challenge in South Africa, which has the largest population of PHIV globally and the largest ART program in the world. To improve HIV treatment outcomes, i.e., achieving viral suppression in >95% PHIV, clinic staff must be able to identify non-adherent PHIV as quickly as possible and provide support to assure improved adherence and retention in care. As part of the ongoing SUSTAIN study testing adherence interventions for PHIV initiating ART, we conducted a cost and cost-effectiveness study to identify the costs of implementing interventions and their impact on treatment adherence for the first 50% of SUSTAIN participants over one year. Cost-effectiveness analyses were conducted using the study costs and interim outcomes, and costs were used to develop a costing model to inform the City of Cape Town should they want to bring any or all the interventions to scale.

Through this analysis we found that scaling up *all* the interventions would represent a significant cost to the City of Cape Town, up to nearly 10% of their existing ART budget. Pending the results of the SUSTAIN trial, which will identify the cost and cost-effectiveness of the most optimal intervention package, the results from this dissertation research can be used to identify strategies to optimize and focus delivery of these interventions. The primary consideration for future implementation of these interventions would be to employ a differentiated care approach which prioritizes use of the most sensitive (and costly) adherence monitoring intervention, electronic adherence monitoring, only for those patients who are in most need of support – either due to reinitiating ART or those who have been flagged as nonadherent through another

mechanism. Until final SUSTAIN study results can point to which support intervention is more effective, reserving enhanced adherence counselling for patients reinitiating ART and/or who have been flagged as nonadherent can help to save a large amount of program budget. These considerations could help decision-makers to prioritize interventions that will improve adherence to ART and thus overall health outcomes, while also maximizing limited resources.

APPENDIX 1. DETAILED STAFF OBSERVATION LOG

Date	Clinic	Activity	Intervention	Time Spent	Notes
Mar-8-2023	A	Follow-up call and logging notes	Cross-intervention	0:10	Reviewing participant logbook and making calls
		Follow-up call and logging notes	EAM[1]	0:04	Calling patient who was flagged by EAM – she had just given birth and was in the hospital without her device
		Follow-up call and logging notes	EAM	0:05	Call/WhatsApp with same patient previously described, asking questions about unfamiliar looking ART bottle provided in hospital
		Participant visit	EAM	0:22	Returned for month 8 visit, reviewed EAM together with CRW
		Participant visit	EAM	0:16	Participant returned to get support putting pills into EAM
		Follow-up call and logging notes	Cross-intervention	0:03	Reviewing participant logbook and making calls
		Reviewing next day's schedule	Cross-intervention	0:09	
Mar-9-2023	A	Following-up call and logging notes	EAM	0:02	Checking to see if participant is coming to clinic after being flagged
		Reviewing patient records on tablet	Cross-intervention	0:35	
		Checking pharmacy records	PRM	0:09	Checking patient's file in the record room – they were flagged as not picking up meds through PRM system, but file showed they had gotten medications so this will be resolved in the system
Mar-10-2023	A	Follow-up call and logging notes	EAM	0:06	Calling 2 flagged participant
		Follow-up call and logging notes	Cross-intervention	0:01	
		Conducting counselling	EC	0:38	

Mar-13-2023	A	Reviewing EAM data with participant	EAM	0:20	
		Follow-up call and logging notes	Cross-intervention	0:04	
Mar-13-2023	C	Preparing to make calls	Cross-intervention	0:20	
		WhatsApp from participant	Cross-intervention	0:02	
		Follow-up calls	Cross-intervention	0:06	
		Putting results of calls into REDCap	Cross-intervention	0:20	
Mar-14-2023	C	Reading email regarding new flaggings	Cross-intervention	0:04	
		Changing intake time on Wisepill™	EAM	0:02	
		Follow-up call	EAM	0:02	
		Met with participant who needed to change phone number	Cross-intervention	0:04	
		Follow-up call	Cross-intervention	0:01	
		Logging calls on REDCap	Cross-intervention	0:08	
Mar-14-2023	B	Looking for folders and checking PRM data	PRM	0:32	For 4 participants
		Emailing PRM data back to Medical Officer	PRM	0:06	For 4 participants
Mar-15-2023	B	Wisepill™ training with new participant	EAM	0:15	Needed help loading pills into device correctly; CRWs say this is average length to train

[1] PRM = Pharmacy refill monitoring, EAM = Electronic adherence monitoring, EC = Enhanced adherence counselling

APPENDIX 2. SET-UP ACTIVITIES AND TIME

Intervention	Study Role	Tasks	Time (Min)	Date
All	PI[1]	Phone call with City of Cape Town leadership	90	16 Aug 2021
	PI	Email with City of Cape Town – obtaining approvals	5	16 Aug 2021
	PI	Email with City of Cape Town – obtaining approvals	5	17 Aug 2021
	PI	Email with City of Cape Town – obtaining approvals	5	18 Oct 2021
	PI	Emails with City of Cape Town – obtaining approvals	15	19 Oct 2021
	PI	Emails with City of Cape Town – obtaining approvals	15	27 Oct 2021
	PI	Emails with City of Cape Town – obtaining approvals	5	28 Oct 2021
EC	PI	Email with trainers	10	26 July 2021
	SMO	Emails – setting up basic counselling training	20	11 Aug 2021
	SMO	Emails – finalizing training dates	10	23 Sep 2021
	SMO	Emails – confirming manual printing	10	27 Sep 2021
	GM	Emails – processing printing payment	15	26 Oct 2021
	GM	Confirmation of catering	15	26 Oct 2021
	GM	Emails – processing catering payment	15	26 Oct 2021
	D	Transport participants to training (round trip)	120	27 Oct 2021
	D	Transport participants to training (round trip)	120	28 Oct 2021
	CRW	Attend Lifesteps training	6270	27–28 Oct 2021
	SC	Attend Lifesteps training	840	27–28 Oct 2021
	CRW	Attend basic counselling training	3240	12 Sep 2021
EAM	PI	Email with Wisepill™	10	25 Oct 2021
	SMO	Emails with company	10	25 Oct 2021
	DC	Counting and boxing existing devices	180	25 Oct 2021
	D	Delivering Wisepill™ devices (round trip)	80	15 Nov 2021
	SMO	Emails with company – set up of devices and payment	30	31 Jan 2022
	DC	Selecting devices and assigning to clinics	10	24 Feb 2022
	DC	Emails to Wisepill™ to activate devices	10	24 Feb 2022

PRM	PI	Call with City Data Manager to set up missed visit reports	30	19 Jan 2022
	SMO	Call with City Data Manager to set up missed visit reports	30	19 Jan 2022
SMS	SMO	Text with company 1 to obtain contact info	5	5 Oct 2021
	SMO	Text with company 1 to obtain contact info	5	11 Oct 2021
	SMO	Email with company 1 – obtaining quotes	5	28 Oct 2021
	SMO	Email with company 1 – obtaining quotes	5	8 Nov 2021
	SMO	Email with company 1 – obtaining quotes	5	9 Nov 2021
	SMO	Email with company 2 – request for quote	5	9 Nov 2021
	SMO	Email with company 1 – response to quote	5	12 Nov 2021
	SMO	Call with company 2 to discuss quote	30	16 Nov 2021
	GM	Call with company 2 to discuss quote	30	16 Nov 2021
	GM	Reading company contract	15	16 Nov 2021
	GM	Signing company contract, engaging with reps	180	6 Dec 2021
	GM	Completed product forms and sent to company	60	6 Dec 2021
	SMO	Set-up of text message system and pilots	90	15 Jan 2022
	SMO	Training for text message system	30	28 Jan 2022
	GM	Training for text message system	30	28 Jan 2022

[1]PI = Principal Investigator, SMO = Senior Medical Officer, GM = Grants Manager, DC = Data Clerk, D = Driver, CRW = Community Research Workers

APPENDIX 3. STAFF OBSERVATION CALCULATIONS FOR INCLUSION IN COSTING MODEL

Intervention Component	Average minutes spent (per day)	Average minutes spent per month (Per day * 21)	Divisor	Average minutes per participant, per month
Cross-intervention (costs to be applied to all 3 monitoring interventions)				
Follow-up calls and logging notes	*10.8*	*226.80*	*68 participants flagged (EAM, PRM, VL[1])*	*3.34*
Miscellaneous prep	*18.00*	*378.00*	*68 participants flagged (EAM, PRM, VL)*	*5.56*
Electronic Adherence Monitoring				
Follow-up calls – EAM	5.25	147.00	46 participants flagged	5.73
Follow-up calls[2]				3.34
Training	24.33	511.00	20 new EAM enrollments[2]	25.55
Miscellaneous prep – EAM	2.00	56.00	46 participants flagged	6.47
Miscellaneous prep[2]				5.56
Total				***46.65***
Pharmacy Refill Monitoring				
Follow-up calls[2]				3.34
Checking records	9	252	19 participants flagged	9.95
Miscellaneous prep[2]				5.56
Total				***18.85***
Viral Load Monitoring				
Follow-up calls[3]				3.34
Miscellaneous prep[3]				5.56
Total				***8.9***
Enhanced Adherence Counselling				
Counselling session	67.5	n/a – not a daily activity	n/a – not a daily activity	67.5
Total				***67.5***

[1] EAM = Electronic Adherence Monitoring, PRM = Pharmacy Refill Monitoring, VL = Viral Load Monitoring

[2] Used February as a proxy, not collecting information on new enrolments from March 2023

[3] Applied figure for cross-intervention activities

APPENDIX 4. FUTURE COSTING TOTAL DISCOUNTED REAL COSTS, USD/ZAR

Category	Currency	2024	2025	2026	2027	2028
Total	ZAR	31,476,665.2	24,510,138.2	22,711,668.4	21,102,487.3	19,665,718.9
	USD	1,853,465.6	1,443,250.0	1,337,349.3	1,242,594.6	1,157,992.2
General	ZAR	1,993,452.8	1,917,595.4	1,944,768.9	1,975,878.3	2,010,924.4
	USD	117,382.1	112,915.3	114,515.4	116,347.2	118,410.9
Viral Load Monitoring	ZAR	2,184,562.3	2,039,322.1	2,005,084.4	1,973,074.7	1,943,114.2
	USD	128,635.3	120,083.0	118,067.0	116,182.1	114,417.9
Pharmacy Refill Monitoring	ZAR	510,997.1	476,727.5	468,936.2	462,139.1	456,259.9
	USD	30,089.5	28,071.5	27,612.7	27,212.5	26,866.3
Electronic Adherence Monitoring	ZAR	21,773,318.5	15,431,799.7	13,760,269.1	12,263,451.0	10,924,983.9
	USD	1,282,095.7	908,683.0	810,256.9	722,118.6	643,304.6
Check-in Texts	ZAR	2,098,937.7	1,891,540.0	1,794,417.9	1,702,762.3	1,616,135.5
	USD	123,593.4	111,381.1	105,662.1	100,265.1	95,164.2
Enhanced Adherence Counselling	ZAR	2,915,396.7	2,753,153.6	2,738,191.9	2,725,181.9	2,714,301.0
	USD	171,669.6	162,116.1	161,235.1	160,469.1	159,828.4

APPENDIX 4. (CONT.) FUTURE COSTING TOTAL DISCOUNTED REAL COSTS, USD/ZAR

Category	Currency	2029	2030	2031	2032	2033
Total	ZAR	18,383,515.4	17,238,857.4	16,220,321.6	15,313,105.5	13,502,476.3
	USD	1,082,491.2	1,015,089.4	955,114.2	901,693.8	795,077.1
General	ZAR	2,049,926.7	2,092,921.6	2,139,961.8	2,191,115.4	2,246,465.1
	USD	120,707.5	123,239.2	126,009.1	129,021.2	132,280.4
Viral Load Monitoring	ZAR	1,915,043.1	1,888,718.2	1,864,010.3	1,840,803.3	812,982.9
	USD	112,765.0	111,214.9	109,760.0	108,393.5	47,871.5
Pharmacy Refill Monitoring	ZAR	451,232.2	446,997.9	443,506.4	440,713.8	438,581.6
	USD	26,570.3	26,320.9	26,115.3	25,950.9	25,825.4
Electronic Adherence Monitoring	ZAR	9,727,725.6	8,655,446.2	7,696,931.5	6,838,204.9	6,070,607.4
	USD	572,805.4	509,665.6	453,224.6	402,659.5	357,460.4
Check-in Texts	ZAR	1,534,145.4	1,456,439.6	1,382,700.9	1,312,642.8	1,246,005.7
	USD	90,336.3	85,760.7	81,418.7	77,293.4	73,369.6
Enhanced Adherence Counselling	ZAR	2,705,442.5	2,698,333.9	2,693,210.6	2,689,625.4	2,687,833.5
	USD	159,306.7	158,888.2	158,586.5	158,375.4	158,269.8

APPENDIX 5. FUTURE COSTING TOTAL DISCOUNTED REAL COSTS PER CLINIC, USD/ZAR

Category	Currency	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033
Total	ZAR	331,333.3	258,001.5	239,070.2	222,131.4	207,007.6	193,510.7	181,461.7	170,740.2	161,190.6	142,131.3
	USD	19,510.2	15,192.1	14,077.4	13,079.9	12,189.4	11,394.6	10,685.2	10,053.8	9,491.5	8,369.2
General	ZAR	20,983.7	20,185.2	20,471.3	20,798.7	21,167.6	21,578.2	22,030.8	22,525.9	23,064.4	23,647.0
	USD	1,235.6	1,188.6	1,205.4	1,224.7	1,246.4	1,270.6	1,297.3	1,326.4	1,358.1	1,392.4
Viral Load Monitoring	ZAR	22,995.4	21,466.5	21,106.2	20,769.2	20,453.8	20,158.3	19,881.2	19,621.2	19,376.9	8,557.7
	USD	1,354.1	1,264.0	1,242.8	1,223.0	1,204.4	1,187.0	1,170.7	1,155.4	1,141.0	503.9
Pharmacy Refill Monitoring	ZAR	5,378.9	5,018.2	4,936.2	4,864.6	4,802.7	4,749.8	4,705.2	4,668.5	4,639.1	4,616.6
	USD	316.7	295.5	290.7	286.4	282.8	279.7	277.1	274.9	273.2	271.8
Electronic Adherence Monitoring	ZAR	229,192.8	162,440.0	144,844.9	129,089.0	114,999.8	102,397.1	91,110.0	81,020.3	71,981.1	63,901.1
	USD	13,495.7	9,565.1	8,529.0	7,601.2	6,771.6	6,029.5	5,364.9	4,770.8	4,238.5	3,762.7
Check-in Texts	ZAR	22,094.1	19,910.9	18,888.6	17,923.8	17,012.0	16,148.9	15,330.9	14,554.7	13,817.3	13,115.8
	USD	1,301.0	1,172.4	1,112.2	1,055.4	1,001.7	950.9	902.7	857.0	813.6	772.3
Enhanced Adherence Counselling	ZAR	30,688.4	28,980.6	28,823.1	28,686.1	28,571.6	28,478.3	28,403.5	28,349.6	28,311.8	28,293.0
	USD	1,807.0	1,706.5	1,697.2	1,689.1	1,682.4	1,676.9	1,672.5	1,669.3	1,667.1	1,666.0

APPENDIX 6. FUTURE COSTING TOTAL DISCOUNTED REAL COST PER PATIENT, USD/ZAR

Category	Currency	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033
Total	ZAR	2,995.1	2,442.1	2,369.6	2,305.4	2,249.7	2,202.1	2,162.3	2,130.4	2,106.0	1,944.5
	USD	176.4	143.8	139.5	135.8	132.5	129.7	127.3	125.4	124.0	114.5
General	ZAR	189.7	191.1	202.9	215.9	230.0	245.6	262.5	281.1	301.3	323.5
	USD	11.2	11.3	11.9	12.7	13.5	14.5	15.5	16.6	17.7	19.1
Viral Load Monitoring	ZAR	207.9	203.2	209.2	215.6	222.3	229.4	236.9	244.8	253.2	117.1
	USD	12.2	12.0	12.3	12.7	13.1	13.5	13.9	14.4	14.9	6.9
Pharmacy Refill Monitoring	ZAR	48.6	47.5	48.9	50.5	52.2	54.1	56.1	58.3	60.6	63.2
	USD	2.9	2.8	2.9	3.0	3.1	3.2	3.3	3.4	3.6	3.7
Electronic Adherence Monitoring	ZAR	2,071.8	1,537.6	1,435.7	1,339.8	1,249.8	1,165.3	1,085.7	1,010.9	940.5	874.2
	USD	122.0	90.5	84.5	78.9	73.6	68.6	63.9	59.5	55.4	51.5
Check-in Texts	ZAR	199.7	188.5	187.2	186.0	184.9	183.8	182.7	181.6	180.5	179.4
	USD	11.8	11.1	11.0	11.0	10.9	10.8	10.8	10.7	10.6	10.6
Enhanced Adherence Counselling	ZAR	277.4	274.3	285.7	297.7	310.5	324.1	338.5	353.7	369.9	387.1
	USD	16.3	16.2	16.8	17.5	18.3	19.1	19.9	20.8	21.8	22.8

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