Towards A Real-Time Theoretical Perspective into Treatment Adherence: The Case of Tuberculosis Treatment Monitoring Using the Simpill System in South Africa

A Dissertation

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In solidarity with all the comrades fighting to end the burden of Tuberculosis and HIV&AIDS in Africa…..aluta continua, the struggle continues!

Nekumusiki wavanhu, Mwari wavose munazvose…ndinokutendai Changamire!

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To all my family and friends who have been supportive and patient with me as the PhD literally took me away from you all over the course of its duration, thank you so very much, *ndimi maita kuti zipenye-penye*!

To my late father, Charles, If you were here to see this happening I know you would have been proudly singing *'Mavaona here Dhokota!'* Miss you, man.

Declaration

I do hereby solemnly declare that this submission is my own original work, undertaken independently and without any illegitimate assistance. To the furthest extent of my knowledge and conviction, it contains no material previously published by any other person in its current or similar form, neither has it been accepted as or part of a dissertation for the award of any other degree or qualification within the university or any other institution of higher learning. Where reference is made to previous academic work, due acknowledgement of the respective authors is made both in the text and bibliography of this dissertation.

Furthermore, I endevoured to maintain my study as adherent as possible to the 'Guidelines for Good Scientific Practice" (*Leitlinien guter wissenschaftlicher Praxis*) cited under §9 of the *Promotionsordnung des Promotionsstudiengangs "International Development Studies"*, to the best of my ability.

Errors and omissions in this document remain my personal responsibility.

Charlton Chesterman Tsodzo
Bochum, Germany, 2011

List of Acronymns

Aeras	The Aeras Global TB Vaccine Foundation
AIDS	Acquired Immuno-deficiency syndrome
ART	Antiretroviral therapy
BCG	Bacille Calmette-Guérin,
BLT	Behavioural Learning Theory
CIOMS	Council for International Organizations of Medical Sciences
CPT	Cotrimoxazole Preventive Therapy
DOT	Directly Observed Treatment
DOTS	Directly Observed Treatment-Short course
E	Ethambutol
FDC	Fixed Dose Combination
FIND	Foundation for Innovative New Diagnostics
HBM	Health belief model
HIV	Human Immuno-deficieny Virus
ICD	International Classification of Diseases
IEC	Information, Education and Communication
IMB	Information-Motivation-Behavioural Skills Model
INH (H)	Isoniazid
IPT	Isoniazid preventive therapy
MDG	Millennium Development Goal
MDR-TB	Multi-drug resistant Tuberculosis
MEMS	Medication Event Monitoring System
MNL	Multinomial Logistic
MSF-OCA	Médecins Sans Frontières Operational Centre Amsterdam
NIDS	National Income Distribution Survey

OLS	Ordinary Least Squares
OR (ExpB)	Odds Ratio
PAS	Aminosalicylate Sodium
PMT	Protection Motivation Theory
PMT	Protection-Motivation Theory
POM	Point of Medication
PZA	Pyrazinamide
RHS	right hand side parameters of a function
RMP (R)	Rifampicin
RQ	Research Question
S	Streptomycin
SCATM	Sub-Conscious Aversion to Medication
SCT	Social Cognitive Theory
SMS	Short Message Service
SPSS	Statistical Package for Social Sciences
SRT	Self-Regulation Theory
TB	Tuberculosis
TPB	Theory of planned behaviour
TRA	Theory of reasoned action
TTM	Trans-Theoretical Model
UCT	University of Cape Town
UNDP	United Nations Development Programme
UN	United Nations
USA	United States of America
WHO	World Health Organization
ΔExp(B)	Change in odds ratio

Preface to the Thesis

(i) Overview of Problem Statement

Right from the very early days of modern medicine[1] was it observed that patients did not take their medication in accordance with practitioners' recommendations, a phenomenon known as non-adherence. Hippocrates of Kos (*ca.* 460 BC-*ca.* 370 BC), arguably the father of modern medicine, noted that the physician "*….should keep aware of the fact that patients often lie when they state that they have taken certain medicines"* (Jay *et al*, 1984). For centuries therefore, the failure by patients to adhere to treatment regimens as per practitioners' recommendations has resulted in poorer health outcomes and unnecessarily high disease burden globally. There has been even greater anxiety in developing countries, where effective treatment and control of diseases of public health concern such as Tuberculosis (TB) have been significantly hampered by lack of adherence to medications among those infected. Particularly in the case of TB, lack of adherence to treatment by patients has resulted in the emergence of drug-resistance forms of the disease that are more expensive and more difficult to treat, whose potency is even made worse by the nexus and mutually reinforcing relationship between this disease and HIV&AIDS. Consequently, the high death and disease burden rates associated with non-adherence to treatment have had negative impacts on socio-economic development, especially in the developing countries as this study will detail in later sections.

Now in cognizance of the fact that many studies and interventions have been undertaken to reduce non-adherence among patients and yet the challenge still persists, scope was thus seen to undertake this research and perhaps contribute other perspectives into understanding the phenomenon. It was anticipated that such exploration of alternative perspectives could perhaps offer possibilities for the development of more knowledge-based, improved and hopefully more effective interventions against non-adherence to treatment by patients.

Building on the case of Tuberculosis in a developing country context (South Africa), this study problematised the challenge of limited understanding in real-time[2] dynamics of non-adherence, which therefore meant appropriate interventions could not be instituted as and when non-adherence was a problem among patients. It was again the study's contention that treatment scheduling-related factors could also ultimately have a bearing on the severity of other

[1] Medical practice characterized by growing specialization and complex diagnostic and therapeutic technology

[2] Observation of non-adherence exactly at the time it occurs

causative factors of non-adherence. Using data generated from a real-time treatment adherence monitoring device called Simpill (whose functionality is described in greater detail in later sections of this thesis), this study therefore overally sought to investigate the relationship between treatment scheduling-related variables i.e. time scheduling of taking treatment and TB treatment adherence outcomes. The anticipation was thus to contribute alternative theoretical perspectives into the adherence/non-adherence discourse based on a real-time argumentation.

(ii) Research Questions and Methodological Perspectives

The specific research questions for the study, drawn from extensive review of literature and a theoretical framework (detailed later in this thesis) were:

RQ 1: What is the relationship between treatment scheduling-related variables and adherence outcomes?

RQ 2: What are those underlying factors/constructs that are of immediate/precedent importance to (non)adherence in real-time?

RQ 3: What is the effect of a real-time cue to action (in this case the SMS reminder from the Simpill system) towards improving adherence outcomes among TB patients?

Based on a Prospective, Randomized Control Trial and inductive logic, the study sought to answer the above-mentioned research questions through utilization of multinomial logistic regression, ordinary least squares regression and t-tests as data analysis methods. After detailed analysis of the data generated from the Simpill system (supported by literature review), conclusions were drawn on the relationship between treatment scheduling-related factors and adherence outcomes among TB patients, particularly as it related to the way the former interacted with other etiologic (causative) factors of non-adherence. Subsequently, a theoretical model was proposed based on the conclusions.

(iii) Structure of Thesis

This thesis is organized into 6 chapters, and as a case study based on the disease Tuberculosis (TB), the first chapter details the historical perspectives regarding TB, its potency and why it is a developmental challenge. The chapter ends in elaborating on the problem statement as well as giving the study's overall objective.

Chapter 2 delves into extensive literature review on adherence to TB treatment, looking at issues ranging from definitions of adherence, measuring adherence, understanding determinants of the phenomenon as well as looking at interventions that have been implemented to curb the challenge of non-adherence to TB treatment. The chapter concludes with identifying study gaps requiring further enquiry and also discusses the Simpill system forming the basis of this study.

Chapter 3 then explores the theoretical perspectives in adherence to TB treatment, reviewing 5 traditional and an emerging perspective made use of in the quest to understand the phenomenon of treatment adherence. Based on the review, the author then develops a theoretical framework and research questions set to guide this particular study.

Chapter 4 then discusses the study design and methodology employed in this particular study, giving important details on design, study logic, study sites, data collection methods, issues related to ethics and main assumptions in the study.

Chapter 5 then details the findings of the study based on the quest to answer the respective research questions. Chapter 6 finally attempts to rationalize the findings of the study, weight them against previous works and along the way flag alternative theoretical arguments pertaining to etiologic factors of non-adherence. This chapter then ends in proposing a theoretical model, given the name Point of Medication (POM) Model that links various etiological factors to adherence outcomes in real-time.

Chapter 1: Background and Introduction

1.0 Historical Perspectives on Tuberculosis: 'Captain among these Men of Death'

The airborne[3] disease Tuberculosis (TB), caused by the microbe *Mycobacterium tuberculosis*, has for centuries been among the leading causes of morbidity (i.e. illness) and mortality (i.e. death) among human beings. As noted by the author Schoenstadt (2008), forensic studies on skeletal remains of pre-historic humans (4000BC) have shown these to have had Tuberculosis. The same author again notes that tubercular decay has also been found in the spines of Egyptian mummies from approximately around 3000-2400BC. For many years, neither the disease, the microbe causing it nor its transmission dynamics were comprehensible to medical practitioners, although the fatal consequencies of the disease itself were clearly visible. While practitioners such as Hippocrates had around 460 BC described what is now suspected to have been TB then, as '*some form of consumption disease that was invariably fatal*'[4], Ahasan *et al* (2009) contend that the actual tubercle (i.e. the swelling that is the characteristic lesion of Tuberculosis) was first discovered by Sylvius in 1679. According to these authors, Sylvius, writing in his scriptures, entitled *'Opera Medica'* described tubercles as a consistent and characteristic change in the lungs and other areas of 'consumptive' patients.

Another physician, Benjamin Marten, writing in an article entitled *'A New Theory of Consumption'* first came up with the concept of very tiny living creatures being possibly responsible for TB and he also gave insight into the possibility of human to human spread through direct contact (Doetsch,1978). Another author, Daniel (2006) asserts that actual understanding of the pathogenesis (i.e. origin and development) of the disease began with the work of Théophile Laennec at the beginning of the 19th century and was further advanced by the demonstration of the transmissibility of *Mycobacterium tuberculosis* infection by Jean-Antoine Villemin in 1865. Ahasan *et al* (2009) further report that the discovery and isolation *per se* of *mycobacterium tuberculosis* was done by Robert Koch in 1882 through inventing a special

[3] The disease is transmitted when the microbes that cause it are released into the air by coughs, sneezes, or small particles of moisture from an infected person's mouth. These are then taken up by uninfected persons, multiply and if conditions are conducive, result in active TB cases (see (http://www.medicinenet.com/tuberculosis/article.htm)

[4] In fact Hippocrates was noted to have warned physicians not to treat patients at the latter stages of this disease as the result (death) was inevitable and so the physicians' reputation could be ruined as a result of their failure to treat the patients.

technique which enabled visualization of the 'culprit' organism. It is then argued that public health responses against TB began after the discovery and isolation of the bacillus.

In the meantime, while all these advances in Tuberculosis research were going on, scholars such as Daniel (2006) mention that the disease was also claiming its victims along the way. Due mainly to overcrowding in cities and the industrial revolution, the same author points out that TB reached epidemic proportions in Europe and North America during the 18th and 19th centuries, earning the sobriquet, *'Captain Among these Men of Death*'. Spencer (1999) corroborated this by citing cases, one between 1864-1889 wherein Prussian nuns, upon entering the noviciate declared as healthy individuals, would not last 3 years into their service alive due to TB. Another case was cited, wherein between the years 1803-1810, Britain imported some 4000 Mozambican army volunteers to Ceylon (Sri Lanka) to form new regiments. By 1820, the same author notes that 3640 (91%) of these recruits were dead from Tuberculosis.

The author Robert Spencer (1999) cites may other examples, including those of famous people at various levels of society in Europe and America being killed by TB in the 18th and 19th centuries in his book *'The White Death - A History of Tuberculosis'*, thereby underscoring the disease's potency during that period. By 1851, it is reported that TB was actually claiming lives at a ratio of 1:4 in both Europe and America (www.tbalert.org, 30/03/11). Bates and Stead (1993) further argue that the disease actually spread to other parts of the world through European empire-building and colonization.

1.1 Disease of the Poor and Early Efforts Towards Treatment

It is of great interest, as also noted by Robert Spencer (1999) that even in the early days of the disease transforming into a fully-fledged epidemic, TB was observed to be associated with poverty as well as extremely difficult socio-economic and strenuous living conditions. The author elaborates that overcrowding and extremely difficult conditions of living, poor and often high health-risk working conditions made TB a mass killer in England during the first quarter of the 19th Century, time of the advent of the Industrial Revolution. He further mentions that in what is now modern-day Russia as well as in the USA, prisons, by virtue of being overcrowded, were an unending source of TB disease. Before 1910, he further elaborates, no American prisoner on life imprisonment lasted more than 12 years under incarceration due to the disease, and between 1890 and 1895 Tuberculosis was the assigned cause of death in 75% of the prison population in the state of Massachusetts.

It is perhaps the realisation of TB being a disease of poverty that arguably informed early responses and efforts towards treatment. The building of sanatoriums, places into which TB patients were admitted so as to have access to comfortable living conditions, lots of space, fresh air and good nutrition, based on German physician Hermann Brehmer's own personal experiences as a Tuberculosis patient, were among the very first of interventions. The patients recovering in sanatoriums were also reportedly given 'pulmonary collapse' procedures designed to rest infected parts of the lungs and to close cavities. While the sanatorium intervention could certainly have been modest (by comparison to modern-day interventions), it however still did help to contribute in healing of patients in its own way, as noted by Schoenstadt (2008).

1.2 Advances in Tuberculosis Treatment Research

In the meantime, advances in medical research were taking place focusing on finding treatment for Tuberculosis. The textbox below is an excerpt from Schoenstadt (2008) on further developments after the implementation of the sanatoriums intervention:

Text Box 1: Early advances in TB treatment research

Artificial Pneumothorax
Forlanini, an Italian physician, discovered that lung collapse had a positive effect on the outcome of the disease. With the introduction of artificial pneumothorax and surgical methods to reduce the lung volume, active therapy for Tuberculosis began. Although this was an accomplished technique, it was discontinued after 1946 because it proved to be of little benefit.

Radiation
A further significant advance came in 1895 when Wilhelm Konrad von Roentgen discovered electromagnetic radiation, in a range known today as X-rays or Roentgen rays. With this discovery, it was now possible to follow and accurately review the progress and severity of a patient's disease.

Chemotherapy
In the middle of World War II, another breakthrough was discovered - chemotherapy. Administering chemotherapy to other infectious diseases, using sulfonamide and penicillin, had already been underway for several years. However, this method unfortunately turned out to be ineffective against *Mycobacterium tuberculosis*.
Source: Schoenstadt (2008)

In reporting on further advancements in medical research on TB, Daniel (2006) reports on the development of the tuberculin skin test[5] in 1907 by Clemens von Pirquet, through which the latter was able to demonstrate latent TB infection in asymptomatic children in 1910. Research that had been going on around the same time led to the development of the vaccine *Bacille Calmette-Guérin* (BCG), whose first clinical trials began around 1921 and its extensive use began after World War 1**.** The author Daniel (2006) further contends that the modern era of Tuberculosis treatment and control was ultimately ushered in by the discovery of the drugs Streptomycin in 1944 and Isoniazid in 1952, which upon utilisation vastly improved clinical outcomes among TB patients. It would also be noteworthy to point out that in 1960, Dr. John Crofton, a Tuberculosis expert at the University of Edinburgh was the first to propose combination therapy (that involved the drugs Streptomycin, Isoniazid and PAS-Aminosalicylate Sodium) to improve efficacy of the treatment available then. This was among other measures including pasteurization of milk, tuberculin testing of cattle and radiography for early detection of TB that were employed at that time to strengthen TB treatment and control interventions (www.tbalert.org, 30/03/11).

1.3 Tuberculosis towards the turn of the 21st Century: A Developmental Concern

The United Nations Development Programme (UNDP) notes in its Human Development Report (2003) that the 1990s were a very significant period with regards to reversal of human development indicators, particularly in the third world countries. In the backdrop of failed economic structural adjustment programmes and declining volumes of international aid, previous gains in various aspects of development (e.g. access to education, health, employment, food security, rural development etc.) began to decelerate and in worst case scenarios reverse. Global poverty increased dramatically, but with a skew towards developing countries, and Sub-Saharan Africa in particular, according to the same sources. In this context, without concidence at all, cases of Tuberculosis (*disease of the poor*) also began to rise in Sub-Saharan Africa in the 1990s, and this was complicated by the then-worsening HIV&AIDS pandemic[6]. The organization TB Alert (www.tbalert.org, 31/03/11) reports on how in the year 1993, the World Health Organisation (WHO), in cognizance of the escalating crisis induced by

[5] A tuberculin skin test is done to see if one has ever had Tuberculosis (TB). The test is done by putting a small amount of TB protein (antigens) under the top layer of skin on one's inner forearm. If one has ever been exposed to the TB bacteria (*Mycobacterium tuberculosis*) their skin will react to the antigens by developing a firm red bump at the site within 2 days.

[6] See section *1.4.5* for more detail

Tuberculosis, finally declared the disease a global emergency[7], estimating that one third of the world's population (2 billion people) were latently infected with TB and 7-8 million cases of active TB occurred each year. In that year TB was also noted to having killed more people than in any other previous year in history. That was the period in which the Directly Observed Treatment-Short course strategy (DOTS) was set out and implemented by the WHO as a roadmap towards effectively containing the devastating impacts of the disease and controlling its further spread at the global scale. The DOTS strategy comprises of a multi-pronged approach aimed towards mobilizing financial and administrative support to fight TB, diagnosis of patients by quality-ensured sputum smear miscroscopy, standardized short course anti-TB treatment given under direct and supportive observation, ensuring regular, uninterrupted supply of quality anti-TB drugs as well as standardized recording and reporting on Tuberculosis treatment (http://www.who.int/tb/dots/en/,11/04/05). The component of DOTS which is within the scope of this study i.e. *standardized short-course anti-TB treatment given under direct and supportive observation'* will be explored further in Chapter 2.

1.4 Analysis of Current Trends in Global TB Disease Burden (1990-2008/9)

1.4.1 Defining Disease Burden

According to the World Health Organisation's Global TB Report of 2010, 'disease burden' is a construct essentially made up of 3 components, namely: the disease's Incidence, Prevalence and Mortality rates. These are defined as follows:

Incidence Rate: The number of new and relapse cases of Tuberculosis (all forms) occurring in a given year. Relapse cases are defined as people who have been previously treated for TB and for whom there was bacteriological confirmation of cure and/or documentation that treatment was completed. Such cases may be true relapses or a subsequent episode of TB caused by re-infection.

Prevalence Rate: This is defined as the number of cases of TB disease (all forms) at a given point in time (*usually* at the middle of the year).

Mortality Rate: This is defined as the number of deaths caused by TB, excluding deaths occurring in HIV-positive TB cases, according to the definitions used in the 10th revision of the

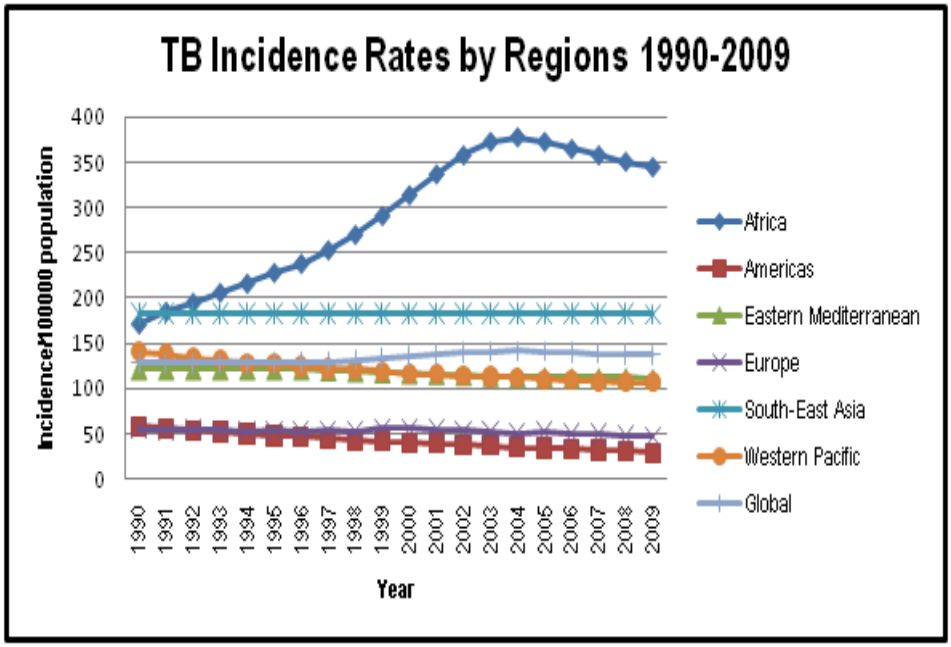
[7] See also Grange&Zumla (2002)

International Classification of Diseases (ICD-10). Estimates of deaths caused by TB in HIV-positive cases are presented separately.

Using the above defined indicators therefore, the following section will seek to show further proof why Tuberculosis has warranted global attention as a major public health concern from the early 90s into the new millennium.

1.4.2 Global Incidence Rates

The graph below gives global Tuberculosis incidence rates between 1990 and 2008, including scenarios in which patients had HIV co-morbidity (approximately 15%).



Source of data: WHO (2010)[8]
Fig 1.1: Tuberculosis Incidence Rates by Regions 1990-2009

As noted in the MDGs report of 2010 and in the graph, Fig 1.1 above (generated using WHO data), there seems to be emerging evidence of the global incidence of Tuberculosis gradually receding. The data shows incidence dropping to about 137 [131-145] cases per 100000 people in 2009, a fall from the approximated 142 [135-149] cases per 100000 (peak incidence rates) in 2004. The Global Tuberculosis Control Report (2010) however contends that slow reductions in

[8] http://www.who.int/tb/topics/en/, (accessed 13/04/2011)

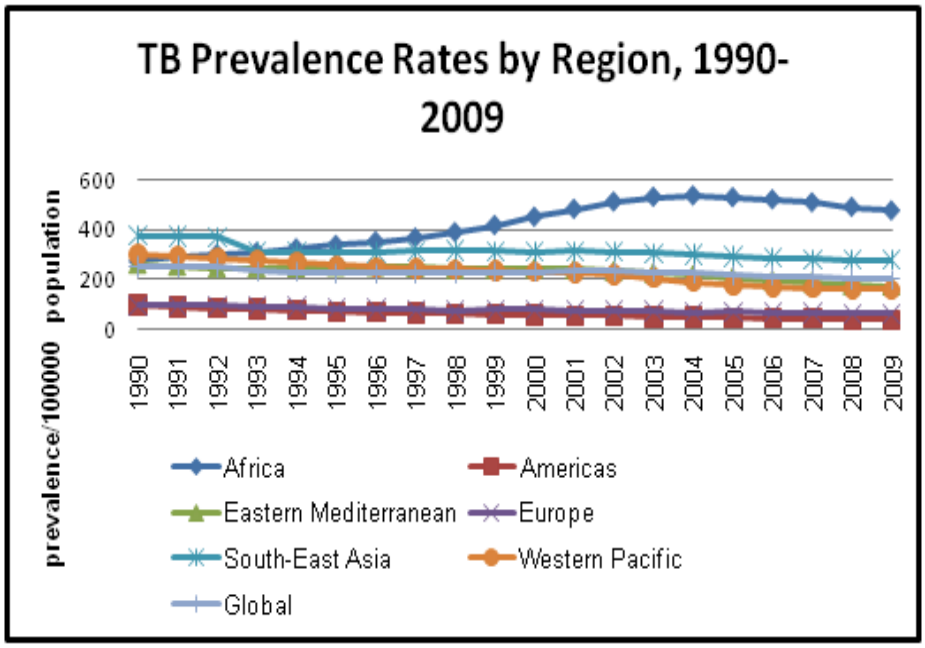
incidence rates per capita continue to be outweighed by increases in population. Attempts at breaking the incidence data available according to sex have reportedly indicated that women (defined as being from 15 years onwards) account for approximately 3.3 million Tuberculosis cases i.e. 35% of all cases.

Based on a further look at the regional data, it can been seen that Africa has had the highest incidence rates over approximately the past 2 decades, and it is also no concidence that the continent (particularly in the Sub-Saharan Africa region) has some of the world's highest poverty levels[9]. Indeed conditions of poor health infrastructure, unsustainable population growth and increasing poverty have created fertile ground for the proliferation of the Tuberculosis epidemic in Sub-Saharan Africa. It is also evident that the afore-mentioned global peak in incidence rates (2004) was in fact as a result of the sharp peaking of TB cases in Africa at that same period. In fact, some countries on the African continent deserve special mention as they are shown by the latest data (2009) to be among the top 5 countries with the highest TB cases in the world, and these are notably South Africa and Nigeria.

1.4.3 Global Tuberculosis Prevalence Rates

The graph, Fig. 1.2 below shows TB prevalences by WHO region from 1990-2009. The aggregated global rates are also part of the curve for comparison purposes. In looking not only at the global prevalence rates but also at the regional level, the general message appears to be that the prevalence of the disease has been gradually dropping over the past 2 decades. UNDP (2010) notes that while an increasing number of patients with TB are being successfully treated, hence explaining the general decline in the number of TB-related deaths between 1990-2008, morbidity (i.e. illness) will still remain in its millions due to inadequacy of interventions against the disease, including among other things quality of care. This is so especially in the developing regions of the world in general and sub-Saharan Africa more specifically (see also WHO, 2010).

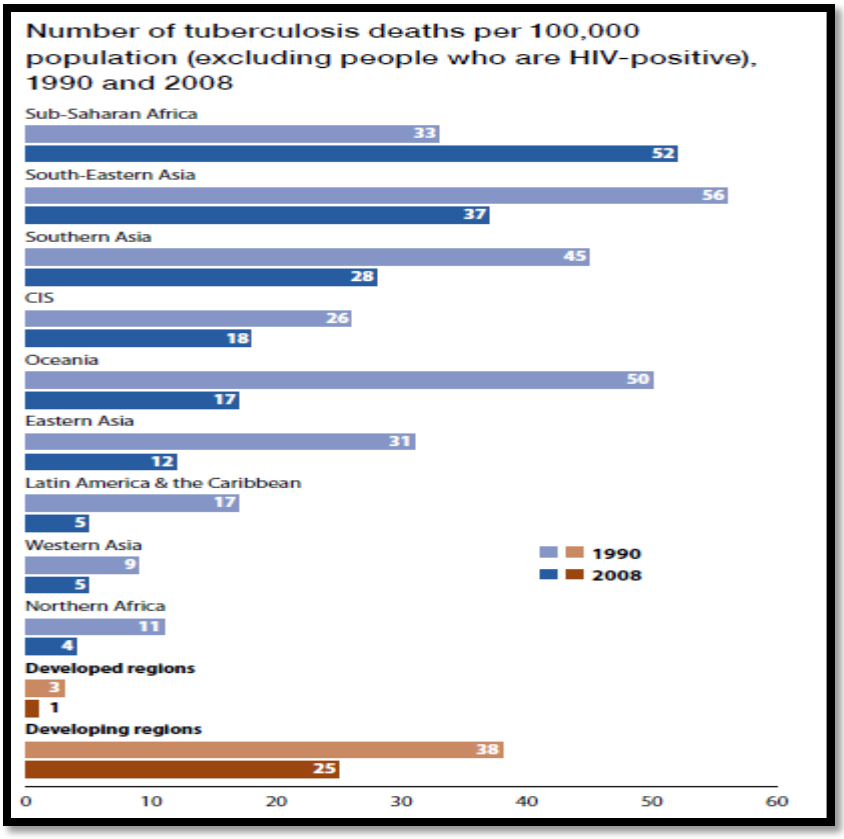
[9] Note again, disease of the poor



Data source: WHO (2010)
Fig 1.2: TB prevalence by regions (1990-2009)

1.4.4 Global Tuberculosis Mortality Rates

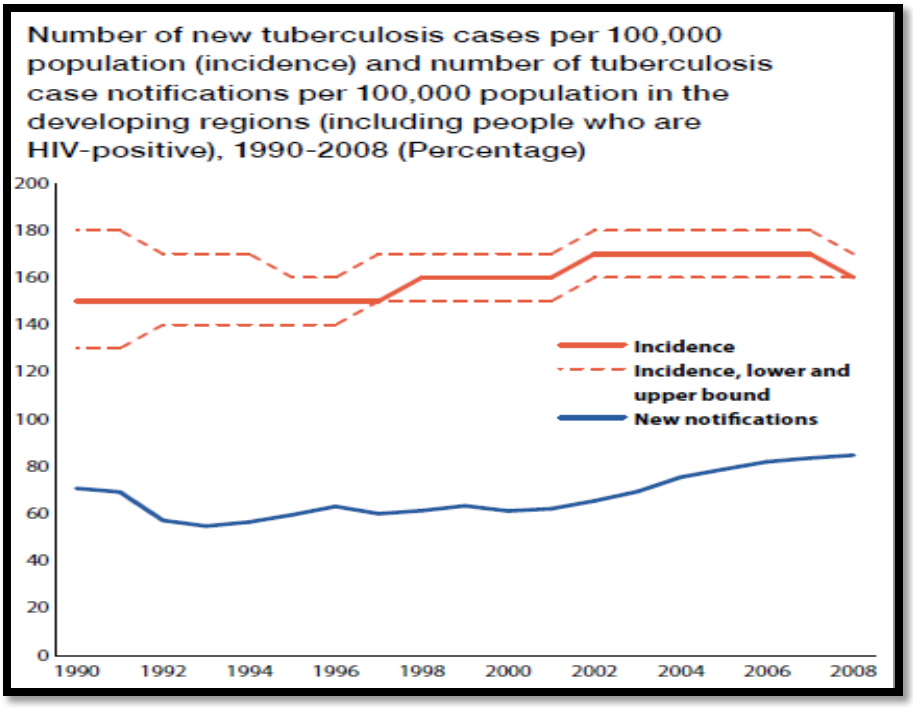
The final indicator for disease burden is mortality rates, and with respect to that particular indicator, current trends show, as estimated by the TB Alliance (2010) that the disease kills an average of about 2 million people per year world over, an astonishing rate of a person per second! Fig. 1.3 below illustrates the differences in mortality rates between the years 1990 and 2008 by region. Based on the evidence from the graph, it is also of concern that, while mortality rates appear to be on the decline in other regions world over, rates in Sub-Saharan Africa in fact seem to be increasing. This is sadly a consequence of the nexus between the disease and HIV&AIDS (discussed further in the next section *1.4.5* to follow), which has resulted in the proliferation of a double-edged pandemic whose disease burden impacts, including increased mortality rates, are disastrous.



Source: UNDP (2010)
Fig 1.3: TB Deaths per 100000 population by Region, 1990 & 2008

1.4.5 The Nexus between TB and HIV&AIDS in Developing Countries

The nexus and mutual reinforcement between TB and HIV&AIDS has been extensively researched on and documented (see UNDP, 2010; WHO, 2010; www.tbalert.org, 30/03/11, MSF-OCA, 2007; Haas and Des Pres, 1994, *inter alia*). Proliferation of the HIV&AIDS pandemic has unfortunately also resulted in the reversal of gains attained in the fight against Tuberculosis. It is a sad reality therefore that while TB incidences have been gradually falling, as discussed earlier on, HIV&AIDS is worsening new case notifications. The graph, Fig 1.4 below, which shows TB incidence rates in developing regions, including patients with HIV, validates this argument as well as show-cases the public health concern that Tuberculosis continues to be in these developing countries.



Source: UNDP, 2010
Fig 1.4: Incidence and new notifications of TB in developing Regions 1990-2008

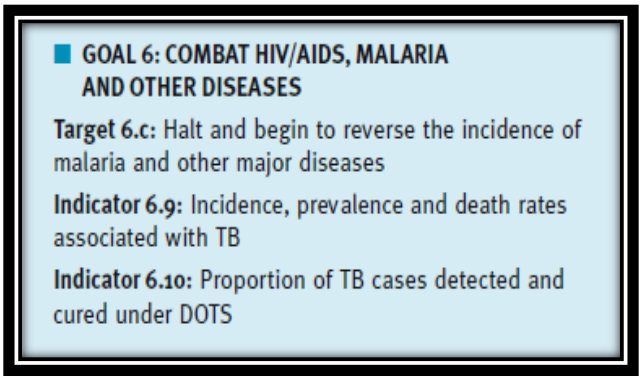
1.5 TB Disease Burden as a Threat to Human Development

Ultimately therefore, the high disease burden induced by Tuberculosis has had the highest cumulative impact in the hardest-hit developing countries, as reported by Raviglione *et al* (1995), particularly through straining already limited health-care facilities and budgets, as well as debilitating the most economically productive and reproductive individuals. High morbidity and mortality rates have also been linked with reduced quality of life, increasing dependency ratios (as the most economically productive die or cease to work) and in all these consequencies, resulting in the stagnation of human development or even reversal of past gains in developing countries. In their assertion of TB causing and deepening poverty, the organization TB Alliance (2010) reports of a case-in-point from one of their studies in which they established that a TB patient's income declined about 30% during their time of illness. With the contention by Corbett *et al* (2003) that TB was responsible for more years of healthy life lost than any other infectious disease except AIDS and Malaria (with AIDS being the only one with higher mortality rates), the urgent need to have global targets to control the negative human development impacts of Tuberculosis getting into the 21st Century could thus never be over-emphasised.

1.6. Global targets for Reducing Tuberculosis Disease Burden into the 21st Century

Since the turn of the 21st century, in due realization of the far-reaching impacts of Tuberculosis disease burden at the global scale, the United Nations (UN) and its major multi-lateral aid partners prioritized prevention and control of the disease in key development cooperation frameworks meant to facilitate and enable global human development. For starters, when the UN's Millennium Development Goals (MDGs)[10] were set as a roadmap for eradicating poverty and promoting human development in the new millennium, effective management of the TB epidemic was considered as one of the crucial milestones that was set to have been achieved by 2015, hence the coining of related targets under MDG 6, as shown in the textbox below:

Textbox 2: MDG Goal 6



Source: www.undp.org/mdg (accessed 05/04/11)

The other global roadmap with Tuberculosis prevention, management and control targets is the Global Stop TB Partnership's 'Stop TB Strategy[11]', which basically has 6 main aspects that are outlined below:

- Pursuance of high-quality DOTS expansion and enhancement,
- Addressing TB/HIV, MDR-TB, and the needs of poor and vulnerable populations,
- Contributing to health-system strengthening based on primary health care,
- Engaging all care providers,
- Empowering people with TB, and communities through partnership and
- Enabling and promoting (TB-related) research

[10] See Appendix 6
[11] see Appendix 5

1.6.1 The Stop TB Partnership's Global Plan to Stop TB, 2006–2015

This plan was launched in January 2006 and it mapped out the magnitude to which interventions included in the Stop TB Strategy needed to be implemented in order to realize the 2015 targets. In the year 2010, as the mid-point of the original 10-year plan drew closer, the plan was updated. This updated version of the plan, which covers the five years from 2011 to 2015, includes an updated set of targets (WHO/HTM/STB/2010.2). The major targets for 2015 in this updated plan were defined as follows:

- diagnosis, notification and treatment of approximately 7 million cases;
- a treatment success rate among sputum smear-positive cases of 90%;
- HIV testing of 100% of TB patients;
- enrolment of 100% of HIV-positive TB patients on Cotrimoxazole preventive therapy (CPT) and antiretroviral therapy (ART);
- provision of Isoniazid preventive therapy (IPT) to all people living with HIV who are attending HIV care services and are considered eligible for IPT;
- testing of 100% of previously treated TB patients for MDR-TB, as well as testing of any new TB patients considered at high risk of having MDR-TB (estimated globally at around 20% of all new TB patients);
- enrolment of all patients with a confirmed diagnosis of MDR-TB on treatment consistent with international guidelines;
- mobilization of US$7 billion per year to finance implementation of the Stop TB Strategy, plus around US$1.3 billion per year for research and development related to new drugs, new diagnostics and new vaccines.

The textbox below gives the targets set with respect to fighting the Tuberculosis scourge in the context of the Stop TB Partnership process

Textbox 3: Stop TB Partnership Targets

Source: WHO (2010) (WHO/HTM/STB/2010.2)

It must once again be re-emphasised that DOTS remains at the core of the Stop TB Strategy and is anticipated to be the main driver behind realization of the Tuberculosis disease burden reduction targets under both the Millennium Development Goals and the Stop TB Strategy. The World Health Organisation has reported that through DOTS, high treatment success rates have been attained. The organization reports that out of a total of 49 million patients that have been treated under DOTS programmes between 1995 and 2009, 41 million of them have been successfully treated. The organization further claims that up to 6 million lives have also been saved through implementation of DOTS and the Stop TB Strategy between the same time period (WHO, 2010). It is indeed without doubt that these statistics are most definitely encouraging.

1.7 Problem Statement

It certainly is without question that to date, significant milestones have been attained with respect to prevention, treatment and control of the Tuberculosis epidemic at the global scale, as shown in some of the evidence above. However, it is unfortunate that the age-old threat of treatment non-adherence among patients (i.e. not taking medication as recommended by the health practitioner) still remains a major challenge in the battle against the Tuberculosis epidemic. An otherwise easy-to-treat disease, whose treatment regimens could otherwise provide at least 90% life-long protection from active disease and development of drug resistance has over the years been spiraling out of control, with treatment adherence challenges among sufferers playing a key role (Barnes and Barrows, 1993). Even under the World Health Organisation-promulgated DOTS programme, which is an international flagship in TB treatment, scholars such as Smith (1999), Bello (2010) and Jaggarajamma *et al* (2006) have noted the

continued existence of treatment non-adherence challenges, especially in developing country contexts. Marshall (2007) further notes with concern, of cases where adherence rates as low as 40% having been recorded under DOTS, a far-cry from the ideal 85% envisaged under the strategy. Indeed such levels of non-adherence surely are a cause for concern and a major drawback in the successful treatment and prevention of further spread of the disease. This is particularly so in cognizance of the fact that non-adherence to anti-TB treatment among sufferers has been attributed to be among the chief causes of the emerging threat of Multi-Drug Resistant[12] (MDR) and Extensively Drug Resistant[13] (XDR) TB strains. It goes without saying that these drug-resistant forms of TB, being more difficult and more expensive to treat as well as having higher case fatalities[14] pose a greater danger from a public health perspective upon being spread (see Ahllburg, 2000; Berry and Kon, 2009). The situation would even be worse in many developing countries where an increase in MDR and XDR-TB cases could further entrench an already devasting nexus between ordinary TB and HIV&AIDS, whose high disease burden effects already choke grossly underfunded health service delivery systems (also see Snider and La Montagne,1994). Such context therefore necessitates further research aimed at enhancement of the understanding of treatment adherence issues in TB patients, so as not only to support already existing interventions aimed at managing and controlling the disease, but to also potentially contribute towards mitigating a looming public health disaster due to MDR and XDR-TB. This is the thinking upon which this study is based. Now in its own attempts to contribute towards a deeper understanding of the age-old challenge of treatment non-adherence, this study argues that there are lurking gaps in appreciating the real-time[15] perspectives of non-adherence, hence its focus on empirically validating this premise. While the detailed argumentation for the study is further built upon from Chapter 2 onwards, below is its overall objective.

[12] MDR TB is caused by Mycobacterium Tuberculosis strains that are resistant to at least Isoniazid and Rifampicin,the most potent first-line anti-TB drugs

[13] Extensively drug-resistant Tuberculosis (defined as MDR-TB plus resistance to a fluoroquinolone and at least one second-line injectable agent: amikacin, kanamycin and/or capreomycin).

[14] The risk of death from the forms of TB that patients possess

[15] The concept of 'real-time' in this case refers to appreciating the dynamics and causative factors of adherence/lack of it as and when it exactly happens

1.8 Overall Study Goal

This study therefore seeks to explore the real-time dynamics of treatment non-adherence among Tuberculosis patients i.e. building appreciation on the role of treatment scheduling/timing on adherence outcomes, as well as increasing understanding on what effects a real-time response to non-adherence can ultimately have on treatment success. This will be achieved through the empirical analysis and modeling of patients' data generated by the Simpill treatment adherence monitoring system (whose functionality is decribed in latter sections), from a pilot study in the Western Cape Province of South Africa.

1.9 Chapter Conclusive Remarks

Now after having explored the history of the disease Tuberculosis, its disease burden and developmental impacts over the years as well as advances in efforts to control its spread, this chapter then went on to problematise the issue of treatment adherence as well as setting the study's context through stating the overall research goal. With this important background therefore, the next step is to get deeper into the issues of adherence, defining it as well as looking extensively at literature on the subject matter, a feat that the following Chapter 2 intends to achieve.

Chapter 2: Literature Review on Adherence to Therapeutic Regimens

2.1 Defining Adherence

> *[The physician] should keep aware of the fact that patients often lie when they state that they have taken certain medicines ….***Hippocrates of Kos *(ca. 460 BC – ca. 370 BC)***
>
> ***Quote in Jay et al (1984)***

The above quote by Hippocrates of Kos (*ca.*460 BC - *ca.*370 BC) shows that the problem of patients' not adhering to treatment has been in existence since the beginning of modern medicine[16]. As noted by Litt and Cuskey (1980), the subject of adherence has increasingly grown in importance over the years in the medical field, if the amount of researches, publications and international discourse dedicated to the subject area are anything to go by. Although granted and universally accepted that the challenge of patients failing to adhere to treatment is a major problem in the field of human health, where there seems to be a long-standing disagreement among practitioners however is on the actual definition of adherence itself and what parameters actually make up this definition. It is of interest to observe that while conventional research on adherence has mainly focused on intake of medication, and hence the various extents to which patients followed health practitioners' instructions on how to take prescribed drugs, this view has not been without its fair share of critique. For instance, citing a conclusion from its 2001 Adherence Committee meeting, the World Health Organisation noted the conventional 'medical' focus in defining adherence as having been too narrow and not adequately taking into cognizance all the other numerous health-related behaviours (e.g. exercising, dieting, check-up appointments etc.) that extended beyond taking prescribed pharmaceuticals and yet still required being adhered to (WHO, 2003). As further critiqued in the same adherence committee discussions of the WHO, the term *'instructions'* also used in traditional adherence definitions was again noted to imply that the patient would just be relegated to merely being a passive, yielding recipient of expert advice compared to being a more proactive collaborator in the whole treatment process .

[16] Medical practice characterized by growing specialization and a complex diagnostic and therapeutic technology

Based on the earlier work of Haynes (1979) and Rand (1993), the World Health Organisation settled on a hybrid definition for adherence, i.e. *"the extent to which a person's behaviour…taking medication, following a diet, and or executing lifestyle changes, corresponds with agreed recommendations from a health care provider"* (WHO, 2003 pp9).

This definition was therefore seen to be more broad-based and taking into account the issues of concern, as raised above. It is indeed therefore important to acknowledge that adherence takes many other forms of health behaviour beyond just the taking of pharmaceutical drugs. However, this study, because of its greater interest in anti-Tuberculosis medication and for purposes of focus, will narrow down to medication adherence, defined by Cramer *et al* (2008) as referring to the act of conforming to the recommendations made by the health service provider with respect to timing, dosage and frequency of medication taking. The same authors further go on to put the definition in another manner, as the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen.

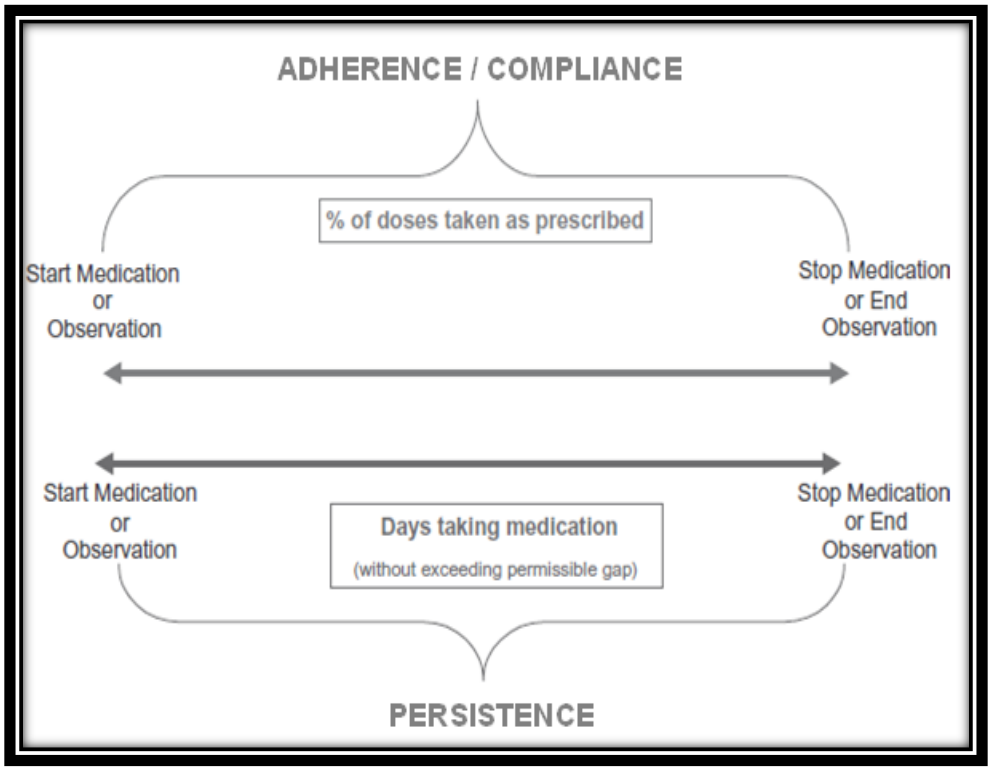
2.2 Adherence Vs Compliance?

It does also appear like the World Health Organisation's perspective seeks to differentiate between adherence and compliance, with their argument being that in the case of adherence, there is patients' agreement to the recommendations by the health practitioner, whereas the latter could be more 'command-driven' (WHO, 2003). However, Cramer *et al* (2008), presented a different argument, opting instead to use the term 'compliance' as primary term and 'adherence' as the synonymn, after their extensive review of literature from journal indexing services such as MEDLINE[17] and PubMed[18] overtly supported this assertion. The same authors further went on to posit therefore that they had not found any authoritative support that *'adherence'* was less derogatory and was better preferred by patients compared to *'compliance'*. In a way giving an apparently opposing view to that of the WHO, Feinstein (1990) had earlier on stated that in his view, the term adherence was '*too sticky'* for his liking, opting rather for the term compliance. Being that as it may however, this report will go with Cramer *et al* (2008)'s perspective and between the two interchangeable options (adherence and compliance), will opt for use of the term *'adherence'*. Interestingly still, Cramer *et al* (2008) furthermore seem to

[17] MEDLINE is the United States' National Library of Medicine's premier bibliographic database covering the fields of medicine, nursing, dentistry, veterinary medicine, the health care system, and the pre-clinical sciences.

[18] PubMed is the freely accessible online database of biomedical journal citations and abstracts created by the U.S. National Library of Medicine (NLM®). MEDLINE is a component of PubMed.

suggest that there is rather greater scope in attempting to distinguish between adherence/compliance and persistence, as in the diagram below:



Adapted from Cramer *et al* (2008)
Fig 2.1: Difference between adherence/compliance and persistence

In seeking to distinguish adherence/compliance from persistence, the above-mentioned authors note that medication persistence is when a patient conforms to the recommendations of taking treatment for the prescribed length of time, in other words, the duration of time from initiation to discontinuation of therapy. In spite of this separation however, it still follows that both concepts (i.e. adherence/compliance and persistence) are equally important in ensuring successful treatment outcomes among patients on treatment for chronic[19] ailments such as Tuberculosis. Not only would it be important for the patients to conform to treatment prescription recommendations (i.e. adherence/compliance), but it would also be just as important to take the treatment for the recommended period (i.e. persistence).

[19] Diseases which have one or more of the following characteristics: they are permanent, leave residual disability.are caused by non-reversible pathological alteration, require special training of the patient for rehabilitation, or may be expected to require a long period of supervision, observation or care (Dictionary of Health Services Management 1982)

2.3 Adherence to Tuberculosis Medication

Just like in many other chronic diseases, a lot of research and attention has been put into understanding Tuberculosis treatment adherence, so as to perhaps improve the disease's prevention and control, in cognizance of its already discussed public health impacts. In the views of this author, four main strands are quite apparent from TB treatment adherence literature. The first one is the debate on how best to measure adherence itself, the second being on determinants of adherence, the third being on interventions to improve TB treatment adherence and the fourth pertaining to discourse on theoretical underpinnings in studying TB treatment adherence. The rest of this chapter will, over the next sections discuss the first 3 strands and the fourth one will be dealt with in Chapter 3 to follow.

2.3.1 Measuring TB Treatment Adherence

Urquahart (1996) posits that measuring adherence for Tuberculosis has conventionally either been based on process-oriented or outcome-oriented definitions. In the case of outcome-oriented definitions, the end-results of treatment i.e. completion and/or cure rates are deemed to be the indicators of success. In the other case of process-oriented definitions, variables such as pill counts, prescription refill rates and appointment-keeping have been used as indicators of adherence. The table below attempts to categorise adherence measures into the 2 afore-mentioned definitions.

Process-Oriented	Outcome-Oriented
• Measurement of serum concentration of the medication, its biological marker etc. • Direct Observation • Assessment of clinical response at periodic intervals • Prescription refill rates • Electronic monitoring systems	• Treatment completion rates • Cure Rates

Data source: Marshall (2007); Urquahart (1996).
Table 2.1: Process-oriented and Outcome oriented adherence measures

It is of interest to note from literature, that this categorization alone inevitably leads into the debate over which methods most accurately measure treatment adherence among Tuberculosis patients. Authors such as Jay *et al* (1984) argue that quantitative or qualitative analysis of body fluids to determine the presence/absence of the prescribed medication, its metabolite or an

added marker substance provides the most objective adherence measure. This argument seems also to find support in the article by Elizaga *et al* (1997), which was based on the monitoring of adherence among TB patients through detection of the drug Isoniazid[20] (INH) in urine samples. Without taking away any merits from this assertion however, a number of weaknesses have been observed in this method of measurement. For instance, a number of scholars such as Pozsik(1993), Meichebaum and Turk(1987) and Gordis (1979) have critiqued the use of urine tests for residues of INH, as these could vary as a consequence of time of medication ingestion as well as varying levels of bio-availability according to patients. Cost implications and practicality of such analyses, as well as their utilization as adherence measures beyond clinical trials have also been questioned by Jay *et al* (1984).

Other methods such as self-reporting have also had their own fair share of critique. Dubanoski and Cohen (1998) warn that self-reporting could be prone to bias by the patients themselves, as they might misrepresent their patterns of taking treatment to appear adherent e.g. through quickly ticking their treatment records before the next visit to the clinic. Although Haynes and colleagues (1980) still insist that self-reporting, if done in a non-judgemental and non-threatening manner could yet still yield positive results with respect to giving an idea of when and how often patients missed taking treatment, in a latter article in 1982, Haynes himself reports that though some patients would open up about non-adherence, the risk of under-estimation still remained significant. The shortcomings in this method would also closely link with those for pill counts, where patients, out of the need to be seen as having been adhering, can easily alter the amount of medication in the container before the pill count by the health-worker/practitioner, as argued by Durnbar (1980). It means therefore that having the 'right' balance on the number of pills at pill-count might not necessarily guarantee that a patient would have been taking their medication appropriately prior to the pill count.

The use of appointment-keeping or frequency of visits to the clinic as measure of patients' adherence, while credible, could easily be determined or compromised by proximity to the clinic where the patient would be undergoing directly observed treatment (DOT)[21]. Such counter-argument is clear from Shargie and Lindtjørn (2007)'s study of TB treatment adherence determinants in Ethiopia.

[20] Isoniazid (INH) is a first-line drug used in the treatment of Tuberculosis,see Appendix 1

[21] DOT is a component of the Directly Observed Treatment-short course (DOTS) scheme for treating Tuberculosis where patients are observed by a health practioner or primary carer as they take medication

Yet another method of measuring adherence to treatment, the use of electronic monitoring devices, emerged in the later stages of the 20th Century. One of the leading devices under this domain is the Medication Event Monitoring System (MEMS). Developed by the Swiss company Aardex Ltd, the MEMS is premised on a computerized system whereby a micro-processor chip is built into the cap of an ordinary pill dispensal bottle, and everytime it is opened, the event is recorded and stored in a computer server (see e.g. Cramer *et al* 1989 ; Feinn *et al*, 2003). Aardex Ltd itself has documented a bibliography of at least 694 studies since the year 2000 in which their device was being used as a means of monitoring and measuring adherence for a wide range of illnesses. Of course while the electronic monitoring of adherence through the use of devices such as the MEMS has been deemed the most effective means of measuring adherence, against which other methods have even been benchmarked (Marshall, 2007), the limited spread of the method due to high costs of access (see WHO, 2003) have limited its use in developing countries. Tuberculosis-related studies found as part of the rigorous review of literature for this thesis and based on use of the MEMS (e.g. Aillinger *et al*, 2008) were noted to having been done in the developed countries, particularly in the USA on Latent Tuberculosis[22] Infection cases. This was taken to mean the general non-availability and limited usage of not only the MEMS but other electronic treatment adherence monitoring systems in developing country contexts. Instead, there was wide documentation on the utilisation of the other non-electronic monitoring methods already discussed above. This suggested such methods as having being more feasible (cost-wise), hence their sustained use as the more realistic adherence measurement methods in less developed countries.

[22] Infection with *M tuberculosis* that has been contained by the host's immune system and thus does not infect others. (McGraw-Hill Concise Dictionary of Modern Medicine. © 2002 by The McGraw-Hill Companies, Inc.)

2.3.2 Outcome-based Adherence Indicators

Outcome-based indicators (i.e. completion rates and cure rates), which have also been used in measuring adherence to TB treatment, in their own right do make useful proxies as well, as asserted by the WHO (2003). The argument for utilization of completion rates as a proxy for adherence is that a patient who does not complete their treatment or at least take it to an acceptable minimum number of times has not been adherent, while the thinking with respect to utilization of cure rates as proxies for adherence is that, after exposure to a cocktail of antibiotics for the requisite minimum period, the Tuberculosis infection in a patient should at least succumb and at best be eliminated. For the latter case it implies therefore that for those patients failing treatment after the 6-9 month period, this should generally point towards inconsistencies in taking of medication. However, this deduction for adherence measure based on cure rates would need to be treated with caution, as warned by Jay *et al* (1984) when they assert that with most therapies, the correlation between drug dosage and therapeutic response is nowhere near being discreet. In other words, other co-morbidities or other unknown inhibiting factors might confound the relationship between taking of drugs and treatment outcomes, so this would need to be kept in mind when using treatment outcome as a proxy for lack of adherence. This is particularly so when considering negative treatment outcomes.

2.4 So What is the Best Way to Measure Adherence?

Based on the discussions above, it must then be emphasized at this point that there seems to be no general agreement among scholars and practitioners on what could be deemed the 'gold standard' in measuring adherence among patients on TB medication. Even in looking at the electronic monitoring systems, there still remains a weakness in that opening of the pill bottle might not necessarily translate to the patient actually ingesting the medication. Dubanoski and Cohen (1998) advocate for composite measures, in which various measures of adherence are combined to give one aggregated measure. They argue that having a composite measure of adherence, capturing various types of information (from both outcome and process-based indicators) would provide a more comprehensive, more stable (shared error variance among individual measures) and a more internally consistent measure. While this study generally agrees with the above-mentioned authors, it still contends however, not-withstanding the merits and/or de-merits of either measure, that process-oriented measures of adherence could in fact be considered more important than outcome-based adherence measures with respect to TB treatment (and perhaps even for other chronic illnesses too). The question then would be why? In response, it is this study's argument that if non-adherence is accurately predicted and

observed during the course (i.e. process) of treatment, then appropriate response strategies could be implemented before such behaviour compromises a patient's health. This would be in contrast to having to wait until the end of treatment when perhaps it could be too late for non-adherers, either through treatment failure or development of drug resistance etc.

2.5 Adherence as a Diagnostic Issue

Jay *et al* (1984) report that adherence is conventionally defined in absolute binary terms i.e. a patient is either adhering (the desirable) or not adhering to treatment (the undesirable), and this premise has also generally guided empirical work on the subject matter. The same authors however contend that instead of just considering non-adherence as an aberrant behaviour (which ultimately it is, of course); it could be more useful for a health practitioner to view it as an important diagnostic tool. This implies that it can be useful in differentiating and providing further understanding into the various socio-cultural, socio-economic, psychological and iatrogenic[23] causatives as to why patients do not take medication as recommended by their health practitioner. In other words, detection of occurrence of non-adherence among patients during the course of treatment can assist in identifying underlying causes and then result in the activation of appropriate response strategies to mitigate the problem. What these authors (Jay *et al*, 1984) were however not clear about was how then incidence of non-adherence during the course of treatment could be more efficiently noted and used to determine its major causatives and thereafter perhaps find use as a means of improving treatment success among patients. This is the point, according to arguments in this thesis, that the issue of real-time detection and response to non-adherence thus becomes paramount.

This study therefore contends that there is a certainly a missing link in terms of a widely used approach (at least according to reviewed literature) that could help in detecting non-adherence at the point that it happens among TB patients and thereafter stimulate one form of immediate intervention or another. Such approach would contribute towards filling a gap that had been identified by authors such as Urquahart (1992), whose argument was that there is need for a much stronger emphasis on timing of treatment (i.e. looking at outcomes when treatment is/was supposed to have been taken) into the definition of (non)adherence so as to have a more holistic picture of the phenomenon. This particular research indeed anticipates to add value

[23] Caused by treatment or diagnostic procedures. An iatrogenic disorder is a condition that is caused by medical personnel or procedures or that develops through exposure to the environment of a health care facility (Mosby's Medical Dictionary, 8th edition. © 2009, Elsevier)

towards a more detailed understanding of TB treatment adherence dynamics in real-time through studying data from the Simpill monitoring system, a tool with the potential to close the above-mentioned gap in real-time treatment monitoring and intervention, as will be discussed in detail later in this Chapter. Meanwhile, the next section discusses literature that elaborates on determinants of treatment adherence among TB patients.

2.6 Understanding Determinants of Treatment Adherence

2.6.1 Socio-economic factors

Numerous studies have for many years been conducted to establish the determinants of patients' adherence to Tuberculosis treatment world over. Authors such as Robert Spencer (1999) note that as early as the beginning of the 19th Century, TB was already being associated with poverty, dire living and working conditions as well as insufficient nutrition among other related factors which made it easier for the microbe *Mycobacterium tuberculosis* to easily spread. Even after the discovery of treatment, studies further went on to show that poverty-related factors still had a bearing on patients' adherence to treatment itself as well (see Liefooghe *et al*, 1995). Other studies, for instance, Mateus-Solarte and Carvajal-Barona (2008) pointed to factors such as overcrowding having a negative effect on patient adherence, while low incomes meant poor patients could not buy anti-TB drugs for themselves in cases of drug stock-outs, as noted by Bello (2010) in a study in Nigeria. Tanguis *et al* (2000) also showed the positive correlation between low socio-economic status and low adherence. Just to emphasise on the links between poverty and non-adherence, Baussano *et al* (2008) also showed in their study how homelessness correlated positively with non-adherence. A lot of other studies, including among them the Ethiopian case study by Shargie and Lindtjorn (2007) have also demonstrated the impacts of structural challenges, which are related to low socio-economic status, such as staying too far away from the nearest clinic, inability to afford transport to the nearest health centre to access treatment, as being significant challenges in as far as patients failing to adhere to their anti-Tuberculosis treatment was concerned.

2.6.2 Supportive Networks around the Patient

The mere fact that Tuberculosis is an infectious airborne disease presents extreme difficulty with regards to having adequate support for treatment adherence around a patient. With family members/co-habitants having concerns about becoming infected themselves upon being in close proximity to the TB patient; it thus becomes quite easy for the patient to be stigmatized and not be given enough psycho-social support requisite for them to adhere to treatment. This is evident in studies such as done by Sukwa *et al* (1999) in Zambia and the one by Cramm *et al* (2010) in the Eastern Cape province of South Africa. Stigma and discrimination against TB patients is noted to even be worse off in scenarios where family and community members have limited knowledge about the disease and its epidemiology, as evidenced by such studies as Ponyk *et al* (2001) and Glynn *et al* (2001). The authors, Odusanya and Babafeni (2004) also showed in their study in Lagos, Nigeria, how because of stigma and discrimination there was low care-seeking behaviour among TB patients. Lack of supportive networks around a TB patient might also come in the form of deprival of food and other non-food essentials important for their recovery as a patient, and this is bound to be more problematic in families with a low socio-economic status (see Shrestha-Kuwahara *et al*, 2004).

A supportive environment for the recuperating TB patient goes beyond just the family to also encompass the health care providers, be they at the nearest clinic/hospital or community-based health workers. Studies such as Lewin *et al* (2001) have indeed shown the important relationship between patient satisfaction with health care provision and adherence to treatment. Kaona *et al* (2004) further elaborate that there are factors considered important by patients that give them confidence to go to their clinics/health service centres to access treatment, and key among these include privacy and confidentiality when being treated and receiving medication.

To add further, the pattern of health care delivery system has also been argued to have a strong bearing on patients' adherence patterns. As noted by WHO (2003), many of the ambulatory[24] health care settings responsible for Tuberculosis case control are only meant for patients with acute illnesses[25], therefore staff might lack the skills required to develop long-term TB case management. Such scenarios are even worse in regions with extremely high TB prevalence

[24] Health services provided on an outpatient basis to those who visit a hospital or another health care facility and depart after treatment on the same day (Mosby's Medical Dictionary, 8th edition. © 2009, Elsevier)

[25] Any illness characterized by signs and symptoms of rapid onset and short duration. It may be severe and impair normal functioning (Mosby's Medical Dictionary, 8th edition. © 2009, Elsevier).

rates coupled with HIV and AIDS, where due to generally high disease burden, the patient's role in self-management is neither fully facilitated nor supported, thereby making follow-up sporadic, according to the same sources.

2.6.3 Treatment-related Factors

While the use of current regimens of anti-TB drugs under the DOTS scheme has been argued to be the most effective way of treating patients who have Tuberculosis (see WHO/TB/93,173), the issue of side-effects has for long been noted to be a major hindrance towards adherence. Shakya *et al* (2005) assert that hepatotoxicity[26] from the first line drugs Isoniazid (INH), Rifampicin (RMP), and Pyrazinamide (PZA) is common and may indeed limit their use and often can lead to interruption of therapy. The World Health Organisation, had also earlier on reported in a 1997 document (WHO/TB/94/177) that the number of tablets patients had to take as well as other side-effects besides toxicity, such as night flashes, temporary visual and hearing impairments in extreme cases, rashes, colouration of body fluids among others (depending on the drugs)[27] acted as a deterrent to continuing with treatment. Researchers such as Kaona *et al* (2004) also reported on some patients in Zambia saying they had stopped taking treatment because it was 'too strong', underscoring the undesirable effects of anti-TB medication in patients.

2.6.4 Individual/Patient-related Factors

It must be acknowledged that quite a lot of research effort has gone into understanding how individual/patient-related factors correlate with adherence. For instance, Gebremariam *et al* (2010) showed the importance of beliefs regarding severity and curability of Tuberculosis as key determinants in adherence behaviour, and this corresponds with the work done by Dick and Lombard (1997) which highlighted on belief in efficacy of medication as well as knowledge about TB as determinants of adherence. It also is of note that belief in the better efficacy of traditional medicines/cultural healing methods compared to allopathic[28] medicine has also been reported to influence adherence patterns in studies done in developing regions, particularly in sub-Saharan Africa (e.g. Mothlake, 2005). The authors Mateus-Solarte and Carval-Barona

[26] The tendency of an agent, usually a drug or alcohol, to have a destructive effect on the liver. (Mosby's Medical Dictionary, 8th edition. © 2009, Elsevier.)
[27] See Appendix 3
[28] Pertaining to conventional medical treatment of disease symptoms that uses substances or techniques to oppose or suppress the symptoms (Gale Encyclopedia of Medicine. Copyright 2008 The Gale Group, Inc)

(2008) assert from their study that patient motivation-related factors were crucial determinants in patients completing anti-TB treatment, and the same authors also go on to discuss the importance of patients' possession of requisite behavioural skills necessary for them to adhere to treatment. Findings from these authors are also supported in the work by Dick *et al* (1997) that also underscored motivational issues as being important in adherence behaviour among TB patients. Sackett and Snow had also earlier on reported in their study in 1979 that pill-taking was a lifestyle change in patients, and so having to continuously take the medication for at least 6 months had a bearing on the extent to which patients chose to adhere to their anti-Tuberculosis medication. The same authors again noted that in cases where patients perceived no improvement in their condition, hopelessness also became a key determinant of adherence behaviour. The author Mothlake (2005) in her study in South Africa also gave detail of how patients' going through psychological phases such as denial, low self-esteem, stress, acceptance, response to stigma and discrimination etc. played key roles in determining adherence or lack thereof to anti-Tuberculosis medications. Cramm *et al* (2010) were also able to demonstrate how the importance of perceptions towards TB and its treatment were key drivers of whether patients adhered or not.

The WHO (2003) also speaks of other behavioural traits among patients such as drug abuse as important determinants of adherence. Other patient-related factors such as sex, age, ethnicity and gender have also been explored and although studies do not necessarily agree on the extent of the predictive power, there is general consensus in their importance as predictors of adherence among Tuberculosis patients (e.g. Diwan and Thorson,1999 ; Farmer 1997; Shargie and Lindtjorn, 2007; Jaggarajamma, 2007; Bello, 2010 among others).

2.7 Determinants of Adherence: Strength in Numbers of Predictors

The authors Mateus-Solarte and Carval-Barona (2008) make a very important observation pertaining to prediction of treatment adherence. As a conclusion to their paper, they emphasise that a number of variables/determinants of adherence in their individual capacities would tend to have low predictive power, however upon being combined, their predictive strength grows. This observation is important in that it opens the scope towards the continued establishment of new predictors of adherence as well as refinement of already established ones, with the full knowledge that at the end of the day, prediction of treatment adherence as a phenomenon is enriched. Such rationale therefore forms important justification for this study, seeking to establish the role of real-time treatment scheduling variables in prediciting adherence. In other

words, if treatment scheduling-related variables are established to be valid predictors of adherence, this could essentially strengthen the already existing body of knowledge in the subject matter. Subsequent studies also taking consideration of the scheduling-related variables (in addition to already existing determinants), would thus have stronger predictive power with respect to treatment adherence behaviour.

2.8 Need for more Studies from Developing Country Set-ups

Notwithstanding the merits of all the efforts that have been put for so many years into undertaking research aimed at improving knowledge on treatment adherence among Tuberculosis patients, the WHO (2003) laments the limited number of studies done in developing country contexts. This is particularly important because diseases like TB wreck their worst havoc in developing countries where they merge with the already devastating HIV and AIDS pandemic, as discussed earlier in Chapter 1. Hence an increased number of studies in these contexts would be useful, particularly in not only concretising understanding of etiological factors for adherence, but also development of more focused and knowledge-based interventions for such contexts. This study therefore, as a case study from South Africa, one of the worst countries affected by TB, becomes a significant contribution towards comprehending the dynamics of TB treatment adherence/lack of it in developing country contexts. Greater detail of the South African country context, on which this study was based, is given in Chapter 4 ahead. The notion of site-specificity in studies aimed at gaining a deeper understanding of treatment adherence is also supported by Sumartojo (1993), who had established that various social, economic and demographic contexts would bring variation in adherence-based study findings across countries or regions.

2.9 Interventions to curb Non-Adherence among TB patients

In reviewing materials related to what this study considers as the third strand of adherence literature i.e. interventions meant to curb non-adherence among TB patients, what was perhaps considered to be some of the most radical views have been expressed and spearheaded by the organization TB Alliance. The organization argued in their 2010 report that there has essentially not been any truly novel TB drugs in the last half century and their main area of contention with current first-line TB treatment is that the course is taken over too long a period (i.e. at least 6 months), which in their view inevitably leads to adherence problems among patients. TB Alliance therefore suggests that in this era of TB/HIV co-infection, there is even greater scope for research and development of medication taken over a shorter period of time (that would be

much easier to adhere to) and that has stronger efficacy in order to tackle the growing and evolving pandemic. The organization has thus been leading advocacy, research and development in this regard, alongside some of its partners such as The Aeras Global TB Vaccine Foundation (Aeras) and the Foundation for Innovative New Diagnostics (FIND) (http://www.finddiagnostics.org 11/04/11). However, moving to the more conventional strategies that have been developed and attempted in the quest to improve treatment adherence among TB patients, WHO (2003) provides a list, given in the textbox below whose components can be noted as being predominantly socio-economic and psycho-social in perspective.

Textbox 4: Interventions to improve TB Treatment Adherence

Interventions to Improve TB Treatment Adherence

- Staff motivation and supervisions :-including training and management processes aimed at improving the way in which providers care for patients with TB in the workplace
- Defaulter action:- the various actions taken when a patient fails to keep a pre-arranged appointment
- Prompts:- routine reminders for patients to keep pre-arranged appointments
- Health education:- provision of information about Tuberculosis and the need to attend clinics for treatment
- Incentives and re-imbursements:- giving of payments in cash or kind to reimburse the expenses of attending the treatment centre or to improve the attractivenss of visiting the treatment centre
- Contracts:- agreements (written or verbal) to return for an appointment or course of treatment
- Peer assistance:- people from the same social group helping someone with Tuberculosis to return to the health centre by prompting or accompanying him/her
- Directly Observed Treatment (DOT)- an identified, trained and supervised agent (healthworker, community volunteer or family member) directly monitors patients swallowing their anti-TB drugs.

Source (WHO, 2003)

The World Health Organisation (2003) notes that there are gaps with respect to rigorous experimental research on the efficacy of interventions meant to improve Tuberculosis treatment adherence amongst patients. Following is a brief critique of various interventions that have been attempted and their efficacy thereof. Beginning with Directly Observed Treatment (DOT), the 'supervised swallowing' component under the DOTS strategy, studies such as done by Volmink and Garner (2001) have pointed to the fact that utilization of this approach in isolation would not

necessarily result in improved adherence levels. Similar messages seem to also have come from other authors such as Marshall (2007). Other arguments on the shortcomings of DOT with regards to facilitating and fully enabling treatment adherence pertain to logistical difficulties of travelling to the nearest clinics to take treatment under observation of health care workers (including lack of money for transport), inconveniences of having treatment under direct observation (feeling of being policed/mistrusted with one's own treatment procedure) and failure of healthworkers (and community-based carers) to cope with high numbers of patients needing treatment monitoring in cases of extremely high TB morbidity *inter alia* (see Smith,1999; Bello, 2010; and Jaggarajamma *et al*, 2006). It still needs to be reiterated however, that some programmatic studies on the efficacy of the DOT strategy have in cases shown high rates of treatment success, as contended by The Lancet Journal (1996) and Suarez *et al* (2001). What it simply implies then is that continued effort to plug in the identified gaps will strengthen the efficacy of Directly Observed Treatment.

The WHO (2003) also report of studies that have attempted to show the efficacy of some of the interventions in the textbox above. For instance, one cited study, Paramasivan *et al* (1993), showed that reminder letters sent to patients who had failed to come into clinics for monitored treatment uptake seemed to be of benefit even in cases where patients were illiterate. Other studies such as Krishnaswami *et al* (1981) had earlier demonstrated the efficacy of home visits in encouraging patients to complete their treatment, and the authors Tanke *et al* (1997) argued that prospective phone-calls were bound to even have better efficacy in promoting adherence as they reminded patients to keep appointments. What would obviously be a down-side to these interventions is their virtual inapplicability to country contexts of lesser development, where patients would not have regular access to phones or mailboxes, or even where there are extremely high TB prevalence rates e.g. in Southern Africa, thus complicating patient follow-up on a case-by-case basis (WHO, 2003).

Interesting work has also been done in the United States of America, which showed that giving patients financial incentives to come to the clinics for treatment improved appointment keeping and adherence in general (e.g. Pilote *et al*, 1996). However it must be emphasized that this was among the homeless and drug abusers, who perhaps had other 'survival' motivations to come to the clinics i.e. for the extra cash. The point still remains though that in cases of high poverty and low socio-economic status, giving financial incentives (e.g. for transportation costs, for food etc.) would be useful to get patients to come into clinics for treatment, as demonstrated by Sylla *et al* (2007)'s work in Senegal.

Studies have conflicted on the efficacy of health education on patient adherence, with some, such as done by Salleras *et al* (1993) and Leafooghe *et al* (1999) being affirmative on the positive correlation, and authors such as WHO (2003), Morisky *et al* (1990) and Mallotte *et al* (1998) being in contradiction, particularly based on methodological and empirical arguments. However there seems to be a common line of thinking among the divergent authors; this being that the use of this particular intervention in isolation would not be able to significantly result in improvement of adherence among patients. This again also underscores the importance of multiple interventions towards improving patient adherence in Tuberculosis cases. Other important interventions shown to have various levels of efficacy in supporting patient adherence to treatment include improved patient counselling and communication, patient choice of DOT supporter, decentralization of treatment and reinforcement of anti-Tuberculosis treatment supervision (e.g. Sylla *et al*, 2007; Jin *et al,* 1993 *inter alia*).

2.10 The Real-time Gap and Introducing the Simpill System

It is of interest to note that after a thorough review of the main literature on measuring adherence and interventions to improve adherence in TB treatment, there is certainly an apparent gap in the concept of monitoring adherence in 'real-time' i.e. detecting adherence/lack of it when it happens and thereafter instituting an immediate response. Save of course for the MEMS device, which as already discussed has not found much use at intervention level (if any) in developing countries because of cost limitations, methods emphasizing on real-time detection and response to non-adherence among patients are virtually non-existent (Marshall, 2007). To put this argument into perspective, we could take for example the use of letters in reminding and motivating patients to take treatment. A patient might receive the letter a day or two after they would have already began not adhering, or might even continue not taking their treatment soon after receiving the letter and it would most likely go undetected for a while. The same could be said about telephone calls. Particularly in high prevalence cases like in Sub-Saharan Africa, patients who stop coming to their nearest clinics for directly observed treatment might actually not be detected for a while due to the high numbers of other TB sufferers visiting the same facilities for treatment. Related to this could also be the issue of using community-based treatment supporters, who could easily become over-whelmed by the number of patients they would need to visit and directly observe while taking their anti-TB medication. Indeed, in perusal of literature on interventions developed to improve adherence levels among TB patients, the apparent gap of not being able to detect and react to non-adherence in real-time is a common thread.

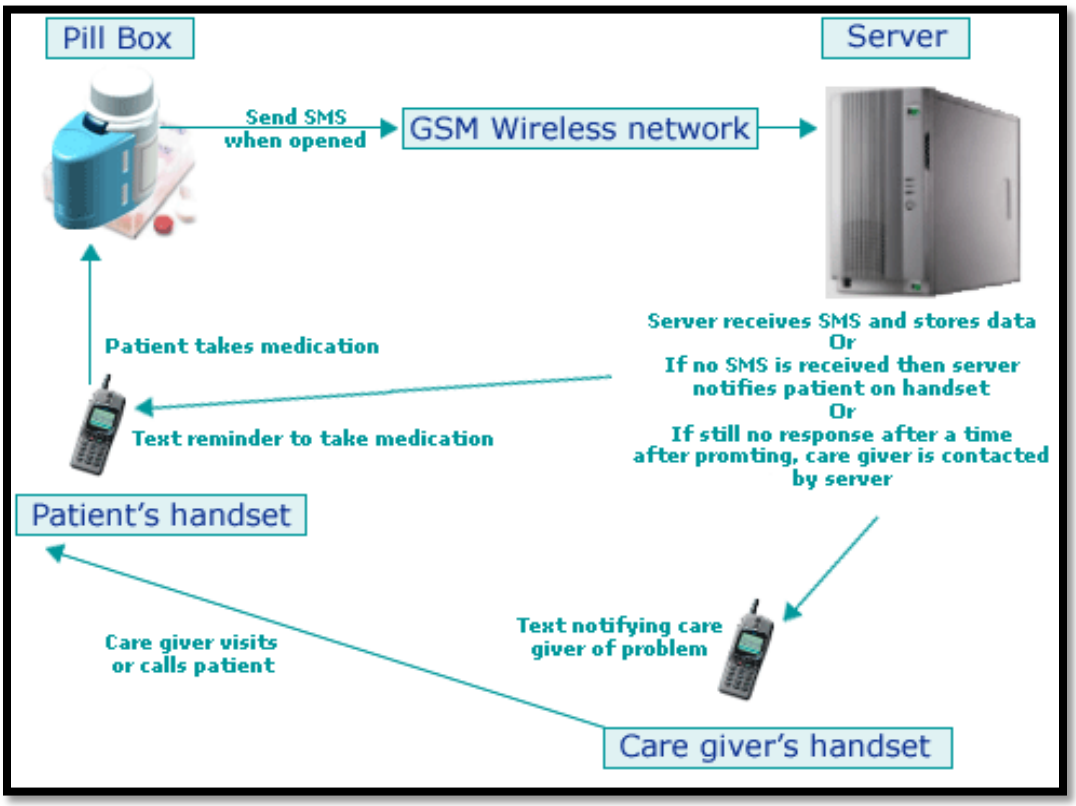
It is in view of this gap that this study narrowed down on an emerging intervention, the Simpill device, with the capacity to detect non-adherence in real-time and institute an urgent response, to see whether analyzing the data it generated and interrogating the efficacy of its real-time intervention could help contribute some knowledge into the above-mentioned missing link. The Simpill system is described in detail below:

2.11 The Simpill System

The Simpill system is a real-time treatment adherence monitoring technology developed by Dr. David Green, a medical doctor and health technologist in Cape Town, South Africa, in the year 2005. This was after the observation that approaches to monitoring non-adherence to Tuberculosis treatment were not able to detect non-adherence when it happened among patients, hence the lack of personalized interventions at the appropriate time when non-adherence was a problem (Marshall, 2007). The Simpill system comprises a standard pill bottle to which is attached a sensor and a radio frequency module (transmitter). Medication is therefore dispensed into this bottle, and so when it is opened as a patient is taking their treatment (medication event), a text message is sent to a central server using the GSM mobile telephone network (Tellumat, 2007; www.simpill.com, 2009). The server would then register the medication event against the patient's record in its database. The system also captures and stores other system management information i.e. battery strength and GSM signal strength for each of the pill bottles in use.

As further noted by Marshall (2007), data captured at the point of dispensing (dispensary) include patient details, prescribed medication, time and frequency of taking the medication as well as a time tolerance which provides a window for taking the medication. Citing an example, the same author elaborates that in an instance where a patient is scheduled to take treatment at say 08.00 daily with a time tolerance of 60 minutes, they will have a window period between 07.00 and 09.00 to take medication. If the bottle is opened (hence a medication event registered by the server) during this window period, it would be considered a 'right time' medication event. If the pill bottle is not opened during this period, and hence no medication event received by the Simpill server, a reminder is then sent to the patient's cellular phone by SMS text message to remind them to take their medication. Still if no medication event is recorded after a further time tolerance, a text message notification is sent to a primary care giver to encourage the patient to take their treatment. Care-givers at this level could be a family member, friend or work colleague

designated by the patient or a community-based health worker, depending on the context. Again if a medication event is still not recorded after the elapsing of a third and final time tolerance, then the responsible person at the dispensary is notified by text message as well, who is then encouraged to undertake follow up on the patient immediately for support and counselling purposes. If a patient then opens their pill bottle to take treatment (hence the server receiving a medication event notification) in response to any one of these multiple reminders, the event is recorded as a 'reminded' medication event. Should a medication event be recorded at any other time it is recorded as a wrong time event. If no event is recorded at all before half of the time has elapsed before the next dose is scheduled, then a missed event is recorded. Figure 2.2 below gives a summarized schematic of how the Simpill system works.



Source: Marshall (2007)
Fig 2.2 : How the Simpill System Works

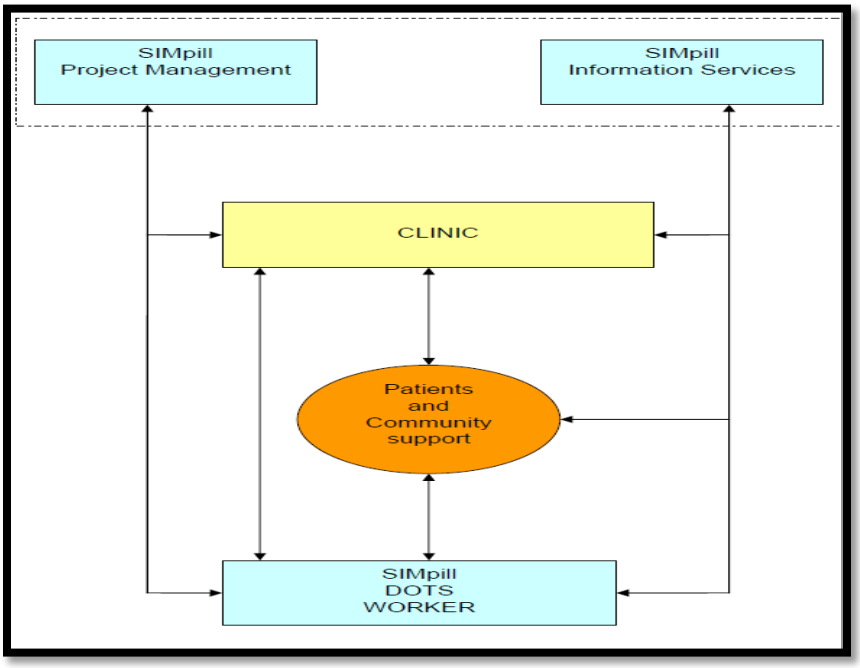
2.12 Simpill Procedure and Patient Management

The Simpill technology as a system for adherence management is premised on 2 major components: - Information system management and project management (Marshall, 2007). The developers of the system also came up with a 25-week procedure for utilization of the technology during treatment, stages of which include intensive psycho-social support for patients in the first 2 weeks of treatment, training on use of Simpill, then self-medication of patients thereafter (see Appendix 4 for procedure details). According to the same author, the Simpill procedure again includes the engagement of Directly Observed Treatment-short course (DOTS) workers, in fact called 'Super-DOTS workers' at the community level, equipping them with additional skills and competencies to manage up to 50 patients each. Within the procedure is also the engagement of a project manager, who is in constant communication with the community-based 'Super-DOTS' workers (day-to-day basis in actual fact), giving them information on non-adherers and discussing requisite interventions on a case-by-case basis. The advantage of the Simpill procedure, according to Dr. David Green, the inventor of the technology (Green, 2011, *personal communication*) is that since only treatment defaulters are targeted for follow-up, more time is therefore made available to give treatment support to those needing it the most. In other words, if patients are adhering to treatment or taking it within acceptable window periods, there would be no need for urgent follow-ups and special attention. In a sense this would then take away the feeling among patients of being 'policed' to take treatment unnecessarily, a challenge earlier on raised by Ian Smith in his 1999 journal article entitled *'Stop TB:Is DOTS the Answer?'*

The developers of the techonology contend that use of Simpill comes with 3 feedback mechanisms to help patients adhere to treatment:

- Patients receiving their text message reminders directly from SIMpill, this serving as an automatic and real-time cue to action
- Community-based health workers receiving their daily defaulter list and contacting defaulters, applying appropriate corrective measures.
- Clinics receiving patient adherence reports and comparing these with actual laboratory results. (Marshall, 2007)

The figure 2.3 below shows a diagram of the Simpill management scheme.



Source: Marshall (2007)
Fig 2.3: Simpill Management Model

With such a comprehensive supportive system around a patient therefore, starting with the patient's cellphone (as the first 'monitor' of adherence), followed by the immediate treatment supporter who lives with the patient, then the community-based Super DOTS worker, then finally the health service centres (clinics), adherence is highly likely to be optimized. In reality, Simpill need not necessarily be viewed as an isolated intervention on its own, but it more or less strengthens community-based DOTS. To reinforce on the overall goal of the study already mentioned in Chapter 1 therefore, this study will seek to empirically analyse real-time data generated from the Simpill pilot study carried out in Cape Town, South Africa, to see if this can help improve understanding on adherence, and perhaps even profer theoretical suggestions for enhanced conceptualization of the phenomenon of treatment adherence. A latter part of this study will indeed further seek to draw efficacy comparisons between conventional DOTS and the Simpill-enhanced procedure based on treatment success rates, among other analyses premised on data from the Simpill system. In the meantime, the next chapter of this thesis will delve deeper into the theoretical underpinnings that will guide the empirical component of this study.

Chapter 3: Study Theoretical Framework

3.0 Introductory Remarks

After defining adherence and then exploring the first 3 strands of 'state-of-the-art' on Tuberculosis treatment adherence research in Chapter 2 i.e. looking into means of measuring adherence, interrogating determinants of adherence and then detailing on the various interventions that have been tried out to respond to non-adherence, the beginning of this chapter explores the fourth strand of literature i.e. theoretical underpinnings in studying TB treatment adherence. A critique will therefore be provided, which will end with the identification of gaps in the current theories utilized in studying, predicting and understanding Tuberculosis treatment adherence. An alternative theoretical framework, upon which the study's argumentation would be based, will then be proposed and elaborated upon.

3.1 Theoretical Perspectives in Treatment Adherence: Why Bother?

Authors such as Mateus-Solarte and Carvajal-Barona (2006), Michie and Abraham (2004), Eccles *et al* (2005) as well as Redding *et al* (2000) among others reiterate in their respective studies on the importance of using theoretical perspectives in studying health behaviours. The common thread in their assertions is that theory enhances deeper understanding of health behaviour among patients, is useful in directing research as well as facilitating the transferability of an intervention from one health issue, geographical area as well as health-care scenarios to another. While this could be generalized for numerous other health behaviours, Munro *et al* (2007) and other authors such as Dubanoski and Cohen (1998) underscore the importance of theoretical modeling in TB treatment adherence, arguing further that predictive models facilitate early detection of non-adherence among patients and hence enable the design of appropriate interventions in time. Even the WHO (2003) emphasizes on the importance of strengthening theoretical modeling as a point of departure towards designing more effective intervention strategies and in that regard recommends further research in the subject area. This is perhaps in recognition of the apparent gaps in utilization of theoretical underpinnings in TB treatment adherence intervention strategies, observed by Munro *et al* (2007).

3.2 Theories used to Study Treatment Adherence Behaviour

Michie *et al* (2005) report that there are at least 30 psychological theories of behaviour change, therefore making it especially difficult to choose the ones on which to base development of health behaviour change interventions. However, with respect to narrowing down to treatment adherence behaviour, the scholars Leventhal and Cameron (1987) in their paper entitled *'Behavioural theories and the problem of compliance',* argued towards 5 umbrella theoretical perspectives most relevant to adherence. It is important to mention at this juncture that some of the perspectives encompass at least one theory while others have none relevant to adherence behaviour, as will be elaborated later. The list of the perspectives is as given below:

- The biomedical perspective
- The behavioural (learning) perspective
- The communication perspective
- The cognitive perspective, and
- The self-regulatory perspective

Munro *et al* (2007) also further report that yet another perspective; the 'stage perspective' emerged at the end of the 1970s and is also quite important as a framework for understanding adherence behaviour. This perspective, which contains the transtheoretical model, will be discussed in greater detail later. The authors Brawley and Culos-Reed (2000) and Redding *et al* (2000) observed that the most commonly used theories in studying adherence behaviour have been those in the cognitive perspective as well as the trans-theoretical model. The following section however details and critiques each of the afore-mentioned perspectives and their respective theories where appropriate.

3.2.1 The Biomedical Perspective

This perspective is premised on what is termed in conventional medicine *'The germ theory of disease'*, whereby microorganisms, such as bacteria or viruses are deemed as the major etiological factors responsible for illness among patients. Interventions thus prioritised with regards to treatment of illness under this perspective focus chiefly on development and roll-out of medication with the requisite efficacy to eliminate whatever microbes causing the illness in patients. The second line of focus pertains to ensuring that patients do consume the medication as per the medical practitoner's instructions so that they can essentially rid their bodies of whatever microbes causing them illness (Blackwell, 1992; Ross and Deverell, 2004). What is

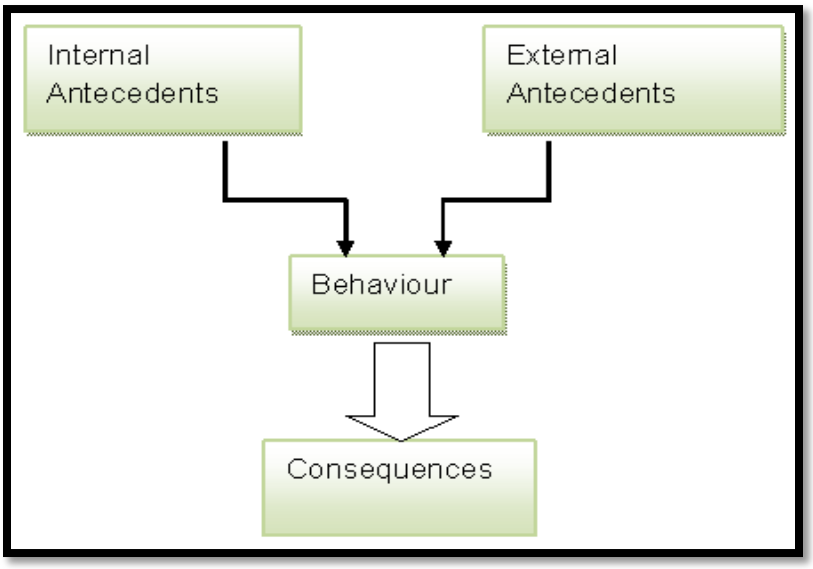
considered as the underlying assumption in this perspective is that patients are merely passive recipients in the treatment process; theirs is simply to 'comply' with the instructions from medical practitioners.

Key critics of this perspective argue that in essence, it has a narrow base in its focusing only on *'medicinal'* factors and patient characteristics (i.e. generally being interested in patients' uptake of medicine according to physicians' instructions, patients' reactions and side-effects from drugs by age, sex, weight etc). This is in spite of the reality that many other non-medicinal factors may as well impact on adherence behaviour, such as patients' views of their own illness, psycho-social influences as well as the impact of the socio-economic environment (WHO, 2003; Blackwell, 1992). Contrary as well to the underlying assumption in this perspective that considers patients as being mere passive recipients of medical practitioners' instructions, the authors Munro *et al* (2007) further contend that patients are in actual fact generally more pro-active in determining their own treatment uptake dynamics. Other scholars, such as Jay *et al* (1984), in building a case for the importance of effective patient-physician communication as well as getting the patient more involved in their treatment, argue that there are certain iatrogenic[29] cases where a physician can initiate or accentuate non-adherence. Citing a scenario where a patient would not adhere to taking a certain drug because they do not understand why the medication has to be taken at whatever prescribed frequency, how the medication works and how it will make them better, these authors also showcase another shortcoming in the bio-medical perspective as it would essentially overlook the impacts of the medical practitioner's 'instructions' on the patient's adherence behaviour.

[29] Induced in a patient by a physician's activity, manner or therapy. Used especially for an infection or other complication of treatment.

3.2.2 The Behavioural (Learning) Perspective

At the core of this perspective is the Behavioural Learning Theory given in figure 3.1 below



Adapted from: Munro et al (2007)
Fig 3.1: Behavioural Learning Theory

As noted by the WHO (2003), this theory places particular emphasis on the importance of positive and negative reinforcement as means of influencing behaviour and it narrows in on the utilization of the principles of antecedents and consequencies as well as their subsequent influence on behaviour (Skinner, 1938). Antecedents, according to the same authors, would be either internal (e.g. thoughts from a patient such as *'I should take my anti-TB medication'*) or external (e.g. environmental cues such as a patient being reminded to take their drugs by their alarm clock), while consequencies might either be punishments or rewards for a particular behaviour (i.e. in our case of Tuberculosis treatment, these could either be side-effects from the drugs or being cured from the illness).

Indeed the Behavioural Learning Theory (BLT) has been noted to inform interventions, as demonstrated by studies such as done by Dunbar *et al* (1979) and Haynes *et al* (2002), which showed the utlisation of components drawn from the BLT e.g. reminders having a positive effect on adherence. Munro *et al* (2007) however contend that further research should be put into understanding the efficacy of interventions meant to improve adherence based on this theory, as more recent studies (e.g. Mainnheimer *et al*, 2006) seem to show conflicting results from the

earlier studies i.e. approaches based on the BLT not necessarily showing any better adherence rates compared to those not based on the theory.

In critiquing this theory, the author Blackwell (1992) argues that the BLT has limitations as it lacks an individualized approach, underscoring on its shortcomings pertaining to the non-consideration of less conscious influences on behaviour. Examples of such influences, as contended by the author, would typically include lack of acceptance of a diagnosis, past habits and behaviour. It is furthermore argued that the theory has a weakness in overtly focusing on external influences of behaviour.

3.2.3 The Communication Perspective

While no specific communication theories have been pin-pointed and linked expressly to treatment adherence studies, the basic underpinning in this perspective, noted to have emerged in the 1970s, is premised on communication being the most important component in a patient-practitioner relationship, and thus having a bearing on patients' adherence/lack thereof (Ross and Deverell, 2004 ; WHO, 2003). Achievement of an optimal patient-healthcare worker relationship would be based, according to this perspective, on the latter having the requisite communication skills which they would make use of to comprehensively educate the former on various aspects related to treatment adherence (Munro *et al,* 2007). The same authors further note that the perspective also places emphasis on the timing of treatment, instructions and comprehension.

Blackwell (1992) observes that critics of the communication perspective contend that it disregards motivational, attitudinal and interpersonal factors that may act as barriers to the healthcare worker-patient communication, as well as over-simplifying the subsequent translation of adherence knowledge/education into actual behaviour change by the patient. Certainly, owing to the issue of external factors, it would be too difficult to expect interventions based on the communication perspective to sustainably yield positive results for adherence to long-term treatment in illnesses such as Tuberculosis. This could perhaps account for mixed results in terms of efficacy of components derived from this perspective in adherence studies, as highlighted by authors such as Ley (1988) and Munro *et al* (2007). The WHO (2003 pp140) in an interesting observation note that *'adopting a warm and kind style of interaction with a patient is necessary, but is insufficient in itself to effect changes in the adherence behaviours of patients'.*

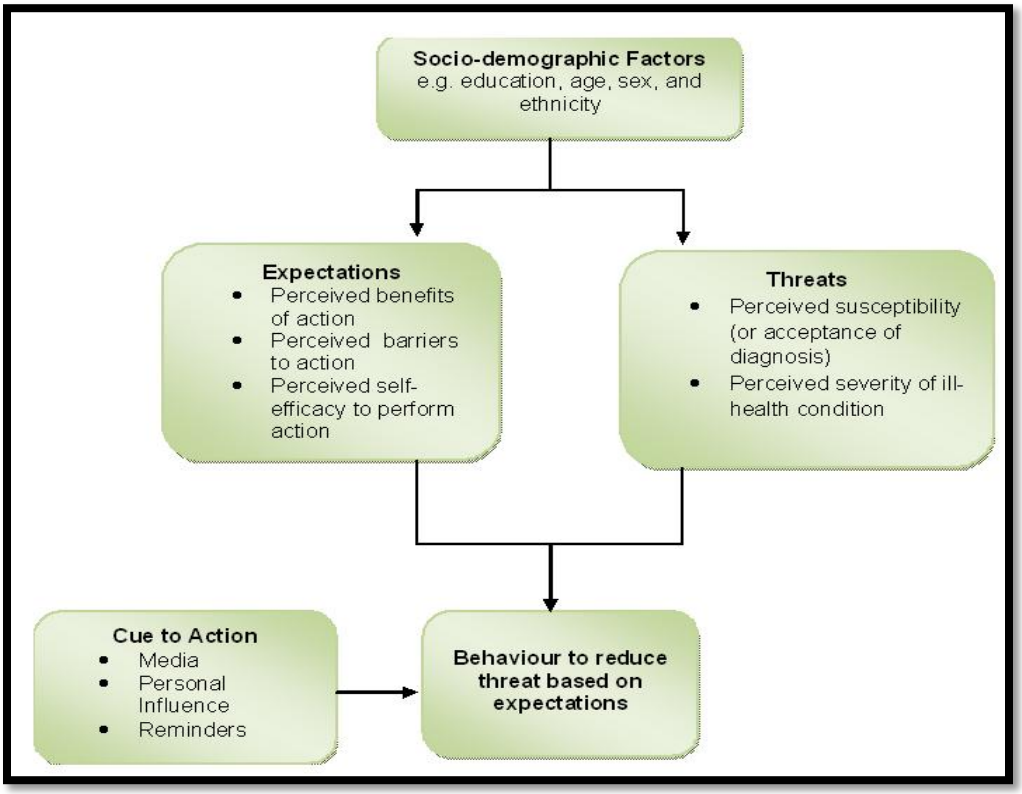
3.2.4 The Cognitive Perspective

WHO (2003) and Munro *et al* (2007), report that the most utilized theoretical underpinnings in studying adherence behaviour under this perspective are, in no particular order:

- Theory of planned behaviour (TPB)
- Health belief model (HBM)
- Social cognitive theory (SCT)
- Theory of reasoned action (TRA)
- Protection motivation theory (PMT)

As pointed out by Munro *et al* (2007), a common thread in these theories is that they focus on cognitive variables as part of behaviour change. Other authors such as Gebhardt and Maes (2001) as well as Stroebe (2000) further elaborate that these theories share the common assumptions that attitudes, beliefs as well as expectations of future events and outcomes are major determinants of health behaviour. According to these authors, the theories commonly propose that individuals will choose the actions that will most likely lead to positive outcomes when faced with various alternatives. The following sub-sections will look at each of these theories in detail, as well as seek to critique their relevance to studying treatment adherence behaviour.

3.2.4.1 Health Belief Model (HBM)



Adapted from Rosenstock *et al* (1994)
Fig 3.2: Health Belief Model (HBM)

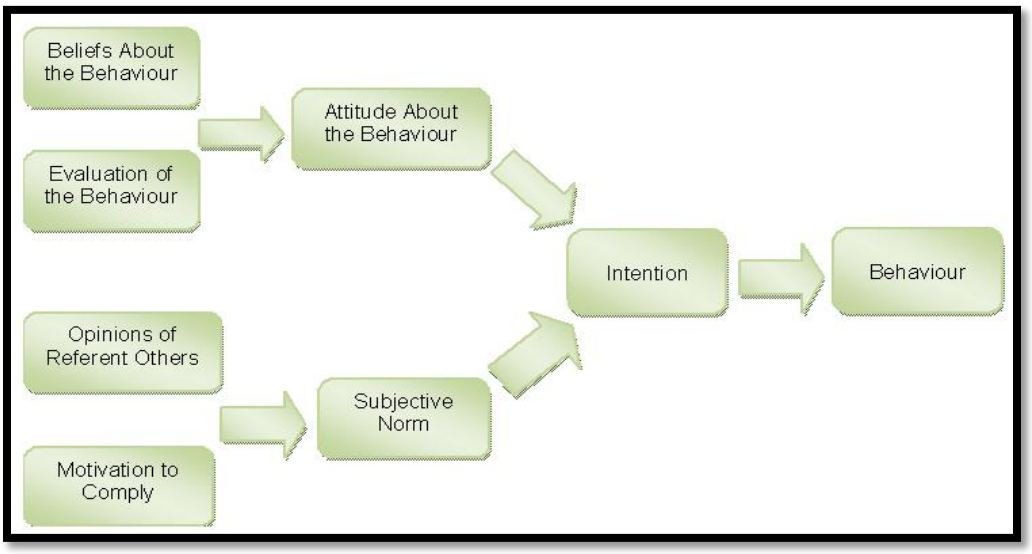
According to Blackwell (1992), the Health Belief Model (HBM) considers health behaviour change as being based on an individual's rational appraisal between the benefits and barriers of undertaking a health action. As elaborated further by WHO (2003), an individual's perception of health threat is directly influenced by a combination of his/her perceptions of the health condition's seriousness as well as their susceptibility. For instance in the case of TB, if a patient was to perceive non-adherence to anti-Tuberculosis medication as not being a cause of any severe health consequences e.g. a view like '*It will not do me much harm if I skipped taking my medication here and there'* or if they felt for one reason or another that they would not be susceptible to any such consequences e.g. '*With the way I feel now, I don't think I will suffer any effects from not adhering to treatment here and there',* then these perceptions would determine that patient's overall perception of the health threat as a result of non-adherence. The same authors further note that the perceptions of benefits and barriers have a bearing on an individual's perception of effectiveness of undertaking a specific health behaviour. In the case of a TB patient therefore, the extent to which he/she feels the anti-TB medication can make them

feel better, combined with their view on say side-effects, will have an effect on whether they believe they can adhere to their drugs throughout the treatment course or not. It also is important to note that the above-elaborated perception variables are over-arched by socio-demographic variables e.g. age, sex and education etc. As shown in the diagrammatic representation of the model above, Cues to Action also have some influence on an individual's undertaking of a given health behaviour. Cues to Action, as elaborated on by Rosenstock *et al* (1994) are events, which could either be bodily (e.g. physical symptoms of a health condition) or environmental (e.g. media, reminders etc.) that motivate people to take action. These authors also note that 'Cue to Action' is a component of the Health Belief Model that has not been methodically studied, a gap in knowledge that this study hopes to contribute towards filling, through interrogation of real-time cues to action and their effectiveness in improving adherence outcomes among Tuberculosis patients. This will be discussed in latter parts of this thesis. Stretcher and Rosenstock (1997) also report that another variable; self-efficacy has recently been added to the Health Belief Model, thus also accounting for the need for an individual to feel confident before changing health behaviour in the long term.

In utilization of this model to inform health behaviour change interventions, including treatment adherence, the perceptions and socio-demographic variables have been considered as independent predictors. This however also forms the basis for the criticisms that the HBM has generally encountered as a framework for understanding health behaviours, including treatment adherence. The argument of lead critics such as Stroebe and de Wit (1996) lies in there being no clearly defined/elaborated inter-connections between the variables, implying that the variables in the model have a cumulative effect on health behaviour and are not moderated by each other. In further work entitled *'Social psychology and health'*, Stroebe (2000) builds a case for some extent of interaction amongst variables in the HBM and also critiques the lack of 'behavioural intention' as a moderating and antecedent construct before the actual health behaviour. Additional issues of contention among other critics of this model (e.g. Rosenstock *et al* 1994) pertain to the effects of social norms and peer influence/role of significant others on health behaviour. This is another gap that this study intends to help fill as will be elaborated later. Another gap of course in the HBM concerns its 'disregard' of economic factors influencing behaviour, as well as the general assumption of rationality in the undertaking of health behaviours on the part of patients. To substantiate arguments against the overt assumption of rationality, Rosenstock in earlier work (1990) gave an example of smoking, which with time becomes an addictive habit and so what it means therefore is that even after having made the

decision to quit smoking, the habit cycle still influences the smoker's action, no matter the supposed 'irrationality' of doing so. It might as well be possible that there could be certain habits or perhaps routines that a TB patient has and these could be key determinants in influencing their adherence behaviour, no matter the irrationality. This thesis will explore further on routines and how they affect adherence behaviour as well.

3.2.4.2 Theory of Reasoned Action



Source: http://www.soc.iastate.edu/sapp/soc401FAM.html, (accessed 20/02/11)
Fig 3.3: Theory of Reasoned Action

Fishbein and Ajzen in formulating the Theory of Reasoned Action made the assumption that individuals are usually quite rational, make systematic use of information available to them and generally consider the repurcussions of their actions before they decide to engage or not to engage in a given behaviour (Ajzen & Fishbein, 1980). In other words, as put across by Munro *et al* (2007), the theory makes overt assumptions of the majority of socially relevant behaviours being under volitional control. Proponents of this theory from the developers themselves to latter scholars e.g. Sutton (1997) explain further on its components by saying that behavioural intention is the most immediate antecendent proxy to the actual behaviour itself, and that intention is directly influenced by attitude about the behaviour and subjective norms. Attitude would itself have been affected firstly by beliefs about the behaviour and secondly by evaluation of the behaviour. In our case of Tuberculosis treatment adherence as the desired health behaviour for instance, a patient would be having views such as 'if *I finish the course of medication I will be healthy'* (beliefs) and *'being healthy is desirable'* (evaluation). From the

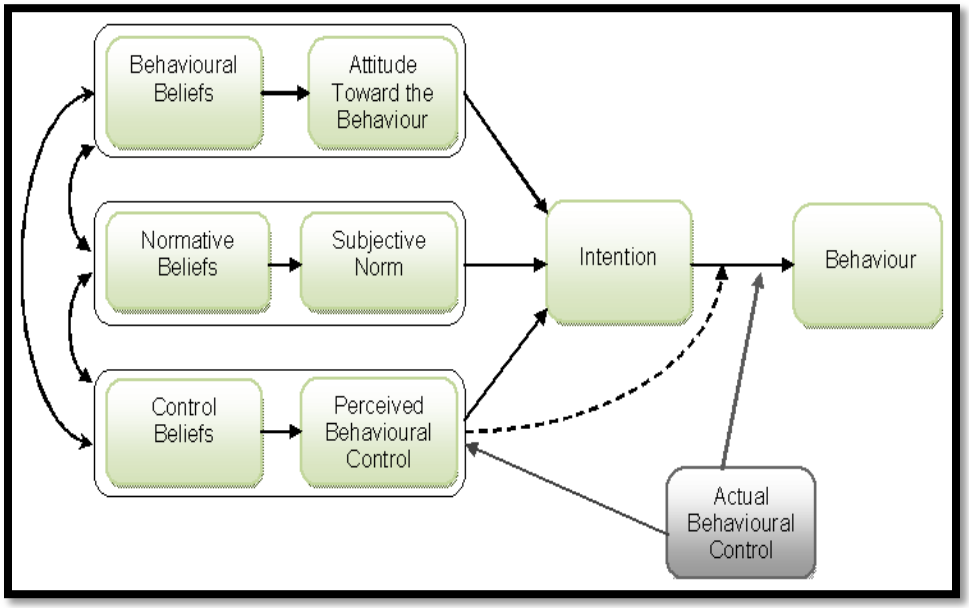
diagram above, it can also be noted that 'subjective norm' would have been influenced by opinions of referent/significant others as well as motivation to comply. Again in our case of TB treatment adherence, these variables would be represented by patients' views such as *'my family and friends think I should take my medication'* (signifying role of significant others) or *'I want to do what they want me to do'* (motivation to comply/role of significant others)[30].

Criticism of the Theory of Reasoned Action stems initially from the study by Sutton (1997), in which a meta-analysis interrogating this theory established that it had limitations in explaining variances in behaviour based on intentions. Such premise, according to Munro *et al* (2007), points to the suggestion that actual support for this theory is limited. Another gap of course in this theory is perhaps the 'over-assumption' of rationality among individuals, and as contended by Stroebe (2000), behaviour might not always be under volitional control, and it could also be possible that past behaviours might have an effect on present behaviours.

In view of these shortcomings, as stated by Munro *et al* (2007), Fishbein and Ajzen then extended the TRA to include another variable, *'behavioural control'* and so they called the expanded version the Theory of Planned Behaviour (TPB). The diagrammatic representation of the TPB is given in figure 3.4 below.

[30] See also Munro *et al* (2007)

3.2.4.3 Theory of Planned Behaviour

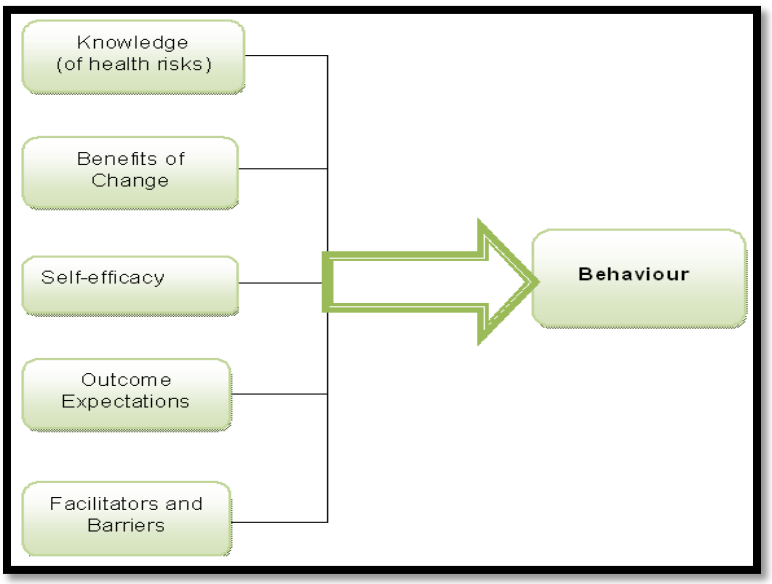


Source: Ajzen (2006)
Fig 3.4: Theory of Planned Behaviour

Now the new construct, 'behavioural control' found in the TPB, as elaborated by Mackenzie and Jurs (1993) indicates how an individual's motivation to perform a certain behaviour is influenced by their perception of how easy or difficult performing the behaviour would be, and also his/her perception of how successfully the behaviour can or cannot be undertaken. In trying to provide further explanation, the same authors go on and say that if an individual has strong/weak control beliefs about the existence of factors that would facilitate the undertaking of the behaviour (e.g. a TB patient saying *'Remembering to take my medication would be difficult/easy'*), then this would influence whether that individual tends to have low or high perceived control over the behaviour itself. The author Stroebe (2000) suggests that the concept of behavioural control is similar to the concept of self-efficacy, including knowledge of relevant skills, emotions, past experiences, influential norms around the individual as well as anticipation of upcoming circumstances (St Claire, 2003; Mackenzie &Jurs, 1993). The author Sutton (1997) further contends that behavioural control is assumed to even have direct control on the actual behaviour itself (over and above just the behavioural intention), a premise also supported by Ajzen (2006) in his diagrammatic representation of the theory in figure 3.4 above.

In as far as the critics are concerned; the need for more clarification and definition of constructs in the TPB is brought up, a case in point being critique by St. Claire (2003) and Sutton (1997). This is notwithstanding the fact that meta-analyses focused on establishing the usefulness of this theory's components have shown promising results, according to Munro *et al* (2007). The other major weakness cited by critics of the TPB (e.g. Mullen *et al* 1987) is its overt dependence still on rational processes, despite the fact that rationality is not always guaranteed in real-life decision-making, as discussed earlier on in the HBM and TRA.

3.2.4.4 Social Cognitive Theory



Adapted from Munro et al (2007)

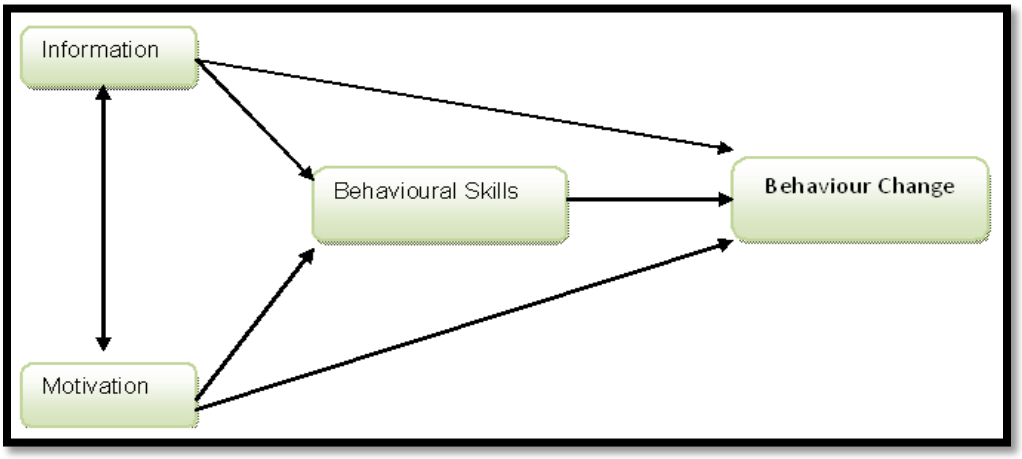
Fig 3.5: Social Cognitive Theory

The Social Cognitive Theory (SCT), developed by Albert Bandura (see Bandura 1977) from the Social Learning Theory, defines human behaviour as being triadic i.e. a dynamic and reciprocal interaction of personal factors, behaviour, and the environment. As further elucidated by Munro *et al* (2007: pp6) the theory *'posits for a multifaceted causal structure in the regulation of human motivation, action and well-being, and offers both predictors of adherence and guidelines for its promotion'*. Proponents of this theory such as Redding *et al* (2000) even contend that it could be as yet the most comprehensive behaviour change theory available thus far.

According to this theory, health behaviour change is a function of 5 main factors. The first one would be knowledge of health risks (e.g. *I know what TB is and what danger it poses to me*),

followed by appreciation of benefits of undertaking a certain health behaviour (e.g. *taking anti-TB medication will make me feel better*). These first 2 are in fact identified by Bandura (2000) as being the pre-requisite factors to behaviour change. The other factors are self-efficacy (i.e. a patient believing he/she can take their anti-Tuberculosis medication to the end of the course), outcome expectations (e.g. a patient's view being *'if I take my anti-TB drugs I will feel better'*) and finally the presence/absence of facilitators and barriers that either enable or inhibit the required health behaviour. The presence or absence of these factors, according to this theory, will cumulatively lead to modification (positive or negative) of the health behaviour in question, in this case treatment adherence. The extent to which these factors moderate each other is also not clear in this theory, of which this thesis argues that to be one of its main weakenesses. The authors Munro *et al* (2007) also seem to suggest that owing to the SCT's wide-ranging focus, it is difficult to operationalise and they cite Stone (2006), who in turn further notes that as a result of the same wide-ranging nature, the theory has often been used only in part. The former authors then go on to question the overall usefulness of the SCT in developing interventions focused on improving treatment adherence consequently.

3.2.4.5 Information-Motivation-Behavioural Skills Model (IMB)



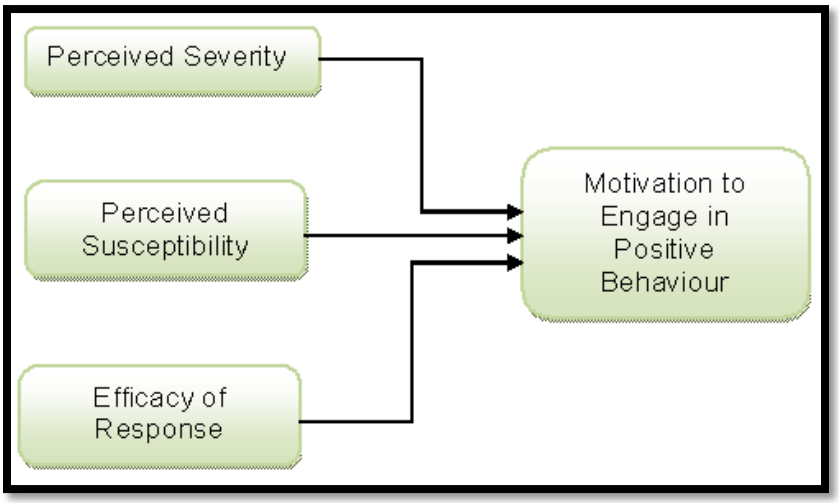
Adapted from WHO (2003)
Fig 3.6: IMB Model

Initially designed to promote the use of contraceptives as well as preventing the transmission of HIV, the Information-Motivation-Behavioural skills (IMB) model was reportedly developed to be simple and generalisable, according to Fisher *et al* (1999) and Fisher&Fisher (2000). The model asserts that information is a 'must-have' component of any behaviour change process, a

premise supported by earlier works such as Mazzuca (1982), although the information component must be complemented with motivation and behavioural skills to ultimately effect behaviour change (Fisher *et al,* 1996). The authors Munro *et al* (2007) explain that 'information' in this model relates to basic knowledge about a medical condition, in our case Tuberculosis. The construct 'motivation' would consist of components such as personal attitudes towards adherence, subjective norms, and an individual's past experiences relating to the health condition (whether personal or observed on others). The third construct, behaviour skills would include aspects such as availability of strategies, tools and the requisite skills to undertake the desirable health behaviour (in our case, TB treatment adherence). Fisher *et al* (2006) also further elaborate on the importance of self-efficacy (i.e. the belief of being able to achieve) among the individuals expected to undertake the health behaviour.

In raising critique around this theory, authors such as WHO (2003) raise the argument pertaining to the weak relationship between information and motivation constructs i.e. they contend that in practical terms, availability of relevant information might not necessarily lead to high motivation, saying it could also be possible that a highly motivated person might have little information and vice-versa. As elaborated by Fisher *et al* (2006), factors such as access to health services and socio-economic conditions are among other factors that could also moderate the determinants of an individual's undertaking of health behaviour change, but unfortunately the IMB model does not seem to clearly elaborate on such factors' inter-connection with the primary constructs it emphasizes on. It must be underlined all the same that this theory has been credited for its simplicity and ease of use at intervention level.

3.2.4.6 The Protection-Motivation Theory (PMT)



Adapted from Munro *et al* (2007)
Fig 3.7: Protection Motivation Theory

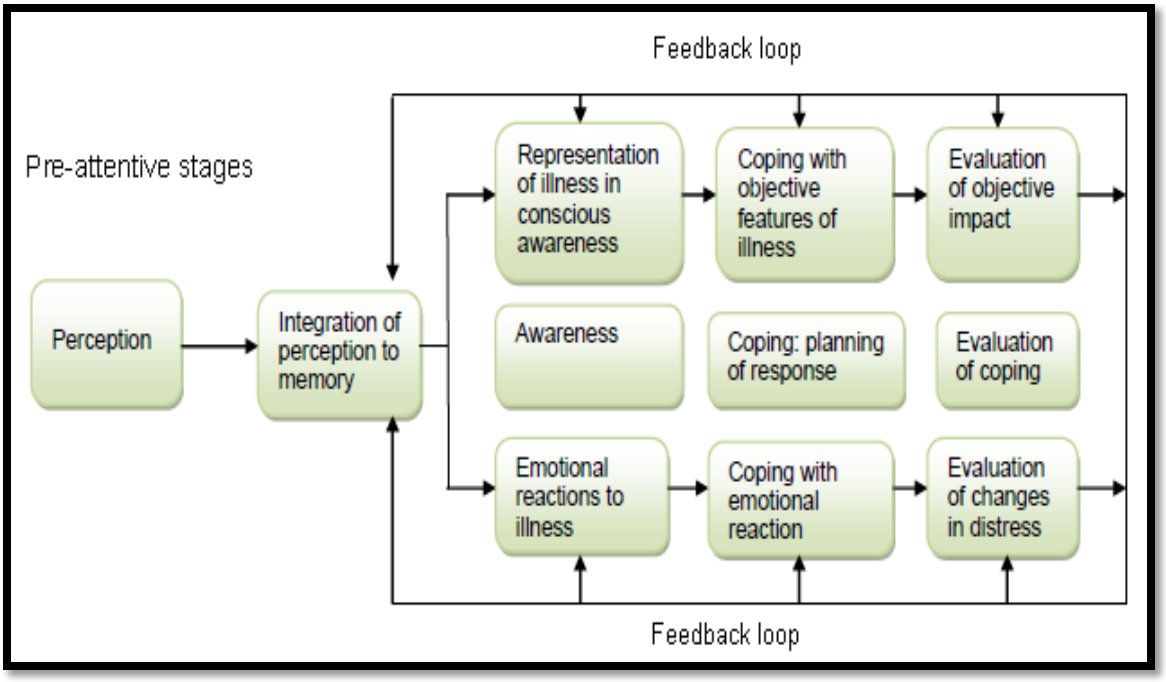
Munro *et al* (2007) assert that the Protection-motivation theory (PMT) is premised on the argument that behaviour change can be attained through appealing to an individual's fears. Citing the scholar Rogers (1975), the authors further elaborate that the theory proposes three components of fear arousal, the first one being the magnitude of harm of a depicted event or condition (e.g. in our case a patient perceiving drug-resistant TB as a killer disease). The second component noted is the perceived probability of the event/condititon occurring (e.g. a patient thinking *'I have seen from other patients/been notified of the deadly consequencies of not adhering to treatment, so this could happen to me'*). The third component pertains to the patient's perceived efficacy of the protective response (e.g. a TB patient believing that adhering to treatment can actually cure him/her and prevent the development of MDR-TB). The author Stroebe (2000) contends that these 3 components combine in a multiplicative fashion to determine the extent of protection motivation, thereby leading to an individual undertaking the desired behaviour in order to protect themselves from danger. This theory is reported to be unique within the wider cognitive perspective as it is the only one which clearly utilizes the costs and benefits of existent and recommended behaviour to predict the likelihood of change (Gebhardt and Maes, 2001).

With regards to this theory's shortcomings, Rogers (1975) argues that it omits important environmental and cognitive variables that could have a bearing on behaviour change, e.g. pressure to conform to social norms (in Munro *et al,* 2007). Expanding on this argument and using an example of a TB patient, this thesis argues that it could be possible that a patient might ***(i)*** be conscious of the severity of not complying to treatment ***(ii)*** be conscious of the fact that they are highly likely to get drug resistance if they do not adhere to treatment and ***(iii)*** believe that the medication would cure them, but still not adhere. This can be brought about by a realistic assessment of perhaps the socio-economic costs of adhering e.g. stigma and discrimination in the workplace and in social circles, possible loss of employment or acquaintances upon being 'discovered' to having been taking anti-TB medication etc. The costs of the desirable health behaviour (in this case adherence) might thus in the patient's view be of more immediate concern than medium-long term benefits, hence their not undertaking of the health behaviour (adherence) effectively. It does appear though that a latter version of the PMT takes the above-discussed issue of an individual's costing of desirable health behaviour into consideration (see Stroebe, 2000). It is also noteworthy that this theory does not assume rationality among individuals, a general weakness in other behavioural theories under the cognitive perspective (Floyd *et al*, 2000).

3.2.5 Self-Regulation Perspective

Under this perspective, Munro *et al* (2007) identify the main theory as being the Self-Regulating Theory (SRT), which proposes on the necessity of examining individuals' subjective experiences of health threats so as to better appreciate their response strategies. It is premised, according to Leventhal *et al* (1980) on the assumption that individuals are pro-active and self-regulating problem-solvers, hence will find motivation to avoid and get treatment for health threats.

The diagrammatic presentation of this theory is given below:



Adapted from Leventhal *et al* (1984)

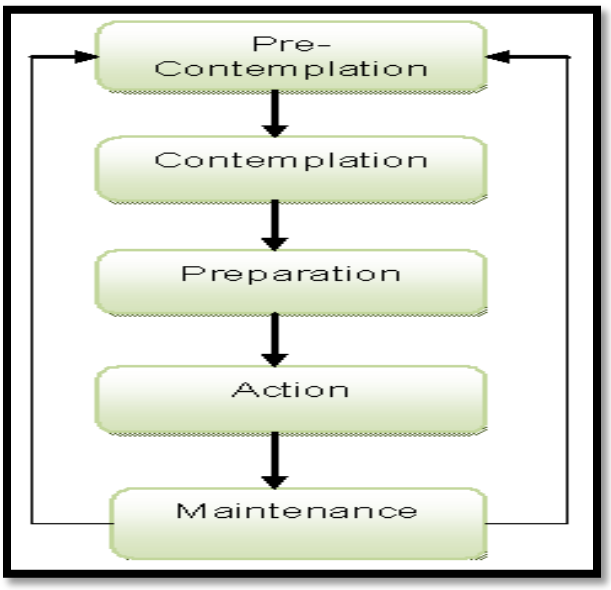
Fig 3.8: Self-Regulation Theory (SRT)

As further explained by Edgar and Skinner (2003), individuals tend to form cognitive representations of health threats (as well as related emotional responses) based on new information and previous experiences (both personal and observed from other parties). It is these cognitive representations that would then steer the individuals' choices of various coping strategies. The same authors further argue that this process of creating health threat representations and development of coping strategies is influenced by the individual's socio-cultural context as well as their personality. Leventhal *et al* (1992) had also written earlier saying that there was interplay between environmental perceptions, symptoms and beliefs about disease causation.

Chief among the critics of this theory is the World Health Organisation (2003), and the organization contends that the SRT provides little guidance with respect to informing treatment adherence intervention design. Munro *et al* (2007) add to this and point out that while the theory sounds well grounded and seems useful, specific suggestions are still needed explaining how the processes under this theory could in actual fact promote adherence.

3.2.6 Stage Perspectives

Under this perspective, WHO (2003) and Munro *et al* (2007) point out that the Transtheoretical Model (TTM), also known as the Stages of Change Model, is the predominant theoretical model utilized. According to Prochaska and Strong (1992), the model is premised on 5 qualitatively distinct stages and processes through which individuals progress as they undergo behaviour change, as shown in the diagram below:



Adapted from Munro *et al* (2007)
Fig 3.9: The Transtheoretical Model (TTM)

As in Figure 3.9 above, the stages in the TTM begin with pre-contemplation, when a patient would be at the earliest stage of considering whether or not to change their health behaviour towards the desired one. At this point, consideration is not serious and the individual could even still not be convinced as to why they should change their behaviour. In our case of Tuberculosis treatment, at this stage a patient could still be saying for instance, '*I'm not seriously thinking about changing - I don't think I should adhere to my treatment'*. The next stage, contemplation, is when the individual now puts serious consideration into the possibilities of behaviour change, and for instance a TB patient could be saying *'seriously, I think I should adhere to my treatment'*.

The following stage, preparation, is perhaps when the individual builds will-power and is more committal towards changing their behaviour through action, and in our case a TB patient could then be saying *'now I'm ready to change'*. Now in the next stage, 'action', the patient would start

acting out the will-power built in the previous stage by attempting to implement the behaviour change itself. A TB patient could at this stage therefore be saying *'I'm doing all I can to ensure that I adhere to my treatment.* In the last stage (maintenance), the individual will be attempting to sustain the behaviour change from the previous stage, lest they relapse and fall back down the stages again. A TB patient could in this stage be saying *'I have managed to adhere to my treatment for the past 5 weeks now''* (see also Munro *et al*, 2007).

According to WHO (2003) and Proschaka *et al* (1992), the TTM is deemed an important theory with respect to providing greater understanding of the process of intentional change, where an individual after due consideration of the *pros* and *cons* of change, then consciously goes on to make the desired behaviour change. One of the major critics of the TTM has been Albert Bandura, who in one of his works (Bandura, 1997), contends that human behaviour is way too multi-dimensional to fit into separate discrete, and narrow stages. In a later publication (Bandura, 2000), he further argued that the theory in fact actually infringes upon all three basic assumptions of stage theories, namely qualitative transformations across descreet stages, invariant sequence of change and non-reversibility. Other scholars such as Armitage and Conner (2000) also added their views to the critique by further arguing that the TTM did not provide adequate detail on how people actually changed, and why the change process worked for others and yet still failed for others. The authors Benyamini *et al* (2004) also criticize the stage definitions in the theory as being flawed, in the process also contending that the time periods assigned to each stage were more or less subjective and random.

3.3 The Missing Link and Study Argumentation

Up to thus far in this chapter, this thesis has endevoured to explore the various perspectives that have been made use of either in studies or interventions related to treatment adherence. It has also proferred a detailed discussion on the main theories under each perspective, highlighting both their strengths and weaknesses in relation to the study of adherence, of course in due recognition of the limitations of the domains in which they were developed. In full acknowledgement of all the merits that the discussed theories have in helping improve understanding of adherence to long-term treatment, such as in the case for Tuberculosis, this thesis then further argues on what the author deems a 'missing link', which will reiforce this study's argumentation and subsequently form basis for its theoretical framework. The said missing link, contended by the author of this thesis to be the construct 'Treatment Scheduling', is elaborated further on below.

3.3.1 The Treatment Scheduling Gap

Review of the main theories used in studying or intervening against non-adherence to long-term treatment, done in above sections shows an apparent gap in due recognition of the role that the treatment schedule (i.e. what month, day, time etc. a patient is supposed to be taking a specific type of medication) could play as a determinant of adherence[31]. Under the communication perspective already discussed in section 3.2.3 above, the issue of timing of treatment is mentioned and given some sort of appreciation, but then there is no specific theory informing this perspective. Now it is the contention of this study that scheduling might in fact end up being the most crucial determinant of whether a patient adheres to treatment or not, because of its capacity to optimize or inhibit the likelihood of uptake of medication. In other words, there is a very real possibility that a patient might have the right individual attributes e.g. attitude towards treatment, motivation to comply etc, and perhaps have enough socio-economic support but still fail to adhere because the scheduled time of taking treatment is not deemed conducive or convenient. This could be so because the patient might be participating in various other socio-economic activities, hence they could either decide to postpone taking treatment or fail to take it altogether. Again owing to the fact that patients will not always make rational decisions with respect to undertaking health behaviours, including taking medication (contrary to the overt assumptions in a number of already discussed behavioural theories), various circumstances might otherwise cause patients to either deliberately or unintentionally miss their treatment altogether or take it later than scheduled.

Considering the already discussed notion that adherence/lack of it occurs in real-time, it might then even be of interest to note whether a real-time cue-to-action can ultimately aid adherence. Attempting to show the influence of a real-time cue-to-action on health behaviour (in our case TB treatment adherence) would contribute towards covering a knowledge gap in theories such as the Health Belief Model and also broadening understanding in a relationship already hinted to be positively correlated under the Behaviour Learning Theory (see sections *3.2.2* and *3.2.4.1* above for earlier discussions). Enriching understanding of this relationship could eventually widen possibilities as regarding the improvement of existing interventions to curb non-adherence.

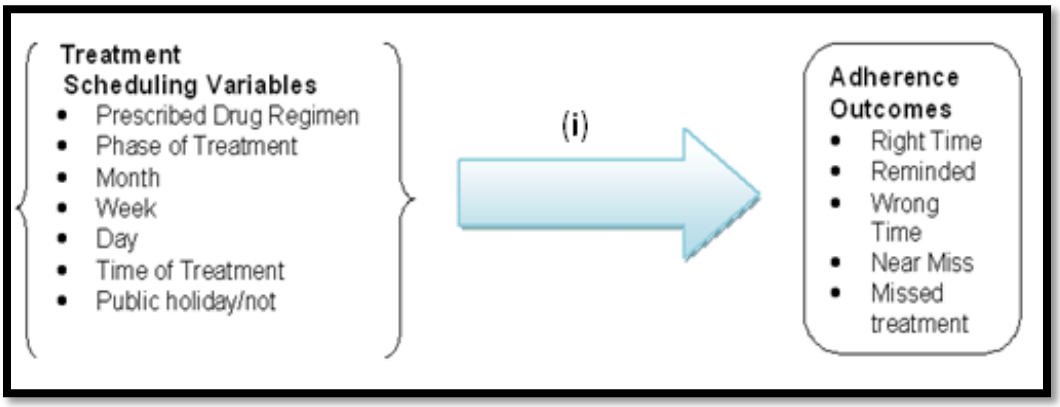
[31] In retrospect, it can now be understood why studies and interventions related to treatment adherence discussed already in Chapter 2 had limitations in more or less similar regard i.e. because the theoretical underpinnings informing them also lack this component, as asserted in this particular section.

Based on these lines of argumentation, this thesis thereby contends that there should be sound theoretical underpinnings giving greater attention to treatment scheduling, as it could potentially be the ultimate decider of adherence behaviour. Failure to have such theoretical perspective could arguably limit understanding on such an important determinant and hence limit possible intervention design that could significantly support adherence among TB patients as well as others on long-term treatment. To that end therefore, this thesis will seek to empirically investigate the relationship between treatment scheduling-related variables and adherence outcomes, considering what happens at that point in real-time when a patient is supposed to take their medication (whether they take it in the right time, wrong time, nearly-miss or miss taking it altogether for any given medication day). It is also hoped that in the process, there would be interrogation of the underlying factors that perhaps lead to the variations in adherence outcomes based on differences in treatment scheduling variables among TB patients. The effect of a real-time cue-to-action (the Simpill SMS reminders) will also be explored through empirical analysis. The theoretical framework to be used in this study, based on the 'treatment scheduling' argumentation is given below:

3.3.2 Study Theoretical Framework and Research Questions

3.3.2.1 Component 1

The study's theoretical framework is basically premised on three sub-components, with the first one essentially pointing to the relationship between treatment scheduling-related variables and adherence outcomes. This is the level at which the core argument of the thesis i.e. the contention that treatment scheduling-related variables can account for a significant amount of variance in adherence outcomes is interrogated. The diagrammatic representation is as given below:



……(1)

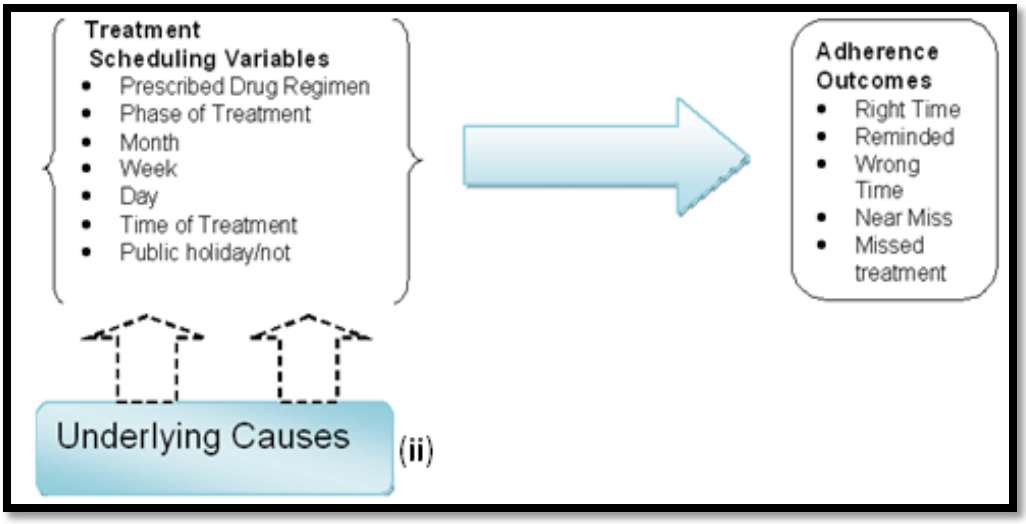
Source: Author
Fig 3.10: Theoretical Framework Component 1

Now based on Component 1, the study's first research question (RQ) is drawn, which is:-

RQ 1: What is the relationship between treatment scheduling-related variables and adherence outcomes?

3.3.2.2 Component 2

Now the anticipation would be that after establishing the relationship between treatment scheduling-related variables and adherence outcomes, the next step would then be to investigate further on the underlying causes why there would have had been specific variability in the dependent variable on account of the predictor variables. In other words, this component would seek to establish the etiological (causative) determinants why adherence might be easier or more difficult under different treatment schedule-related factors than others e.g. day of treatment, month of treatment, phase of treatment, regimen type etc. The diagrammatic representation of this component is as given below:



……(2)

Source: Author
Fig 3.11: Theoretical Framework Component 2

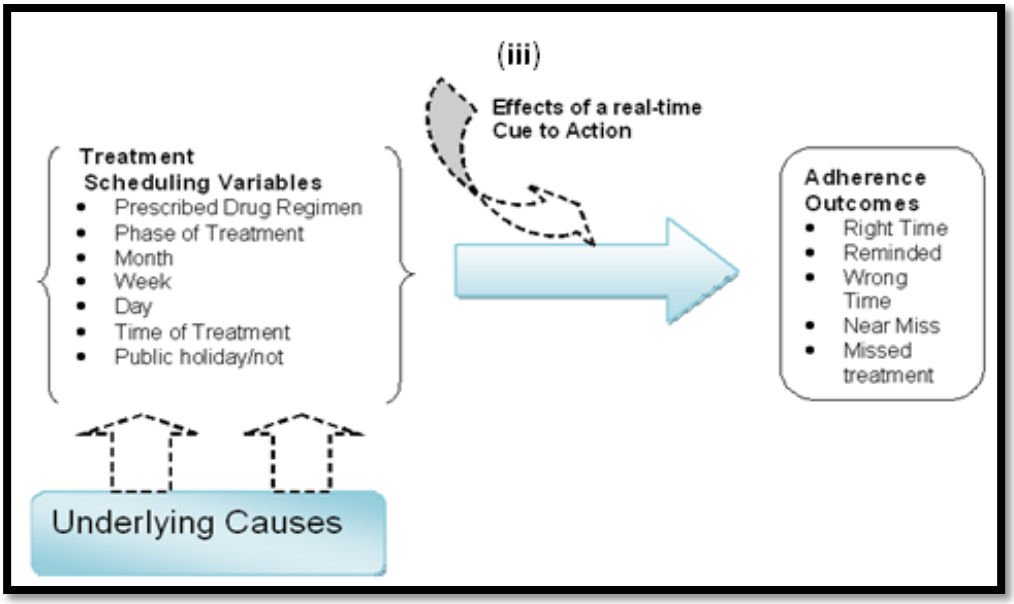
Based on the second component of the theoretical framework therefore, the study's second research question would then arise:

RQ. 2: What are those underlying factors/constructs that are of immediate/precedent importance to (non) adherence in real-time?

In answering this particular question, the study would seek to interrogate the various potential etiologic factors leading to the trends observed under RQ 1.

3.3.2.3 Component 3

Now on the last bit of the theoretical framework is where the issue of the real-time cue-to-action would be further interrogated. Under this question, the study will attempt to investigate whether the Simpill SMS reminders (the real-time cues-to-action) could result in any improvements in attainment of desirable adherence outcomes, as would ultimately be reflected in improvements (or lack thereof) in TB treatment success rates among Simpill-using patients compared to non-users at the end of the treatment period, as shown in the diagram below:-



…….(3)

Source: Author
Fig 3.12: Theoretical Framework Component 3

The research question of interest at this level would therefore be:

RQ 3: What is the effect of a real-time cue-to-action (in this case the SMS reminder from the Simpill system) towards improving adherence outcomes among TB patients?

In other words, in the third research question of the study, it is intended to assess whether TB patients using the Simpill adherence monitoring system would ultimately achieve better treatment success rates (as a result of improved adherence outcomes due to the real-time cue-to-action, by implication) compared to patients on the conventional DOTS procedure (i.e. non-Simpill users).

3.4 Variables in the Theoretical Framework

Now having clearly illustrated the theoretical framework that will inform this study as well as spelling out the research questions, it now becomes important at this stage to discuss the variables (both dependent and independent) that are in the model, so as to contextualize further discussions on methodology. The description of the variables is given below:

3.4.1 Adherence Outcomes (Dependent Variable)

To build onto the already discussed argument by Jay *et al* (1984) that there are potential diagnostic benefits in viewing non-adherence/adherence beyond just the conventional binary manner i.e. patients just being deemed as either having adhered or not, this study proposes to 'unpack' the phenomenon into 5 components. Designated the name 'adherence outcomes' , the thinking behind the unpacking of adherence is that there is arguably a continuum between adherence and non-adherence, and there are stages that a patient's actual medication times can fall into, with desirability of outcome falling from left to right along the continuum (i.e. from adherence to non-adherence) and vice versa. The components of the supposed 'continuum' are thus given below

- **Right Time -** When a patient takes their anti-TB medication at the recommended time
- **Reminded -** When a patient goes beyond the stipulated time to take treatment, but through reminding still takes it within an acceptable window period
- **Wrong Time -** When a patient only takes their treatment after the elapsing of the tolerance period and this is not desirable
- **Near-Miss -** When a patient takes treatment outside the tolerance period (but before scheduled time), falling into the risk of being classified as not having taken treatment at all for a medication day. This is not a desirable outcome
- **Missed Treatment -** When a patient totally misses taking treatment for a given day and this is the least desirable outcome

It is important to emphasise at this juncture that each of these adherence outcome categories and their respective time tolerances (outside the 'right time' category) are based on calculations

that take into consideration the half-life[32] of the respective medication in question, its optimum bio-availability[33] concentrations etc. It therefore means the ranges for these categories differ according to the types of medication and diseases in question. The categorization in this study was specifically for Tuberculosis, based on calculations done by pharmacological experts at Simpill (Pty) Ltd for that specific disease's respective medicines. Assuming this adherence continuum could be empirically proven to exist (through development of a valid empirical model linking it to a number of predictors), the categorization would be useful in giving TB practitioners an idea as to which risk factors lead to the most undesirable adherence outcomes. In other words, there would be keen interest on designing interventions that would attempt to minimize the number of patients falling into the categories of 'Wrong Time, Near-miss and Missing treatment, on the other hand reinforcing those promoting the first 2 adherence outcomes i.e. 'Right time and 'Reminded'. Apart from the company Simpill (see Marshall, 2007) who developed this capacity of adherence outcome measurement (i.e. breaking adherence into at least 3 categories) through their device, the researcher did not find similar level of measurement in any other previous work. Even Simpill (Pty) Ltd had not done any empirical work to develop a real-time model linking this categorized dependent variable with a series of predictors. The researcher was thus keen on pursuing this endevour as part of answering Research Question 1.

3.4.2 The Predictor Variables

Below are the predictor variables that were to be explored based on the theoretical model and the quest to answer the research questions:-

Regimen Type - In this study, in line with World Health Organisation standards, anti-TB treatment was categorized under 3 regimens i.e. Regimen 1 for new adult TB cases[34], Regimen 2 for retreatment adult cases[35] and Regimen 3 for paediatric (children) cases (GoSA, 2000). Appendix 1 gives greater detail into each of the drug regimens.

[32] The amount of time required to reduce a drug level to half of its initial value. Usually the term refers to time necessary to reduce the plasma value to half of its initial value. After five half-lives, 97% of a single drug dose will be eliminated. Mosby's Medical Dictionary, 8th edition. © 2009, Elsevier

[33] The degree of activity or amount of an administered drug or other substance that becomes available for activity in the target tissue. (Mosby's Medical Dictionary, 8th edition. © 2009, Elsevier.)

[34] A new case is defined as a patient who has never had treatment for TB or who has taken anti-Tuberculosis drugs for less than 4 weeks

[35] These are adult cases returning for TB treatment after either relapse of illness, treatment failure or treatment interruption

Phase of Treatment - This predictor variable seperates the first (intensive) phase of taking anti-TB medication from the second (continuation) phase. Again Appendix 1 referenced above gives more detail on what drugs are taken under which phases.

Month of Treatment - refers to the month during the treatment course that medication was taken in.

Week of Treatment - refers to the week during the treatment course in which anti-TB drugs were being taken.

Day of Treatment - refers to the different days of the week on which treatment was being taken over the course of the treatment period. In line with the TB treatment protocol used in South Africa, patients were required to take their medication everyday from Monday to Friday.

Time of treatment - refers to the exact time when the medication was taken by a patient on a particular day.

Public holiday/not - Enquires whether treatment was being taken on a day that was a public holiday or not, according to the South African calendar.

The other factors of interest, mostly being utilized in seeking to answer Research Question 2, are patient's sex (whether a patient was male or female)[36] and age of the patient. A latter section in Chapter 4 will discuss the time and age variables in a bit more detail.

3.5 Chapter Conclusive Remark

Now after having Chapter 3 of this thesis interrogating various theories used in past studies of anti-TB treatment adherence, giving each of them sound critique and eventually developing a theoretical framework (from which research questions were drawn) for this study, the next chapter looks at operationalisation of the derived research questions at the methodological level. In other words, based on an over-arching study design, to each of the research questions is a concise method and data collection technique developed so as to answer it. Chapter 4, which is the next chapter in this thesis, attempts to follow through on the design and methodological aspects of this study.

[36] This predictor variable was to be analysed and rationalized in cognizance of the socio-culturally defined roles, responsibilities and expectations between men and women, hence transforming it qualitatively to the construct 'gender'

CHAPTER 4: Study Design and Methodology

4.1 Introductory Remark

After having built the theoretical argumentation for the study in the previous chapter, this thesis proceeds here in Chapter 4 to look into how the respective theoretical underpinnings and research questions were operationalised at the study design and methodology level. Chapter 4 begins by looking at the study design, and then discusses various other issues ranging from study logic, main assumptions, study site, ethical considerations, up to data collection and empirical analysis methods.

4.2 Study Design: Prospective Randomised Controlled Trial

In reviewing literature (eg Dorak 2010; WSU[37], 2010), it was established and noted that while variables such as age, sex (which this study also intended to explore) were often used as surrogates for etiologic factors in many health-based researches (including studies on adherence as earlier noted in Chapter 2), such variables still needed to be treated as potential sources of confounding. The phenomenon of confounding, as elaborated by writers such as Wunch (2007) and Elwood (1988) occurs whenever an extraneous variable changes systematically along with the independent variable. As a result, the inference of a causal relationship between the independent and dependent variables would be interfered with (Lumley, 2005; Anderson *et al*, 1980). The researcher also found reasonable grounds to suspect that the other independent variables in the study, namely time of taking treatment and the type of anti-TB treatment being taken, could also be potential sources of confounding since their different association with other independent variables could have a bearing on the adherence outcome.

With the possibility of confounding potentially compromising the much-important internal validity[38] of the research, a study design needed to be chosen therefore to control for this

[37] http://www.vetmed.wsu.edu/courses-jmgay/glossclinstudy.htm, accessed 25/03/11

[38] Internal validity is basically truth within a study. It is attained when study conclusions represent the truth for the individuals studied because the results were not likely due to the effects of chance, bias, or confounding because the study design, execution, and analysis were correct (see Last, 2001)

potential problem, and in that respect, the **'Prospective[39], randomized controlled trial'** design was considered as being the most appropriate. This was so in that the design allowed for *ex-ante* randomization i.e. the random selection of patients to be put on the Simpill (i.e. treatment group) and a non-Simpill users group (on the conventional DOTS scheme) being taken as the control group. A latter section under this chapter further elaborates on patient profiling in the treatment group as well as the ethical considerations/justifications of having patients on conventional DOTS as the control group. Such randomization, according to Dorak (2009), would ensure that potential confounders (both known and unknown) would be evenly distributed in the study group. The same author further goes on to say that the avoidance of confounders obtained from randomization can only be sustained if all study participants remained in the group to which they were allocated and no systematic loss to follow-up occurred (i.e. patients leaving the study group for one reason or another). Now to avoid this possibility, as recommended by authors such as Montori & Guyatt (2001); Hollis and Campbell (1999) among many others, the study indeed attempted to maximize follow-up of patients who were on Simpill and therefore made use of the '*intention to treat'* analysis. *"Intention to treat"* is a strategy for the analysis of randomised controlled trials that compares patients in the groups to which they were originally randomly assigned. This is generally interpreted as including all patients, regardless of whether they actually satisfied the entry criteria, the treatment actually received, and subsequent withdrawal or deviation from the protocol (Hollis and Campbell, 1999).

Dorak (2009) further posits that residual confounding could still be controlled at the data analysis stage through the use of stratified analysis (i.e. further breaking down of independent variables into strata/sub-groups to investigate relationships with the dependent variables at that level). Of course while the same writer notes that this has limitations in simultaneous control of confounders, adding other variables would result in a more robust multivariable analysis, which he notes to now actually have the capacity to simultaneously control for confounding factors. This would be so assuming the condition that there are at least ten subjects for every variable investigated (in a logistic regression situation) is satisfied, argues the same author.

[39] The rationale behind the study being 'prospective' was that the events of interest i.e. TB treatment adherence outcomes were being measured concurrent with the study, an attribute of such studies noted by Rothman *et al* (2008).

Based on the need to minimize residual confounding as elaborated above, 2 of the independent variables, already mentioned in *section 3.4.2* of Chapter 3 i.e. *'time of taking medication'* and *'age of patient'* were further 'stratified' into categories as below:-

4.2.1 Time of Taking Medication

Time Category (Time_Cat)	Range
Time_Cat 1	0500-0759 hrs (first part of morning)
Time_Cat 2	0800-1159 hrs (second part of morning)
Time_Cat 3	1200-1359 hrs (first part of afternoon)
Time_Cat 4	1400-1759 hrs (second part of afternoon)
Time_Cat 5	1800-1959 hrs (first part of evening)
Time_Cat 6	2000-0000 hrs (night)

Source: Author

Table 4.1: Stratified time categories

The time of taking medication was essentially broken down into 6 categories as shown in table 4.1 above. The categorization was not just done hap-hazardly; instead, it sought to break down the day into first and second parts of the morning, first and second parts of the afternoon, evening time and night time. As the author to this thesis viewed it, each of the time categories could theoretically have a bearing on a patient's treatment adherence outcome depending on what the patient would have been doing, who they were with or whether whatever circumstances prevailing at that time enabled the taking of medication or not. The study was thus going to empirically interrogate, as part of answering the first research question, what relationship existed between scheduling treatment in any of these time categories and adherence outcomes.

4.2.2 Age of Patient

This variable was broken down into the multiple variable 'Age Categories' as shown in the table 4.2 below:-

Age Category (Age_Cat)	Range
Age_Cat 1	8-14 years
Age_Cat 2	15-21 years
Age_Cat 3	22-35 years
Age_Cat 4	36-49 years
Age_Cat 5	50-63 years
Age_Cat 6	64-84 years

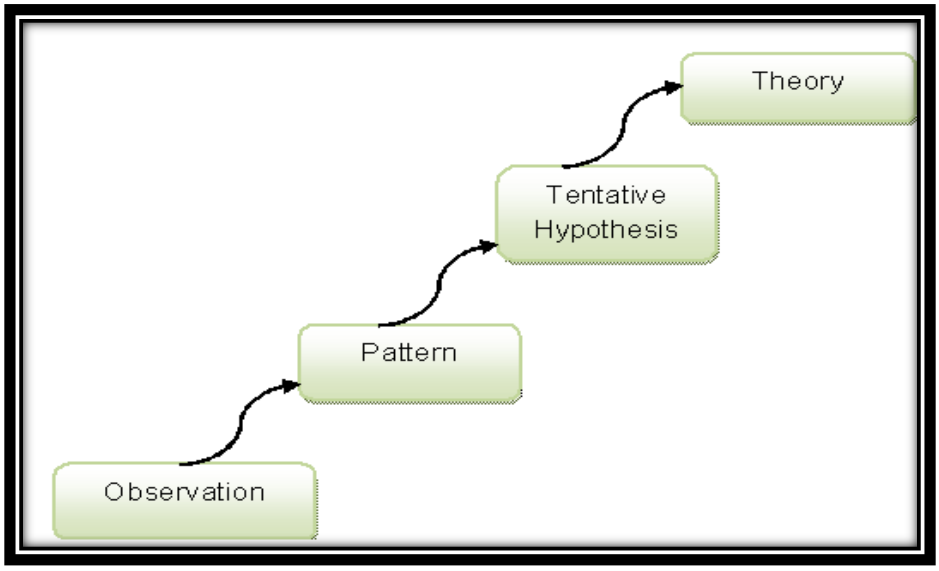
Source: Author
Table 4.2: Age Categories used in the study

Again as in the case of the time variable, the breakdown of the age variable into the 6 categories shown above was not done randomly. In fact, apart from merely intending to overcome the challenge of confounding, it was the researcher's contention that the categories represented various characteristics of the patients that could give insight into potential factors affecting their adherence to anti-TB medication. For instance, Category 1 would consist more or less of children, considered largely incapable of undertaking desirable health behaviours such as in this case treatment adherence without the pro-active help of either parents or guardians. Hence, in the view of this researcher, variation of Category 1 could be used as a proxy to measure the role of care and support in determining adherence outcomes. Category 2 was taken to consist mostly of teenagers and young adults, a group where peer influence would perhaps be the greatest determinant of health behaviour, based on studies such as Pavis *et al* (1997), Varga (1999) and Brook *et al* (2006), among many other studies. The analysis of adherence outcome variation in this age category was thus to be undertaken in this background. Age Categories 3 and 4 were realized to represent the peak life stages of economic productivity (see NIDS, 2009) in the population of South Africa (where this case study was based, see section 4.4 below) and hence analysis of adherence dynamics in these age groups took cognizance of this reality. The last two age categories, 5 and 6 were taken as containing the older members of the population of South Africa (see Statistics South Africa, 2010), and so this opened scope to relate the age group's adherence dynamics to old age-related factors, particularly the increased likelihood of side-effects from anti-TB drugs and general care-related

factors since patients in this category also needed accentuated levels of care and support to adhere due to old age.

4.3 The Study's Logical Framework: Inductive Logic

The study was premised on an Inductive Logic underpinning, which according to Burney (2008) involves the drawing of uncertain inferences based on probabilistic reasoning, such that the reached conclusions would be probable, reasonable, plausible and believable. In further elaboration on inductive logic, also informally called the bottom-up approach or 'hill-climbing'[40], Burney (2008) further notes that inductive reasoning starts with specific observations and measures, in that process taking note of data patterns. From there, tentative hypotheses could then be developed and further interrogated up to the point of developing generalized conclusions or theoretical arguments. The diagram for the logic is as presented below:-



Adapted from Burney (2008)
Fig 4.1: Inductive Logic flow diagram

[40] Looking at the stages from where the logical framework begins and up to where it ends resembles a gradual 'climb' up a hill

4.4 Study Sites

The study was done in the Western Cape Province of South Africa, in the backdrop of that country having one of the world's highest Tuberculosis prevalence rates. As reported by the GoSA (2007) and already mentioned in Chapter 1 of this thesis, South Africa is one of the 22 High TB Disease Burden countries which cumulatively account for an estimated 80% of the global TB burden. According to the same authors there is concern in the country over increase in TB cases due to the disease's nexus with HIV and AIDS, as well as over emerging notifications in drug-resistant TB cases. Provinces such as the Western Cape are noted to be among the leaders in TB cases, particularly amongst the impoverished black and coloured sections of the population who live in squalid informal housing conditions where the spread of TB is easier. Combined with inadequate access to affordable health facilities (since the public institutions are already over-burdened) and the Meditarranean climate of cold and wet winters, TB susceptibility among the poor has been extremely high in the Western Cape Province of South Africa (GoSA, 2007; see also http://www.bridges.org/case_studies/137, accessed 11/05/2011). Thus this high TB susceptibility and prevalence made the piloting of the Simpill technology all worthwhile, with the quest being to potentially find an intervention which could result in improved treatment success rates compared to what had been conventionally realized under DOTS in this province.

Now through the assistance of the Cape Town Metropole District Health Services, 3 high TB burden sites/clinics were randomly selected in 2005 for the study, and these were:

- Michael Mapongwana Clinic - Khayelitsha
- Gustrouw Clinic – Strand
- Kleinvlei Clinic – Kuilsriver

TB patients who had just been registered and about to enroll on treatment were then further randomly selected for the study from these clinics and only those who volunteered to be part of the Simpill pilot were included. After identification of community-based treatment supporters (e.g. family member or someone outside the family), the patients were then taken through counselling and daily treatment monitoring for the first 2 weeks (to also closely monitor side-effects in the first days of treatment), time of which they also received training on use of the Simpill device. The community-based treatment supporters also received the requisite capacity building and from the third week patients were allowed to start self-medicating using the device (see Appendix 4 for the details of the procedure). At the end of the pilot, data was then downloaded from the Simpill server and stored for future use. It is this data, along with data from

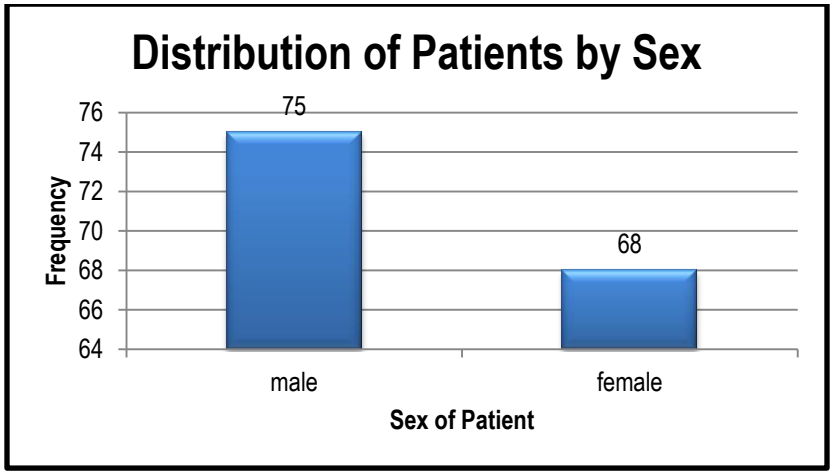
the patients' medical records (i.e. lab test results at the end of the course of treatment) that was used in analysis for this particular study.

4.5 Data Collection Methods

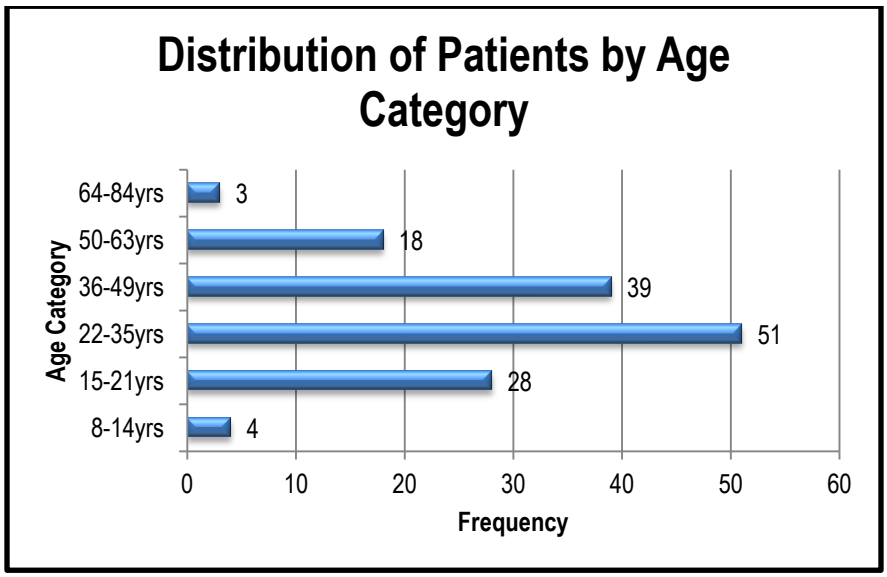
As mentioned in the section above, this study was primarily based on patient data that was downloaded from the Simpill system Server. Appendix 2 shows one of the tools used to collect patients' real-time adherence data on the server. This data was also combined with data collected from patients' medical records, which included demographic data and the treatment regimens patients were put on. A wide literature review was also conducted on previous TB studies (as reported in Chapter 2) and particular attention was paid to South Africa's Tuberculosis Treatment Guidelines (GoSA, 2000), and finally the South African Medicines Formulary (UCT, 2003) for purposes of having a more in-depth pharmacological understanding of the different types of Fixed Dose Combination (FDC) drugs that had been used to treat TB in the case study. For purposes of answering research question 3 that sought to draw comparisons between Simpill and conventional DOTS cure rates, data for the latter was accessed from the Western Cape Department of Health Reports (2005/6 and 06/07). Other relevant literature, including reports from the Government of South Africa and other scholars was also reviewed in building and supporting argumentation on the underlying causes of the various adherence outcomes observed as data was being analysed. The study's bibliography (Appendix 8) acknowledges all these sources.

4.6 Patient Profiling

In total, data from 143 patients, who participated in the initial pilot study between 2005 and 2007, was used for this research. The patients' demographics are as below



Source: Author
Fig 4.2: Distribution of Patients by Sex



Source: Author
Fig 4.3: Distribution of Patients by Age Category

Based on the above-illustrated number of patients therefore, the medication events that were recorded i.e. adherence outcomes for each medication day for the patients throughout the duration of their TB treatment course, which were made use of in this study totalled 9133. These observations were deemed enough a data-set to adequately estimate relationships between the predictor and outcome variables[41]. Now following the already mentioned inductive logic approach, the above-mentioned medication events were analysed in-depth in the study and subsequent inferences drawn from them, as detailed in Chapters 5 and 6 below.

4.7 Main Assumptions in the Study

Four main assumptions were made for purposes of this study. The first one was that patients considered taking anti-Tuberculosis medication as being an 'unnatural' process that represented anything else but a healthy lifestyle. The patients would therefore only be compelled to take the medication when they felt extremely sick or found it convenient to do so. The second assumption made for this study was that the observed medication events (hence the respective adherence outcomes as well) were independent of one another, even for the same patient. In other words, it was assumed that a patient's medication event for one day was influenced by various etiological factors, whose quantities, combination and effects were of necessity 'unique' to each day, to the extent of creating independence between that particular medication event, the ones preceding it and the ones coming afterwards. Thirdly, the study also assumed that the combination and sum-total of the above-mentioned etiological factors influencing adherence outcomes at each of the medication events also effectively controlled for any extra 'motivation' or 'incentive' patients using the Simpill device would have had (to adhere) as a result of using the unique pill bottle.

The fourth assumption made for the study was that use of the Simpill device produced no behavioural learning effect among patients who used it during the pilot. In other words, the thinking here was that the various factors and pressures acting on patients before their medication event (i.e. taking the treatment or failure thereof) could easily overcome any learning induced in patients due to continued use of the device. This was based on arguments from the Classical Conditioning Theory (Huitt & Hummel,1998) which posits that a stimulus (e.g. the SMS reminder) could bring about a reflexive responsive (e.g. in our case a patient taking their treatment after the reminder) without necessarily inducing any learning. It therefore would be

[41] Chapter 5 section 5.0 makes reference to the statistical determination of how these cases were deemed sufficient for the study

plausible enough to suggest that the reminders could simply work as a real-time cue-to-action and not a 'conditioner' so to speak.

4.8 Study limitations

What turned out to be the main limitation of this study was the fact that there was no capacity to capture real-time data for the control group (i.e. non-Simpill users), since there were no real-time treatment monitoring devices used under DOTS as at the time of the pilot study. What could have been ideal, particularly in answering Research Question 3, would have been to compare adherence outcomes between Simpill users and patients on a 'placebo'[42] Simpill without SMS reminders, based on the same statistical models for both groups. Now because there was inadequate funding to have a 'placebo' pillbox for use by the non-Simpill group that still ensured that this group had adequate treatment support so as not to risk their treatment outcomes, this was unfortunately not possible. What it meant therefore was that efficacy of the Simpill system (under Research Question 3) could only be assessed at the comparison of final treatment outcomes, that is a comparison between the Treatment Success rates for Simpill and non-Simpill (i.e. conventional DOTS) using patients. As already discussed in section 2.3.2 of Chapter 2 covering the various measures of adherence, this method was still deemed adequate to interrogate for the efficacy of the Simpill device against the conventional means of treating TB in the study area. In any case, policymakers in the provincial Department of Health had authorized the initial pilot study only to the extent to which it could potentially show improved results from the conventional treatment approach, hence reinforcing the need to compare Simpill results with conventional DOTS as the benchmark. Furthermore, due to ethical issues and the sensitivity of accessing medical records, the researcher in some cases faced difficulties in getting some of the data, particularly the individual medical records from patients in the control group. However a way was also found around this problem, in that there were more easily available and already calculated treatment success average values for the control group, so these, being deemed adequate as well, were made use of in the analysis for RQ 3.

[42] Any dummy medical treatment; originally, a medicinal preparation having no specific pharmacological activity against the patient's illness or complaint given solely for the psycho-physiological effects of the treatment; more recently, a dummy treatment administered to the control group in a controlled clinical trial in order that the specific and non-specific effects of the experimental treatment can be distinguished. (Dorland's Medical Dictionary for Health Consumers. © 2007 by Saunders, an imprint of Elsevier, Inc).

4.9 Ethical Considerations

As a study in the domain of biomedical public health, the research was designed in as far as possible to comply with the "International Ethical Guidelines for Biomedical Research Involving Human Subjects" developed by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (2002). Key among the ethical considerations was the issue of confidentiality. Particularly because the study necessitated the researcher having to sift through former TB patients' clinical records from the period the Simpill pilot was done (2005-07), an undertaking was made by the researcher with respect to keeping information from these records strictly confidential and to access it for purposes of the study only. Former patients' data was thus analysed based on codes since a commitment had also been made to ensure no patient's name was to be attributed to any results in the research report. The researcher also followed up on the initial ethical clearance (through which patients in the pilot had consented to having their data accessed for analysis and research under the Simpill banner) that had been given for the pilot study and renewed this for purposes of this work. As a result of the initial consent having been given through Simpill (Pty) Ltd, the researcher also went under the same banner for purposes of the study.

4.10 Data Analysis

With respect to answering Research Questions 1 and 2, the main data analytical tool that was employed was Multinomial Logistic (MNL) modeling and this was run with the Statistical Package for Social Sciences (SPSS). This method of data analysis was chosen for 3 main reasons, the first being that the dependent variable of interest in the study (i.e. Adherence Outcomes), was polytomous i.e. had more than 2 categories of determination (see Pryanishnikov and Zigova, 2003). The second reason was that it was seen as useful in further controlling for simultaneous and residual confounding, as earlier on discussed in Section 4.2. The third reason was that the method was deemed relatively novel with respect to analysis of treatment adherence data. Among the reviewed journal articles and other literature material on adherence studies, the researcher did not come across any that used this method, hence the incentive to make use of it, particularly in view of its potential to analyse the dependent variable based on a desirable reference point among its sub-categories. This was seen as being of great use especially as the study sought to advance the argument regarding the presence of an adherence continuum, premised on the concept of adherence outcome with more than 2 categories of determination i.e. 'Right Time, Reminded, Wrong Time, Near-miss and Missing'

treatment (see earlier discussion in section 3.3.2 of Chapter 3). The section below explains Multinomial Logistic modeling in greater detail.

4.10.1 Multinomial Logistic Modeling

Multinomial Logistic modeling is best used, according to authors such as Rao *et al* (2008) and Harrell (2001) to establish a relationship between a non-metric dependent variable and metric or dichotomous independent variables. This approach therefore seeks to model the probability associated with each category of the dependent variable based on the values of the predictor variables, with one of the dependent variable categories (usually the one with the highest numeric score) as the reference category. For this particular analysis, the outcome category 'Right time' was used as the reference group.

As elaborated upon by Borooah (2001), the mathematical derivation of the Multinomial Logistic model, based on a categorical dependent variable with K categories, is as in equation (1) below:

$$\mathbf{Pr(Y = i)} = \frac{\mathbf{exp(Z_i)}}{\mathbf{1} + \sum_{h=2}^{K} \mathbf{exp(Z_{hi})}}$$

Where:

$$\alpha_i + \sum_{h=1}^{H} \beta_{ih} X_{ih} = Z_i$$

For the reference category, it's formulated as in equation (2) below

$$\mathbf{Pr(Y = 1)} = \frac{\mathbf{1}}{\mathbf{1} + \sum_{h=2}^{K} \mathbf{exp(Z_{hi})}}$$

After re-arranging equations (1) and (2), the Multinomial Logistic model can be written as in equation (3) below:

$$\ln\left\{\frac{P(Y=i)}{P(Y=1)}\right\} = \alpha_i + \sum_{k=1}^{H} \beta_{ih} X_{ih} = Z_i$$

Where:

i : the *ith* adherence outcome category

β_{ih} , X_{ih} : vectors of the estimated parameters and predictor variables respectively

$\frac{P(Y=i)}{P(Y=1)}$: the probability of adherence outcome category, with the first category as reference

It is important to note that the Multinomial Logistic model translates the relationship between the independent variables and the categories of a dependent variable into a linear function, whose interpretation is the same as that in Ordinary Least Squares regressions.

4.10.1.2 Assumptions and Requirements of Multinomial Logistic Modeling

The main assumption of Multinomial Logistic Modeling is that the relative odds of any two response categories are independent of all other response categories. Unlike Ordinary Least Squares regression modeling, it does not make any assumptions of normality, linearity, and homogeneity of variance for the independent variables. In terms of requirements, Multinomial logistic regression analysis requires that the independent variables be metric or dichotomous. If working in SPSS however, the programme will automatically dummy-code nominal level variables, so they can be included since they will be dichotomized in the analysis (SPSS Inc, 2008; Chan, 2005)

4.10.1.3 Checking Data for Outliers and Interference

As noted by www.utexas.edu (20/12/10) and Harrel (2001), since SPSS does not compute diagnostics for outlying as well as interfering values in the MNL modeling process, the option would be to firstly formulate the identification of such values through the use of the concepts of Cook's Distance and standardized residuals. According to McDonald (2002), Cook's distance (D_i) is an influence measure whose usual criterion is that a point is influential in a regression model if the point's (D_i) value exceeds the median of the $F_{p,n-p}$ distribution, where *p* is the number of regression parameters and *n* the number of data. While the same author reports that there is generally no agreement amongst authors as to what the threshold value for Cook's distance should be, he notes that Chatterjee *et al* (2000) quote D_i>1 as an operational guideline.

Meanwhile, standardized residuals are derived from dividing the error component in a regression model by an estimate of its standard deviation, as elaborated by (http://www.ist.massey.ac.nz/dstirlin/CAST/CAST/HdiagnosticsTwo/diagnosticsTwo4.html[44].

Now if the regression model is linear, approx. 95% of the standardized residuals are supposed to be between -2 and +2, and virtually all of them must lie between -3 and +3. The upper limit >3 would therefore be used in the identification of outliers and interference (see www.utexas.edu , 20/12/10 and Harrel, 2001). Finally, a series of binary logistic regression equations for the whole combinations of the categories of the dependent variable are then run to test whether any of the identified outliers possibly cause any major shifts in results, particularly in the strength of the overall MNL model.

4.10.1.4 Overall Model Fit in Multinomial Logistic Regression

The ascertaining of a relationship between a group of independent variables and the corresponding multinomial dependent variable is premised on the reduction in the likelihood values between the regression model which does not contain any of the independent variables and the model which has the independent variables (Wedagama and Dissanayake, 2009). This difference in likelihood between the 2 models follows a chi-square distribution and is termed the model chi-square. With a null hypothesis of there being no difference between the model without independent variables and the one with independent variables, as expressed below:

H_0: Intercept only model = final model with independent variables

, the significance test for the final model chi-square therefore either confirms/disconfirms the presence of a relationship between the independent and the multinomial dependent variable (www.utexas.edu (20/12/10); Cramer, 2003).

4.10.1.5 Strength of the Multinomial Logistic Model

After running a regression model, it comes quite naturally to want to understand its strength i.e. the extent to which the combination of independent variables can account for variance in the dependent variable. Hu *et al* (2006) point out that one way to measure the usefulness of a regression model is through the so-called R^2 statistics, or the co-efficient of determination. Mittlboeck and Schemper (1996) note that the co-efficient of determination can be classified into two main categories; the more common variance-based R^2 statistic and entropy (or information

[43] accessed 15/05/11
[44] accessed 15/05/11

gain) based R^2, also referred to as the pseudo-R^2 statistic. While authors such as Draper and Smith (1998) and Helland (1987) typically demonstrate the wide extent to which the variance-based R^2 statistics are used in classical linear regression models, Hu *et al* (2006) come in once again with an argument that in logistic regression, the best form of R^2 is not all too clear and so many different co-efficients of determination have been proposed in various studies in the past three decades. In fact it does appear like the stronger inclination in logistic regression modeling is towards the pseudo-R^2 statistic, arguably because the variance-based R^2 statistic does not take into account the error variance structure of logistic modeling and also because its value is not maximized when the maximum likelihood procedure is used in model fitting (*ibid*).

With specific reference to multinomial logistic models, Washington *et al* (2003) argue that the higher the pseudo-R^2 statistic, such as the Nagelkerke's R^2, the better the model. However, Harrell (2001) counter-argues saying that it is not necessarily so, rather asserting that these correlation measures do not really say much about the accuracy or errors associated with the multinomial model. In fact, another set of authors, O'Donnel and Connor (2002) posit that it is common practice to overlook the pseudo-R^2s in MNL modeling for the reason that there are no generally accepted measures for those types of statistics and that they also have theoretical as well as empirical upper limits substantially less than one.

The point of convergence in determining the strength and usefulness of a multinomial logistic regression between a set of independent variables and the dependent variable among various authors however appears to be in what is termed the model's **classification accuracy criteria**. This criterion is defined by www.utexas.edu (20/12/10) as comparing predicted group membership based on the logistic model to the actual, known group membership, which is the observed value for the dependent variable.

The same author goes on to explain that even in a case where there was no relationship between the independent variables and the groups defined by the dependent variable, it could still be expected that predictions of group membership would be correct some proportion of the time i.e. proportional by-chance accuracy. To ascertain the usefulness and strength of the multinomial model in explaining the relationship between the predictor and the outcome variables therefore, there has to be an improvement of a specified margin on the model from the by-chance accuracy level. The authors Bayaga (2010) and Yadollahi *et al* (2009) among others demonstrate in their papers how to undertake the actual calculations that will lead to this determination of usefulness and strength of the MNL model. As shown in work by the afore-

mentioned authors, the proportional by-chance accuracy rate is computed by summing the squared proportions of cases in each group/category of the multinomial dependent variable (as read from the case processing summary of the SPSS output). Now the argument is that for a MNL model to be deemed strong enough to usefully predict the relationship between its predictors and outcome variables, the afore-mentioned proportional by-chance accuracy rate has to be improved by at least 25% in the MNL model with the predictor variables (Wedagama and Dissanayake, 2009). A criteria is therefore set, whereby the **proportional by-chance accuracy rate** is multiplied by 1.25 to give the **proportional by-chance accuracy criteria**. The latter is then compared to the MNL model's classification accuracy rate, found in the classification statistics table generated through analysis in SPSS. If the model classification accuracy rate is larger than the **proportional by-chance accuracy criteria**, then strength and usefulness of the model is therefore supported (see Bayaga, 2010; Yadollahi *et al,* 2009)

4.10.1.6 Likelihood Ratio Tests

Harrell (2001) and www.utexas.edu (20/12/10) point out that in Multinomial Logistic regression models, interpretation for an independent variable is based on its ability to distinguish between pairs of groups and the contribution that independent variable makes to change the odds of being in one dependent variable group rather than the other. The same authors also contend that the significance of an independent variable's role in making distinction between pairs of groups should not be interpreted unless the independent variable itself has an overall relationship to the dependent variable, based on the likelihood ratio test.

4.10.1.7 Parameter Estimates

(i) Numerical Problems

Authoritative writers in Multinomial Logistic Modeling (e.g. McFadden,1974; Harrel, 2001, Borooah, 2001) note that the maximum likelihood method used in this type of modeling is an iterative fitting process attempting to cycle through data points until it establishes trends and relationships between independent variables and the categories of dependent variables. In some cases this process could break down and not find solutions at all, or it might give improbable results, that show unit changes in the independent variables modifying the odds of the dependent variable by hundreds of thousands or even millions. This is attributable to what www.utexas.edu (20/12/10) terms numerical problems, possibly caused among other things by multicollinearity or categories of independent variables having no cases or zero cases. As noted by the same authors and further supported by Yadollahi *et al* (2009), the general approach is therefore not to interpret results where the estimation of the relationship between the dependent

and the independent variable has a standard error value which is larger than 2.0, and so this approach was followed in interpreting the parameter estimates for Research Question 1. This also assisted in strengthening model validity, as it reduced sources of standard error in the model.

(ii) Wald's Test

Polit (1996), among other authors such as Hosmer and Lemeshow (2000) and Gourieroux (2000) describe in detail the important role of the Wald's Test as one of a number of ways to test whether the parameters associated with a group of predictor variables are zero. Similarly in the Multinomial Logistic Model, the Wald's Test plays the role of evaluating if the independent variable is statistically significant in differentiating between the 2 groups in each of the embedded binary logit comparisons. While such role is without doubt important, it is the contention of this research that a significant Wald's Test can only show us that the established relationship can also be generalized to the wider population beyond just the sample, and the reverse is also true for a non-significant result. Furthermore, www.utexas.edu (20/12/10) also notes that it is possible for an independent variable to have an overall relationship to the dependent variable in the Likelihood ratios test and still not be statistically significant in differentiating between pairs of groups defined by the dependent variable. This only goes to underscore the importance of interpretation of parameter estimates using the exp (B) or Odds Ratios in MNL models, an approach followed in this study. The section below elaborates on the interpretation of odds ratio values in MNL modeling.

4.10.1.8 Interpretation of Odds Rations (ORs) in MNL Modeling

As explained by http://www.ats.ucla.edu/stat/spss/output/mlogit.htm, (accessed 15/10/11) the odds ratios (ExpB) in MNL modeling, just like in binary logistic modeling, are an 'exponentiation' of the predictor variable co-efficient. The odds ratio, according to the same source shows the likelihood of an outcome being in the comparison group versus falling in the referent group. As shown in work such as by Yadollahi (2009) and Bayaga (2010), an OR greater than 1 shows that the likelihood of an outcome being in the comparison group relative to the referent group increases as the predictor variable under consideration increases, with the opposite also being true. Put in other words, an OR>1 implies the outcome is more likely to be in the comparison group and an OR<1 implies the outcome is more likely to be in the referent group. Therefore subtracting 1 from the OR value for an outcome in MNL modeling will give the factor of increase or decrease (depending on whether the result is positive or negative) in the likelihood of an outcome falling in the comparison group relative to the referent group with a unit increase in the

predictor variable (see Harrell, 2001). Furthermore in this study, the researcher termed the (OR-1) values the ΔExp(B)values i.e. which showed changes in OR values of an outcome falling in the comparison group relative to its referent group with a shift from one category of the independent variable to the other (since the predictors were essentially categorical). These ΔExp(B) values were then plotted into graphs for purposes of interrogating which predictor variable led to the greatest shift in the OR value under a respective outcome variable category.

4.10.2 Main Assumptions of Ordinary Least Squares (OLS) Regression and the T-test

4.10.2.1 Ordinary Least Squares (OLS) Regression

The study also made use of the ordinary least squares (OLS) regression method (run in SPSS as well), particularly in strengthening the answering of Research Question 2. This was neccessiated by the fact that during the process of creating dummy variables in MNL modeling, some categories of the predictor variables were being made redundant, hence removing data sets that could be useful in deriving important inferences in the study (see http://psych.unl.edu/psycrs/971/altreg/logistic1.pdf , accessed 28/04/11). OLS regression was therefore seen as useful in terms of improving appreciation of the effect of the predictor categories that would otherwise have been removed by MNL on the dependent variable, although of course the interpretation was now based on the OLS co-efficients not odds ratios. The method's key assumptions were therefore taken into cognizance at the theoretical level in this study, and the issues considered are as given below:

- Linearity - the relationships between the predictors and the outcome variable was theoretically assumed to be linear. In other words, according to the explanation of **http://www.xycoon.com/** (accessed 11/05/11), the assumption was that the hypothesized model represented the **true (linear) relationship** such that after extraction of the RHS[45] influences from the endogenous variable, the residual component has an expectation of zero.
- Normality - the errors were taken to be normally distributed
- Homogeneity of variance (homoscedasticity) - the error variance was taken to be constant

[45] RHS indicates the right hand side parameters of a function (http://www.snv.jussieu.fr/~wensgen/Doc/scilab-2.6/internals/node18.html , accessed 11/05/11)

- Independence - the errors associated with one observation were assumed not to be correlated with the errors of any other observation[46]

4.10.2.2 Comparison of Treatment Success Rates Between Simpill and non-Simpill users: The Student's t-test

Now as a means towards answering Research Question 3, i.e. seeking to interrogate the effect of a real-time cue-to-action (in this case the SMS reminder from the Simpill system) towards improving adherence outcomes/behaviour among TB patients, the method of comparing treatment success rates between the Simpill and non-Simpill users (conventional DOTS) was opted for. In that regard, it was reasoned out that higher treatment success rates would show, indirectly, patients who had maintained higher levels of adherence to their treatment regimens, hence having better chances or being cured of TB or at least completing the course of treatment. Using the Student's ***t***-test to show significance of the difference between treatment success rate averages for patients using the Simpill device and those on conventional DOTS would therefore give a clear picture of which method led to better adherence outcomes. The key assumption here was that the likelihood of treatment failure as a result of other causes (e.g. HIV co-infection) had more or less equal chances of occurring among the patients, hence this was considered as a constant[47]. It meant therefore that the observation of treatment success in this case would be narrowed down to adherence to treatment regimen as the etiologic factor. Now if it so turned out that TB patients who were medicating using the Simpill device had better treatment success rates than those on conventional DOTS, then that could be taken as proxy for the efficacy of the device's core functionality, i.e. the SMS reminders (the real-time cue-to-action) as a means of promoting adherence among patients.

[46] (http://www.ats.ucla.edu/stat/stata/webbooks/reg/chapter2/statareg2.htm, accessed 11/05/11)

[47] It is essential to note that this assumption finds importance in minimizing known and unknown sources of confounding in the relationship of interest i.e. the effect of the real-time cue to action on adherence outcomes. It therefore becomes clear that the study design gives credibility to this assumption

Due to the intentions of this study to use the Student's ***t***-test as the data analytical tool for answering Research Question 3, important assumptions for this method were also taken into cognizance of and these are as stated below:

- Samples (both test and control, in our case the TB patients using Simpill and those on conventional DOTS) were randomly drawn from a normally-distributed population
- Independence of the groups under consideration i.e. assuming that between the patients using the Simpill device for treatment and those on conventional DOTS, nothing in one group helped to determine who was in the other group.
- The variable of interest under test i.e. treatment success rate was metric

4.11 Chapter Conclusive Remark

Now after having in great detail described the study design, methodological underpinnings guiding the answering of the study's research questions, among other key issues such as ethical considerations, key limitations and assumptions in this chapter, the next task is to look at the findings from the various analyses carried out. The next section, Chapter 5, will thus endevour to achieve that goal.

CHAPTER 5: FINDINGS OF THE STUDY

5.0 Adequacy of cases for the study

In view of the fact that Multinomial Logistic modeling requires a data set to have a valid case:predictor variable ratio of at least **10:1**[48], a determination was done first and foremost to check if the dataset used in this study was adequate enough to investigate the required relationships. It emerged from a look at the data analysis output[49] that the valid *'case: predictor'* variable ratio was **6950:27**, translating to approximately **257:1**, hence the dataset was deemed sufficient for the analyses under this study. After also satisfactorily checking the dataset for any interfering cases using the method described in section *4.10.13* of Chapter 4, the analyses were undertaken and the results are elaborated on from the section 5.1 below:

5.1 Overall Model Fit of the Multinomial Logistic Regression Model

Based on the detailed discussion of model fit statistics in Multinomial Logistic modeling in section *4.10.1.4* in the methodology chapter above, under the null hypothesis given below,

H_0: Intercept only model = final model with independent variables,

the overall model fit was run to ascertain the existence of a relationship between the combination of treatment scheduling-related variables and adherence outcomes. The results are in Table 5.1 below

Model Fitting Information

Model	Model Fitting Criteria	Likelihood Ratio Tests		
	-2 Log Likelihood	Chi-Square	df	Sig.
Intercept Only	3947.382			
Final	3181.887	765.495	88	.000

Source: Author's Data Analysis Output
Table 5.1: Model Fitting Information for the MNL Model

[48] See Hosmer and Lemeshow,(2000); www.utexas.edu (20/12/10)
[49] See Appendix 7 which shows the case processing summary for the dataset

As can be observed in the above table, the probability of the model chi-square (765.495), with 88 degrees of freedom, was 0.000, a figure which fell into the 'less than or equal to 0.05' level of significance. The $\mathbf{H_0}$ of there being no relationship between treatment scheduling-related variables and adherence outcomes was therefore rejected. Conversely, the existence of a relationship between the combination of treatment scheduling-related variables and adherence outcomes in this study was thus supported. This was noted to be an extremely important result in that it validated the feasibility of breaking down adherence/non-adherence into a polytomous variable i.e. with sub-categories right time, reminded, wrong time, near-miss and missed outcomes. These sub-categories of the adherence outcome variable could thus be laid out more or less into a continuum of outcomes ranging from adherence on one end to non-adherence on the other.

5.2 Strength of the Multinomial Logistic Model

Based also on the explanation already given in section *4.10.1.5* of the previous chapter, a computation was undertaken to determine the strength of the Multinomial Logistic model used in the study. The results and conclusions thereof are in this section.

Case Processing Summary

		N	Marginal Percentage
Adherence Outcome	Right_time	3882	55.9%
	Reminded	1028	14.8%
	Wrong_time	759	10.9%
	Near-miss	304	4.4%
	Missed	977	14.1%

Source: Author's Data Analysis
Table 5.2: Case Processing Summary for the Dependent Variable Categories

Based on the above case processing summary, the by-chance accuracy rate was derived from summing the squared proportions of each of the individual items in the dependent variable, i.e. $0.559^2+0.148^2+0.109^2+0.044^2+0.141^2$ = **0.368083 (36.8%)**. Therefore the **by-chance accuracy criteria**, meaning an increase of at least 25% on the by-chance accuracy rate was determined to be **1.25 X36.8%=46%**

To characterize the Multinomial Logistic model as useful/strong enough to demonstrate a relationship between treatment scheduling-related variables and adherence outcomes, the per-chance accuracy criterion calculated above was compared to the overall model classification accuracy rate highlighted in the table below:

Classification

Observed	Predicted					
	Right_time	Reminded	Wrong_time	Near_miss	Missed	Percent Correct
Right_time	3807	64	0	0	11	98.1%
Reminded	951	67	0	0	10	6.5%
Wrong_time	712	41	1	0	5	.1%
Near_miss	287	15	0	0	2	.0%
Missed	899	21	0	0	57	5.8%
Overall Percentage	95.8%	3.0%	.0%	.0%	1.2%	56.6%

Source: Author's data analysis
Table 5.3: Classification Table for the Dependent Variable Categories

As shown in the table above, the overall model classification accuracy rate was 56.6%, which was greater than the proportional by-chance accuracy criteria of 46%. It means therefore that the criteria of classification accuracy for the Multinomial Logit model, in the relationship between treatment scheduling related variables and adherence outcomes, was satisfied. This also was important in that it confirmed that the multinomial determination of a polytomous adherence variable (continuum) based on treatment scheduling-related predictor variables was credible and strong enough.

5.3 Likelihood Ratio Tests

Once again, drawing from the detailed explanation on the importance of the Likelihood Ratio tests in MNL modeling in section *4.10.1.6* of the previous chapter, the table below gives the likelihood ratio test results showing which of the independent variables (treatment scheduling-related variables) had an overall relationship with the multinomial dependent variable (i.e. adherence outcomes).

Likelihood Ratio Tests

Effect	Model Fitting Criteria: -2 Log Likelihood of Reduced Model	Likelihood Ratio Tests: Chi-Square	df	Sig.
Intercept	3181.887[a]	.000	0	.
Regimen	3309.516	127.629	12	.000
month	3349.347	167.460	32	.000
day	3323.008	141.121	24	.000
Time_Cat	3488.257	306.370	16	.000
phase	3185.165[b]	3.278	4	.512

Source: Author's Data Analysis
Table 5.4: Likelihood Ratio Tests for Predictors in the MNL model

Based on results in the table 5.4 above, the drug Regimen was a significant predictor (p=0.000) of adherence outcome, and so was month of treatment (p=0.000), day of taking treatment (p=0.000) and Time Category of treatment (p=0.000). The variable 'phase' was found not to be a significant predictor (p=0.512), hence it meant that only the first four's effects on adherence outcomes could then be subsequently interpreted using their MNL odds ratio values. Although the phase variable could not as a result of its non-significant p-value be interpreted as part of the multinomial model (see section *4.10.1.6* in methodology chapter), it was still analysed using Ordinary Least Squares, as shown later in the write-up.

Meanwhile, the quantifiable interpretation of the relationship between each of the adherence outcomes and the treatment scheduling-related predictor variables is laid out in detail in the next section below, which looks at parameter estimates:

5.4 Results for Reminded Outcome

In presentation and interpretation of the coefficients in the following tables it must be re-emphasised that these coefficients represent differences to the reference classes of the independent variables as mentioned already on page 79.

Adherence Outcome[a]	B	Std. Error	Wald	df	Sig.	Exp(B)	95% Confidence Interval for Exp(B)	
							Lower Bound	Upper Bound
Reminded								
[Regimen=1.00]	.626	.475	1.738	1	.187	1.869	.738	4.738
[Regimen=2.00]	1.166	.478	5.960	1	.015	3.210	1.259	8.189
[Regimen=3.00]	-.461	.583	.626	1	.429	.630	.201	1.977
[Time_Cat=1.00]	.557	.156	12.825	1	.000	1.746	1.287	2.369
[Time_Cat=2.00]	.173	.130	1.769	1	.183	1.189	.921	1.535
[Time_Cat=3.00]	1.768	.175	101.636	1	.000	5.860	4.156	8.264
[Time_Cat=4.00]	.720	.177	16.599	1	.000	2.054	1.453	2.904
[Time_Cat=5.00]	0[b]	.	.	0	.	.	.	.

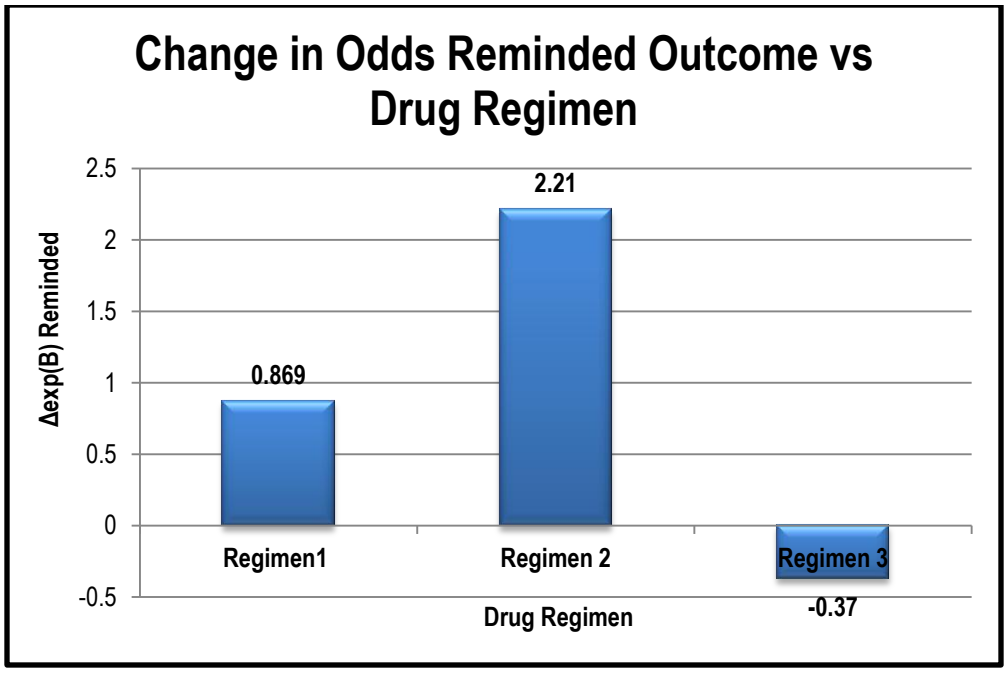
a. The reference category is: Right Time.

b. This parameter is set to zero because it is redundant.

Source: Author's Data Analysis
Table 5.5: Parameter Estimates for 'Reminded' Outcome

5.4.1 Regimen

As evident in the output above from the study findings, a patient on drug Regimen 1 was 86.9%(1.869-1) more likely to be in need of being reminded to take their medication relative to taking it at the right time, all other factors being held constant. In the same manner, a patient who was on drug Regimen 2 was 221% (3.21-1) more likely to be in need of being reminded to take their medication relative to taking it at the right time, all other factors being held constant. A patient on drug Regimen 3 was however shown to be 37% (0.63-1) less likely to be in need of being reminded to take their medication relative to taking it on the right time, other factors being held constant. The graph below plots the change in odds {Δexp (B)} of patients needing to be reminded to take their anti-TB drugs against their prescribed Drug Regimen.



Source: Author
Fig 5.1: Change in Odds for a Patient 'Reminded' Outcome against Drug Regimen

In looking at the above graph that draws comparison in the changes in odds of patients needing to be reminded to take their treatment by drug regimen, it can immediately be observed that a patient taking drug Regimen 2 had the greatest likelihood of needing to be reminded for them to take their anti-Tuberculosis treatment compared to the other regimens. Perhaps for a more meaningful analysis, there might be need to compare Regimen 1 and Regimen 2 on their own initially, since they are both used for treatment in adult Tuberculosis cases, and then thereafter attempt to rationalize the value for Regimen 3 (which is a paediatric regimen) .

Now getting back to the observations, drug Regimen 2, with a Δexp(B) value of 2.21, was noted to present a relatively greater adherence difficulty compared to Regimen 1 { Δexp(B) =0.869} under the 'Reminded' outcome. In other words, it would require relatively more effort to get a patient on Regimen 2 to take their medication compared to one on Regimen 1. This study contends that the major reason to explain this variation has to do with medicinal factors associated with both regimens. Patients on drug Regimen 2 took the Fixed Dose Combination (FDC) drug Rifafour (RHZE 120/60/300/200 mg) and the drug Streptomycin (S) 5 days a week for the first 2 months of treatment (intensive phase), then Rifafour alone in the third month before moving to Rifinah (RH 150/100 or RH300/150 mg) and Ethambutol (E) for 5 months (continuation phase). This was in contrast to patients on drug Regimen 1, who only had to take the drug Rifafour in the first 2 months of treatment (intensive phase) followed by Rifinah for 4

months (continuation phase). Now considering having to possibly endure the side-effects associated with Rifafour (including nausea, vomiting, diarrhoea, general body malaise etc.) for a much longer period, patients on Regimen 2 moreover had to contend with the adverse side-effects associated with the extra drug Streptomycin (including some forms of temporary deafness, body malaise etc.) that was part of their prescription in the third month of treatment. Furthermore these patients on Regimen 2 also had to endure side-effects associated with Rifinah (e.g. jaundice) and Ethambutol (some form of visual impairment) in the continuation phase[50]. Clearly, patients on Regimen 2 tended to have more likelihood and potentially greater severity of drug-induced side-effects to deal with compared with those in Regimen 1, due to the composition of drugs (that were also noted to be more in number per dosage event) and the longer time of taking that regimen.

Taking anti-Tuberculosis treatment was noted to come with the need for regular medical check-ups on say liver and kidney functions for evidence of side-effects, as well as recommendations on limiting the amount of food, hours one had to wait between taking anti-TB drugs and eating, discouragement from driving or operating machinery or other instruments of work after taking some types of medication (due to side-effects) etc. All this was noted to potentially affect patients' day-to-day lifestyles for undesirable periods of time, and these challenges only got worse when the drug regimen (e.g. Regimen 2) had more drugs and hence more complexity in adhering to. Regimen complexity was indeed noted therefore to be a key determinant in treatment adherence outcomes of patients.

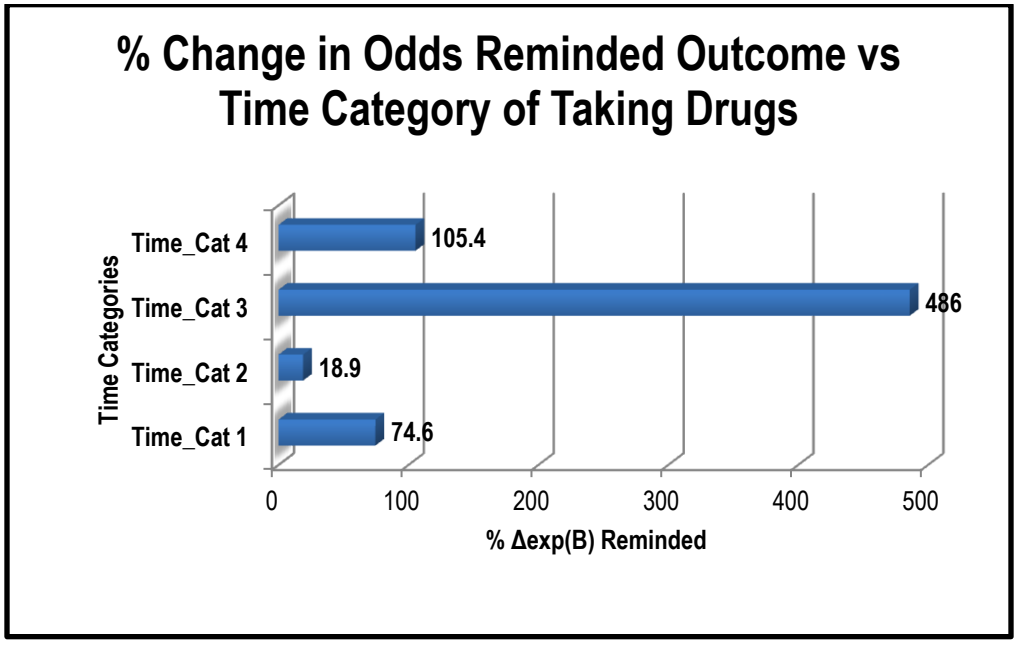
Patients on drug Regimen 3 were paediatric cases (children), who were deemed not capable of self-medicating. In other words their treatment adherence outcomes were a direct function of the level of care and support given to them by a parent, guardian or family member who was responsible for managing their treatment schedule. This explains the very low adherence difficulty {$\Delta \exp(B) = -0.37$} under this outcome, as the children most likely had someone older in the family effectively managing their treatment, and making sure they took treatment more or less as per schedule. Further sections of this thesis will explore and elaborate further on the importance of care and support for patients incapable of self-medicating.

.

[50] See Appendixes1 and 3

5.4.2 Time Category

It emerged from the findings of the study that a patient who was taking their anti-Tuberculosis drugs in Time Category 1 (between 5am-7.59am) was 74.6% (1.746-1) more likely to be in need of being reminded to take treatment relative to taking it at the right time, all other factors being held constant. A patient taking their anti-TB drugs in Time Category 2 (8am-11.59am) was 18.9% (1.189-1) more likely to be in need of being reminded to take treatment relative to taking it at the right time, all other factors being held constant. A patient taking their anti-TB drugs in Time Category 3 (12noon-1.59pm) was 486% (5.86-1) more likely to be in need of being reminded to take their treatment relative to taking it at the right time, keeping all the other factors constant. A patient taking their anti-TB drugs in Time Category 4 (2pm-5.59pm) was 105.4% (2.054-1) more likely to be in need of being reminded to take their treatment relative to taking it at the right time, keeping all the other factors constant. The graph below plots the change in odds {Δexp(B)} of patients needing to be reminded to take their anti-TB drugs against their Time Categories of taking treatment, thus creating an opportunity to compare the changes in odds of a patient needing to be reminded to take treatment by time categories.



Source: Author
Fig 5.2: % Change in Odds 'Reminded' Outcome against Time Category of Taking Drugs

What can be observed from the graph, Fig 5.2 above is that treatment is relatively more easily taken during the morning (Time Categories 1 and 2), i.e. with Time Category 2 seemingly more convenient, as shown by its lower %Δexp(B) value of 18.9 compared to Time Category 1

(%Δexp(B) value of 74.6). Mornings would tend to be easier for treatment possibly because, as the day begins, patients are still at home and would not have started with their daily routines (assuming they are fit enough to resume their normal schedules whether they are in or out of school, or are in any kind of employment), although too early in the morning, as in Time Category 1 might still present challenges i.e. waking up hours. Even for patients who require care and treatment support, the carers themselves would also more likely to still be at home in the morning, hence their availability to support patients' taking of treatment. It could also be argued that taking treatment in the morning would be convenient for patients, since such barriers as stigma or other social pressures from peers would be minimized as they would still be at home or would still not have interacted with so many people and circumstances that could otherwise discourage them from taking treatment.

As the day moves further, the graph shows treatment getting relatively more difficult to take (as in Time Category 3 i.e. between 12noon-2pm) perhaps as daily routines become more pressing and create conditions, whether work-related, school-related or socially-related, that are not conducive for taking medication by patients. For instance, a teenage patient might choose to postpone taking treatment because of fear of stigma at school, or an adult working patient might also choose to push taking treatment by a few hours due to undesirable side-effects[51] induced by the drugs when he/she in fact needs to be working. Going further to Time Category 4 i.e. between 2pm-6pm, as daily routines are gradually being wound up on, the likelihood of needing to be reminded to take treatment also begins to drop {%Δexp(B) = 105.4}, meaning towards the evening, the conduciveness of taking medication also improves.

Although Time Category 5 (between 6pm-8pm), as the last category in the observed data, had been made the redundant code in the creation of 'Time Category' dummy variables in the Multinomial Logistic model, it was still a matter of this study's interest to understand the relationship between that particular category and the 'Reminded' adherence outcome. As a result, based on the 'Time Category' variable, a dummy, *Dummy_Time_Cat 5*, was created to represent Time Category 5 and an OLS regression was run using this as the predictor against the 'Reminded' adherence outcome. The output of the regression is as below:

[51] See Appendix 3 on side-effects of anti-TB drugs.

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	.150	.004		38.565	.000
	Dummy Time_Cat 5	-.045	.012	-.039	-3.730	.000

a. Dependent Variable: dummy variable for reminded outcome

Source: Author's Data analysis
Table 5.6: Regression coefficients for Reminded Outcome versus Time Category 5

Based on the above output, the OLS equation would be as below:

Reminded Outcome = 0.150+ -0.045**[Dummy_TimeCat_5]**

The above equation shows a negative relationship between taking medication in Time Category 5 and the need to be reminded to do so. It therefore confirms that patients tended to find it relatively easier to take treatment in the evenings compared to the afternoons. The reasons for evenings being better for treatment compared to afternoons were perhaps that patients would be at the end of their daily routines, most probably back at home, hence not so much social pressures like stigma as during the day and even if they got side-effects from the treatment, resting would be much easier being at home and perhaps with no need to participate in work, school or other day-to-day schedules. Evenings would also be conducive for treatment because carers would also be back at home from their own daily schedules, hence being available for supporting treatment uptake by patients. It must however be noted that the cases used in this analysis typically 'worked' or were mostly active in socio-economic engagements during the day and were back at home during evening times.

5.5 Wrong Time Outcome

Adherence Outcome[a]	B	Std. Error	Wald	df	Sig.	Exp(B)	95% Confidence Interval for Exp(B) Lower Bound	95% Confidence Interval for Exp(B) Upper Bound
Wrong_Time								
[Regimen=1.00]	.576	.476	1.463	1	.226	1.779	.700	4.522
[Regimen=2.00]	.640	.483	1.759	1	.185	1.897	.736	4.886
[Regimen=3.00]	-.758	.659	1.320	1	.251	.469	.129	1.707
[day=1]	.215	.127	2.859	1	.091	1.240	.966	1.592
[day=2]	.205	.128	2.573	1	.109	1.227	.956	1.576
[day=3]	-.087	.134	.421	1	.516	.917	.705	1.192
[day=4]	.463	.120	15.020	1	.000	1.589	1.257	2.009
[day=5]	.302	.000	.	1	.	1.352	1.352	1.352
[Time_Cat=1.00]	.389	.212	3.359	1	.067	1.476	.973	2.237
[Time_Cat=2.00]	.681	.170	16.067	1	.000	1.975	1.416	2.755
[Time_Cat=3.00]	1.667	.225	55.066	1	.000	5.297	3.410	8.228
[Time_Cat=4.00]	1.689	.198	73.127	1	.000	5.415	3.677	7.976
[Time_Cat=5.00]	0[b]	.	.	0	.	.	.	.

a. The reference category is: Right Time.

b. This parameter is set to zero because it is redundant.

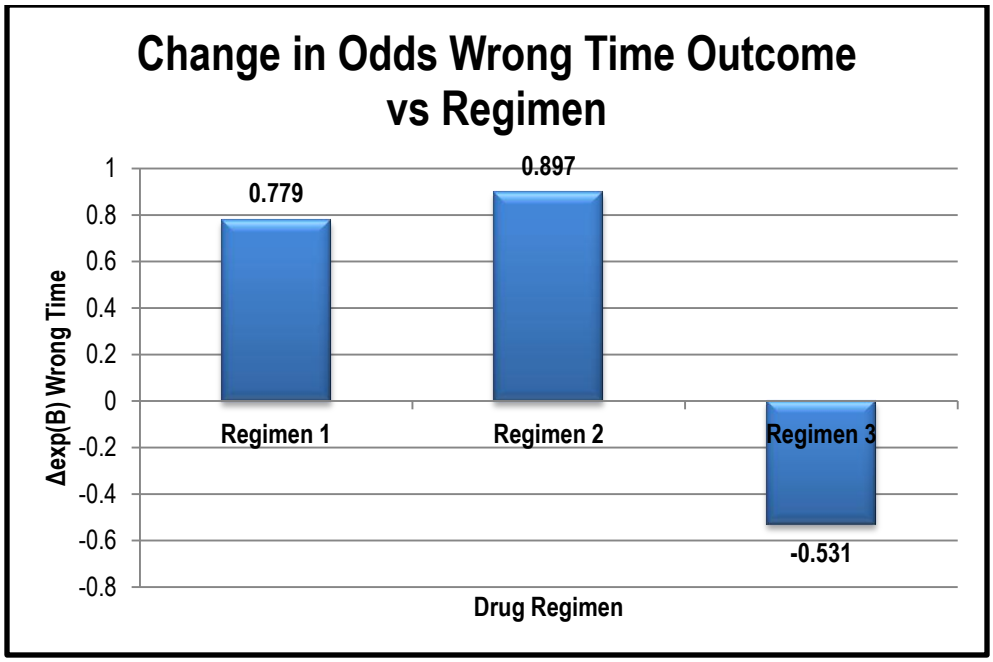
Source: Author's Data Analysis

Table 5.7: Parameter Estimates for 'Wrong Time' Outcome

5.5.1 Regimen

As shown in the results from the study, just as in the table above, a patient on drug Regimen 1 of anti-Tuberculosis treatment was 77.9% (1.779-1) more likely to take their medication at the wrong time relative to taking it on the right time, all factors being held constant. It also emerged that a patient on drug Regimen 2 of anti-TB treatment was 89.7% (1.897-1) more likely to take their medication at the wrong time compared to taking it at the right time, all other factors being held constant. A patient on drug Regimen 3 of anti-TB treatment was 53.1% (0.469-1) less likely to take their treatment at the wrong time relative to taking it at the right time, all other factors being held constant.

The graph below plots the change in odds {Δexp (B)} of patients taking their anti-TB drugs at the wrong time against the drug regimens they were on.



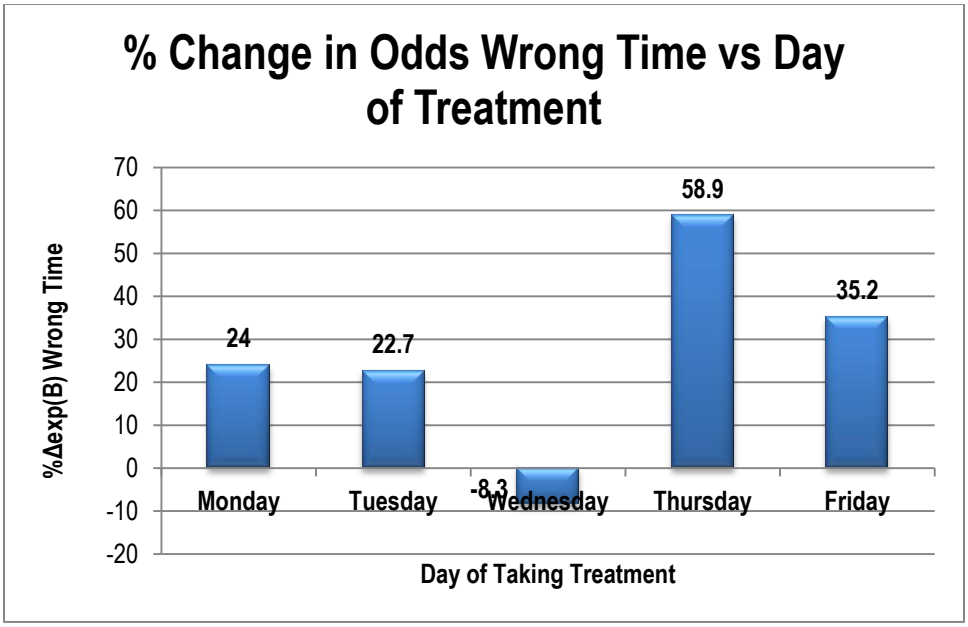
Source: Author
Fig. 5.3: Change in Odds 'Wrong Time' vs Regimen

The graph shows patients on drug Regimen 2 having a slightly higher likelihood of taking treatment at the wrong time {Δexp(B)=0.897}, compared to those on Regimen 1 {Δexp(B)=0.779}. This observation is in line with what was observed in section *5.4.1* under the 'Reminded' outcome observation and can be explained by the greater complexity of Regimen 2, its higher chances of causing drug-induced side-effects and also the fact that drugs under this regimen are taken for a longer period of time. Patients would therefore have a relatively greater adherence difficulty when on Regimen 2 compared to Regimen 1, the latter of which, while still inducing adverse side-effects, it is taken for a relatively shorter period of time and it is also fairly less complex than Regimen 2, again as earlier on explained in section *5.4.1* above. For patients under Regimen 3, being paediatric cases, just like in the previous adherence outcome, were again generally noted not to be in charge of managing their anti-Tuberculosis treatment; instead, a parent, guardian or another responsible adult in the family would ensure they took treatment as scheduled. This therefore explains why even in this case as well, the likelihood of taking treatment at the wrong time was very low {Δexp(B)=-0.531}. In other words, the very low likelihood of taking treatment at the wrong time by paediatric patients shows high level of care and treatment support for this group of patients. By implication from this case therefore, care and support around a patient is thereby supported as an important determinant of adherence outcomes in real-time.

5.5.2 Day of Taking Treatment

Based on the findings of the study, as shown in the Table 5.7 earlier on, a patient taking their anti-Tuberculosis treatment on a Monday (Day 1) tended to be 24% (1.24-1) more likely to take their medication at the wrong time relative to taking it at the right time, all other factors being kept constant. A patient taking their anti-TB treatment on a Tuesday (Day 2) was 22.7% (1.227-1) more likely to take their treatment at the wrong time relative to taking it at the right time, all other factors being kept constant. It was again noted that a patient taking their anti-TB drugs on a Wednesday (Day 3) tended to be 8.3% (0.917-1) less likely to take their treatment at the wrong time relative to taking it at the right time, all other factors being kept constant. A patient taking their anti-TB treatment on a Thursday (Day 4) was noted in the study to be 58.9% (1.589-1) more likely to take their medication at the wrong time relative to taking it at the right time, with all factors being kept constant. A patient taking their anti-TB drugs on a Friday (Day 5) was shown in the study to be 35.2% (1.352-1) more likely to take their medication at the wrong time relative to taking it at the right time, all other factors being held constant.

The graph below plots the % change in odds {Δexp(B)} of patients taking anti-TB drugs at the wrong time against the respective days they took the medication.



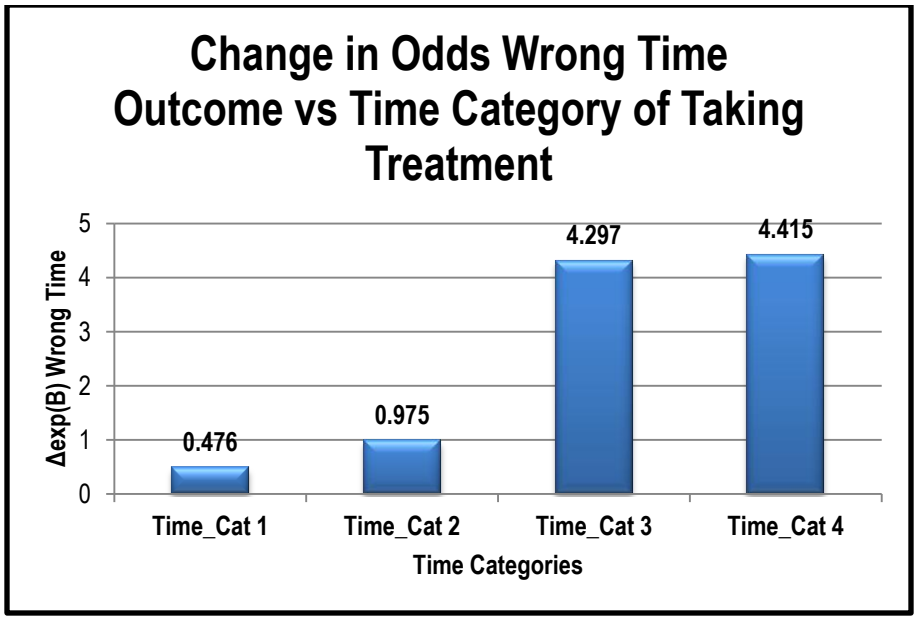
Source: Author
Fig. 5.4: % Change in Odds Wrong Time vs Day of Treatment

The graph Fig. 5.4 above shows us that taking treatment on Thursday presented patients with highest likelihood of taking treatment at the wrong time {%Δexp(B)=58.9} (hence relatively the

greatest adherence difficulty under this outcome). This was followed in descending order of adherence difficulty by Friday {%Δexp(B)=35.2}, then Monday {%Δexp(B)=24}, followed by Tuesday {%Δexp(B)=22.7} and finally Wednesday, which presented the least likelihood of a patient taking treatment at the wrong time {%Δexp(B)=-8.3}. Without necessarily a clearly defined trend in these results, the variability in the relative adherence difficulties by days of the week can best be explained by routine-related factors. In other words, the patient's profile of daily routine will determine which days would present more difficulty (or conduciveness) for taking treatment compared to others e.g. whether the patient works (and what kind of work they also do for a living), whether they are in or out of school, at what point during the day they interact with peers etc. For instance, due to side-effects related to whatever drug regimen a patient is on, they might find it difficult to take medication and still be able to operate machinery, drive, attend to customers at work etc; hence they might choose to delay taking treatment for a while until it becomes more convenient to do so during the course of the day. A patient might be in the presence of peers or significant others who might stigmatise them for taking anti-Tuberculosis medication, hence deliberately not taking treatment as well. For patients requiring treatment support, the availability of treatment supporters may also be a key determinant of whether they have problems taking treatment on specific days or not. So the adherence dynamics would vary across days of treatment depending on the patients' (or their carers') daily routines or schedules.

5.5.3 Time Categories

It was also shown in the study that for a patient taking their anti-TB medication in Time Category 1 (between 5am-7.59am), their likelihood of taking treatment at the wrong time relative to the right time increased by 47.6% (1.476-1). It was also noted that for a patient taking their anti-TB drugs in Time Category 2 (8am-11.59am), their likelihood of taking treatment at the wrong time relative to the right time increased by 97.5% (1.975-1). A patient taking their anti-TB drugs in Time Category 3 (12noon-1.59pm) was noted to have an increased likelihood of taking treatment at the wrong time relative to the right time of 429.7% (5.297-1). A patient taking their anti-TB drugs in Time Category 4 (2pm-5.59pm) was observed to also have an increased likelihood of taking treatment at the wrong time relative to right time of 441.5% (5.415-1). The graph below plots the change in odds {Δexp (B)} of patients taking their anti-TB drugs at the wrong time against the time categories of taking the medication.



Source: Author
Fig. 5.5: Change in Odds Wrong Time Outcome vs Time Category

The above graph again shows that patients in this study found taking their anti-TB medication in the mornings a lot easier compared to later on in the day i.e. the lowest Δexp(B) values were in Time categories 1 and 2 (0.476 and 0.975 respectively), the categories which represented morning hours up to noon. This could be attributed to, as already argued in section *5.4.2* above, that at the beginning of the day, patients would still be having minimum contact with peers, colleagues and other people as they would still be in their respective residential places. This could therefore limit social pressures such as stigma and discrimination, which have already been noted to inhibit treatment adherence. For patients needing treatment support, it would also be highly likely that carers would be available (i.e. would not have embarked on their normal daily schedules) and hence patients could be helped to take treatment. These time categories can be compared to Time Categories 3 and 4 {Δexp(B) values of 4.297 and 4.415 respectively}, which represent the first and second parts of the afternoon, whereby daily routines, be they employment, school or other aspects of social interactions could create conditions that compromise treatment adherence as already explained ealier on in section *5.4.2* above .

Just as in the analysis for the 'Reminded' adherence outcome, a need was realized to observe the relationship between a patient taking treatment at the wrong time and taking the medication in Time Category 5 (between 6pm-8pm), which represented an evening schedule of taking medication. Since it had been made the redundant code in the creation of dummies for time categories in the multinomial model, a data transformation process was undertaken on it and a

separate dummy variable for Time Category 5 was created. This was then regressed as the predictor variable against the 'Wrong Time' outcome, and the results are as below:

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	.122	.004		34.632	.000
	Dummy_ Time Cat 5	-.062	.011	-.060	-5.731	.000

a. Dependent Variable: Wrong Time

Source: Author's Data Analysis
Table 5.8: Regression of 'Wrong Time' versus Time Category 5

Based on the above output therefore, the OLS regression equation would be:

Wrong Time = 0.122 + -0.062**[Dummy_TimeCat 5]**

Once again, the evenings were shown to have lesser adherence difficulty compared to the afternoons, so even if the graph Fig 5.5 above was to be extrapolated, the next point would be a as the result of a sharp fall in Δexp(B) values from Time Category 4 to Time Category 5. This negative relationship between a 'Wrong Time' outcome and taking treatment during the evening (Time Cat 5) once more underscores the importance of a patient taking medication when potential barriers, typically met during their daily routines are at their minimum. In other words, a patient taking treatment in the evenings would not need to worry about dealing with medication side-effects while at work, at school or participating in socio-economic activities with peers and colleagues during the day (since these activities would have passed during the day, and so they can more easily lie down and rest as a way of managing side-effects in the evenings). The less interaction with peers at home in the evening would also perhaps mean less stigma and discrimination for a patient on anti-TB drugs, and arguably the evenings would also be convenient (same as mornings) for patients who need treatment support, since carers are likely to be back home from undertaking various activities on their own respective daily schedules.

5.6 'Near-Miss' Adherence Outcome

Adherence Outcome[a]		B	Std. Error	Wald	df	Sig.	Exp(B)	95% Confidence Interval for Exp(B) Lower Bound	95% Confidence Interval for Exp(B) Upper Bound
Near-miss									
	[Regimen=1.00]	1.109	1.016	1.192	1	.275	3.031	.414	22.203
	[Regimen=2.00]	1.961	1.018	3.712	1	.054	7.106	.967	52.250
	[Regimen=3.00]	-.777	1.428	.296	1	.586	.460	.028	7.551
	[day=1]	.012	.187	.004	1	.951	1.012	.701	1.460
	[day=2]	.014	.188	.006	1	.940	1.014	.702	1.466
	[day=3]	-.105	.190	.308	1	.579	.900	.620	1.306
	[day=4]	-.224	.196	1.307	1	.253	.799	.544	1.174
	[day=5]	-.057	.000	.	1	.	.945	.945	.945
	[Time_Cat=1.00]	.069	.393	.031	1	.860	1.072	.496	2.314
	[Time_Cat=2.00]	1.057	.293	13.025	1	.000	2.878	1.621	5.110
	[Time_Cat=3.00]	2.110	.355	35.333	1	.000	8.248	4.114	16.540
	[Time_Cat=4.00]	1.528	.346	19.484	1	.000	4.608	2.338	9.080
	[Time_Cat=5.00]	0[b]	.	.	0	.	.	.	.

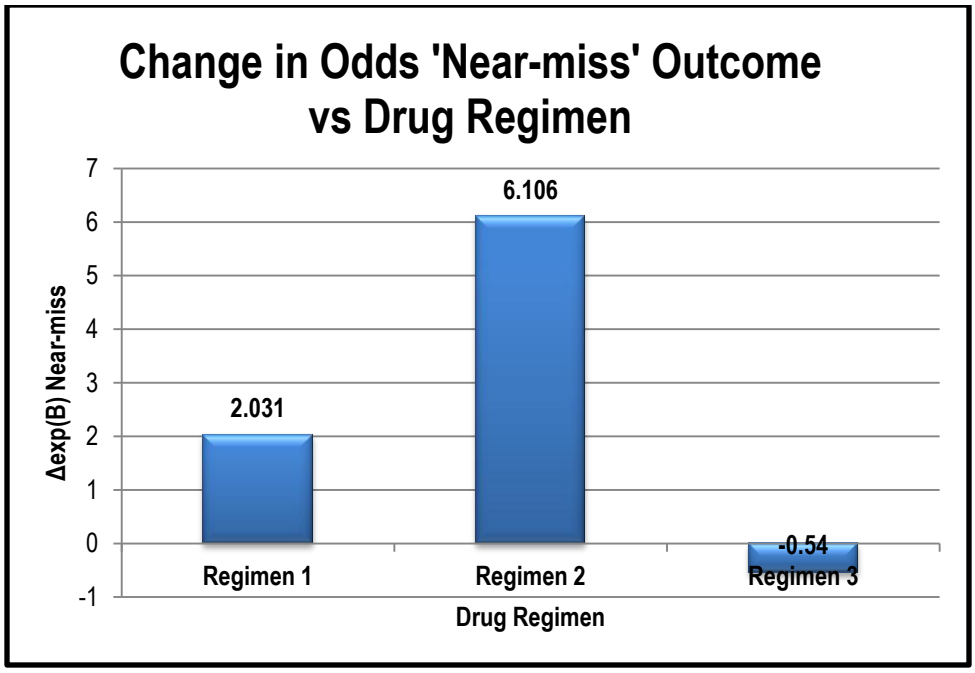
a. The reference category is: Right Time.

b. This parameter is set to zero because it is redundant.

Source: Author's Data Analysis
Table 5.9: Parameter Estimates for Near-Miss Outcome

5.6.1 Regimen

As can be seen in the output above, a patient on anti-TB drugs Regimen 1 was 2.031 (3.031-1) times more likely to 'nearly-miss' taking their medication relative to taking it at the right time, all other factors being kept constant. A patient who was on drug Regimen 2 was 6.106 (7.106-1) times more likely to 'nearly-miss' taking their medication relative to taking it at the right time, all other factors being held constant. A patient on drug Regimen 3 was however 0.54 (0.46-1) times less likely to 'nearly-miss' taking their medication relative to taking it at the right time, all the other factors being held constant. The graph below plots the change in odds {Δexp (B)} of patients nearly-missing taking their anti-TB drugs against the drug Regimens they were prescribed on.



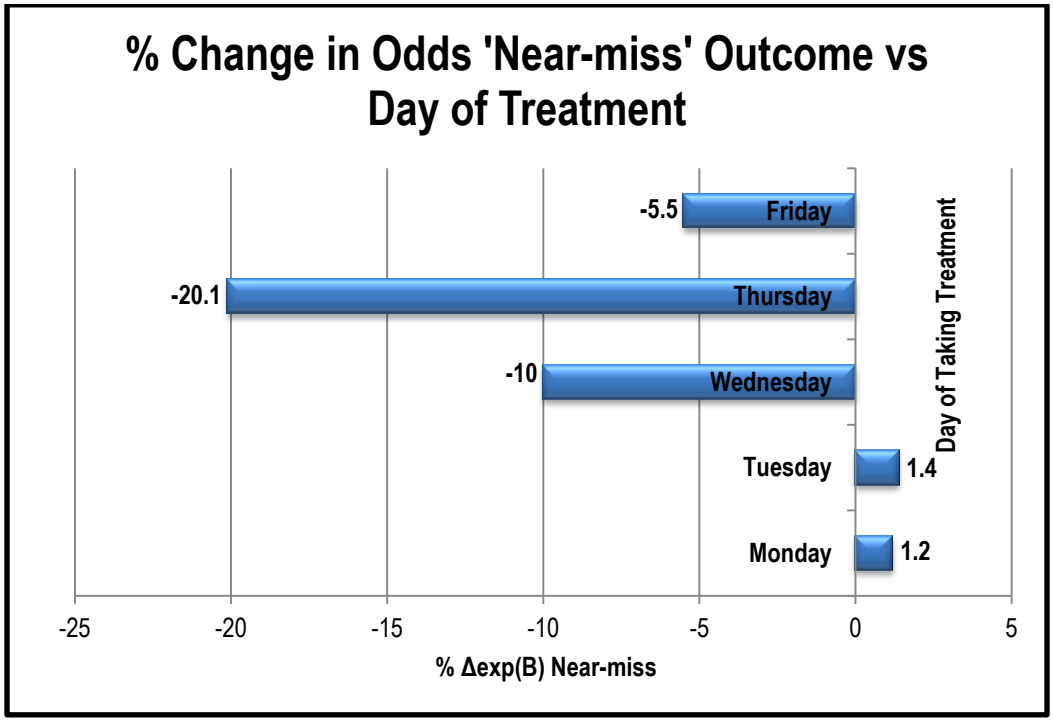
Source: Author
Fig. 5.6: Change in Odds 'Near-Miss' versus Drug Regimen

Once again, the trends in the underlying causes why drug Regimen 2 is relatively more difficult for adherence {Δexp(B)=6.106} compared to drug Regimen 1{Δexp(B)=2.031} are consistent with those already identified in sections *5.4.1* and *5.5.1* above and these have to do with the greater complexity and relatively higher chances of more intense drug-induced adverse effects of Regimen 2 compared to Regimen 1. As in the above-discussed outcomes as well, the low Δexp(B) value for drug Regimen 3 (-0.54) can be explained by the high levels of treatment management, care and support around paediatric cases (children) by either parents, guardians or other responsible adults in the household, hence diminishing patients on that Regimen's odds of 'nearly-missing' treatment in this case.

5.6.2 Day of Taking Treatment

It was shown in the study that a patient taking their anti-TB drugs on a Monday (Day 1) was 1.2% (1.012-1) more likely to 'nearly-miss' taking treatment compared to taking it at the right time, all other factors being kept constant. A patient taking their anti-TB drugs on a Tuesday (Day 2) was 1.4% (1.014-1) more likely to 'nearly-miss' taking their medication relative to taking it at the right time, all other factors being held constant. It also emerged from the study findings that a patient taking their treatment on a Wednesday (Day 3) tended to be 10% (0.9-1) less likely to 'nearly-miss' their medication relative to taking it at the right time, all other factors being

held constant. Again it was noted that a patient taking their anti-TB drugs on a Thursday (Day 4) tended to have a 20.1% (0.799-1) less likelihood of 'nearly-missing' treatment relative to taking it at the right time, all other factors being held constant. A patient taking their medication on a Friday (Day 5) tended to have a 5.5% (0.945-1) less likelihood of 'nearly-missing' treatment relative to taking it at the right time, all other factors being kept constant. The graph below plots the % change in odds {Δexp(B)} of patients nearly-missing taking their anti-TB drugs against the respective days of taking the medication.



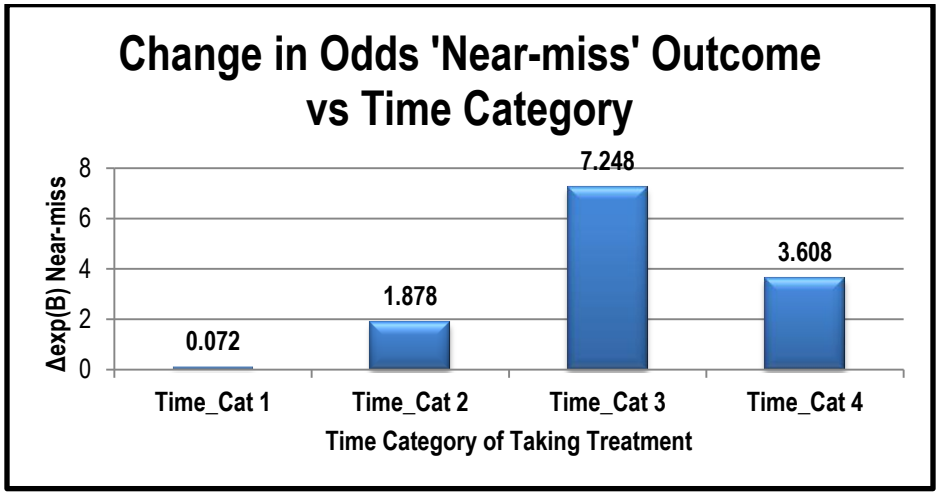
Source: Author
Fig 5.7: % Change in Odds 'Near-miss' versus Day of Treatment

Interpreting the graph above in terms of relative ease for taking treatment, patients taking their treatment on Thursday had the least likelihood of 'nearly-missing' their treatment, as shown by the %Δexp(B) value of -20.1. This was followed in terms of relative adherence ease by taking treatment on a Wednesday {%Δexp(B)= -10} and then Friday {%Δexp(B)=-5.5}. Monday and Tuesday were shown to be days perhaps presenting the least ease of adherence (conversely the highest adherence difficulty), by virtue of having positive %Δexp(B) values (1.2 and 1.4 respectively). Without a clearly distinguishable trend in these results, the variability of likelihood to nearly-miss treatment can best be attributed to daily routine-related factors. Depending on what socio-economic activities a patient participates in during the day, various conditions could then be created on each of the days that would either make taking treatment conducive or not.

For example, a patient on anti-Tuberculosis treatment might refrain from taking treatment at the scheduled time on a day he/she is operating machinery or a vehicle at work because of concerns over treatment side-effects, a patient who is in school might also decide not to take their treatment at the scheduled time because of the presence of peers and would be afraid of being stigmatized against etc. It could also be the case that availability of treatment supporters at certain time periods on the days of the week for patients requiring care and support might be a key determining factor of adherence outcome.

5.6.3 Time Categories

It was noted in the study that a patient taking their anti-Tuberculosis drugs in Time Category 1 (between 5am-7.59am) was more likely to 'nearly-miss' their treatment relative to taking it at the right time by a factor of 0.072 (1.072-1). A patient taking their anti-TB drugs in Time Category 2 (8am-11.59am) was 1.878 (2.878-1) times more likely to 'nearly-miss' their treatment relative to taking it at the right time, all other factors being held constant. A patient taking their anti-TB drugs in Time Category 3 (12noon-1.59pm) was 7.248 (8.248-1) times more likely to 'nearly-miss' their treatment relative to taking it at the right time, all other factors being held constant. A patient taking their anti-TB drugs in Time Category 4 (2pm-5.59pm) was noted to be 3.608 (4.608-1) times more likely to 'nearly-miss' their treatment compared to taking it at the right time, all other factors being kept constant. The graph below plots the change in odds {Δexp(B)} of patients 'nearly-missing' taking their anti-TB drugs against their scheduled Time categories of taking treatment.



Source: Author
Fig. 5.8: Change in Odds 'Near-miss' versus Time Category

The 'Near-miss' adherence outcome further supports the premise that taking medication tended to be easier for patients at the beginning of the day due perhaps to prevalence of conditions more conducive for its uptake, as explained earlier in sections *5.4.2* and *5.5.3*. This is shown by the lowest change in odds for patients 'nearly missing' their treatment being found in Time Category 1 (between 5am-7.59am), with a Δexp(B) value of 0.072. It can then be observed that as the day progresses and as patients and/or their carers embark on their day-to-day socio-economic or other routines, treatment adherence increasingly becomes harder. At Time Category 3 (between 12noon and 1.59pm), taking treatment is noted to be at its hardest with respect to this particular outcome {Δexp(B)=7.248}, supposedly as the day's engagements are at their peak. Another interesting dimension is realized under this outcome, that in some cases, patients would opt to take treatment earlier than scheduled[52], perhaps as a way of intending to either avoid being seen to be medicating or as a way to manage side-effects before peak socio-economic engagements. It is however noted that towards Time Category 4 (2pm-5.59pm) and beyond, adherence difficulty begins to diminish as the daily routines inhibiting adherence are being wound up on and patients as well as their carers return to their places of residence, where chances of treatment uptake are optimised. As in the previous 2 adherence outcomes (see sections *5.4.2* and *5.5.3*) an OLS regression was done with Time Category 5 as the predictor variable in order to verify whether evenings indeed created better conduciveness for uptake of treatment or not, and the results are as below:

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	.040	.002		19.162	.000
	Dummy_Time Category 5	-.026	.006	-.042	-3.985	.000

a. Dependent Variable: Near-Miss

Source: Author's data analysis
Table 5.10: Regression of Near-miss outcome versus Time Category 5

As shown in the output above and the OLS regression equation given below,

Near-Miss = 0.040 + -0.026 **[Time_Category 5],**

[52] This argument emanates from the very definition of the 'near-miss' outcome itself, as it relates to patients (erroneously) taking treatment earlier than scheduled

there is a negative relationship between a patient 'nearly-missing' taking their anti-Tuberculosis treatment and when their scheduled dosage time is in Time Category 5(between 6pm-7.59pm) . This gave further evidence that adherence difficulty indeed diminished as patients took medication in the evenings, supposedly because of removal of most of the hindrances e.g. daily routine-related schedules, social pressures as well as the availability of treatment supporters back at home etc.

5.7 Missed Adherence Outcome

Adherence Outcome[a]	B	Std. Error	Wald	df	Sig.	Exp(B)	95% Confidence Interval for Exp(B)	
							Lower Bound	Upper Bound
Missed								
[Regimen=1.00]	-.226	.321	.497	1	.481	.797	.425	1.497
[Regimen=2.00]	-.503	.333	2.280	1	.131	.605	.315	1.162
[Regimen=3.00]	-1.438	.474	9.226	1	.002	.237	.094	.600
[Time Cat=1.00]	.290	.160	3.284	1	.070	1.337	.977	1.830
[Time_Cat=2.00]	.170	.126	1.822	1	.177	1.185	.926	1.518
[Time_Cat=3.00]	.568	.212	7.158	1	.007	1.764	1.164	2.674
[Time_Cat=4.00]	1.082	.160	45.650	1	.000	2.949	2.155	4.036
[Time_Cat=5.00]	0[b]	.	.	0	.	.	.	.

a. The reference category is: Right Time.

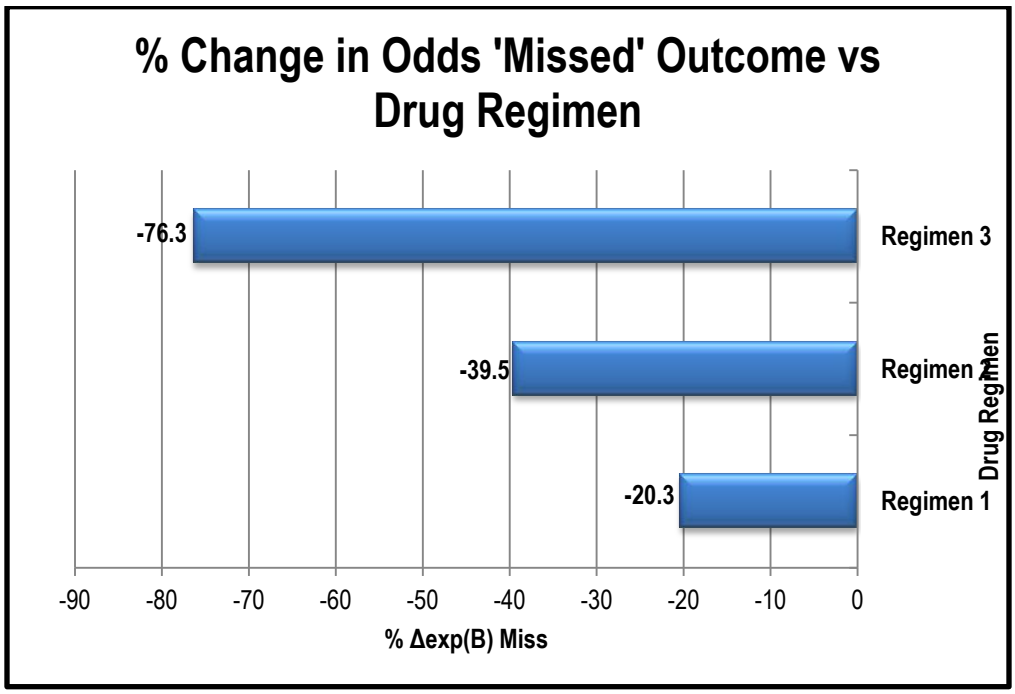
b. This parameter is set to zero because it is redundant.

Source: Author's Data Analysis
Table 5.11: Parameter Estimates for 'Missed' Adherence Outcome

5.7.1 Regimen

It was observed in the study, as shown from the output above, that a patient who was on anti-TB drug Regimen 1 was 20.3% (0.797-1) less likely to miss taking treatment altogether for any given medication day relative to taking it at the right time, all other factors being held constant. It was again seen that a patient on anti-TB drug Regimen 2 was 39.5% (0.605-1) less likely to miss taking treatment altogether for any given medication day relative to taking it at the right time, all other factors being held constant. A patient on anti-TB drug Regimen 3 was noted to be 76.3% (0.237-1) less likely to miss taking their treatment altogether for any given medication

day relative to taking it at the right time, all other factors being held constant. The graph below plots the % change in odds {Δexp (B)} of patients 'missing' taking their anti-TB drugs against their prescribed drug regimens.



Source: Author
Fig. 5.9: Graph of %Change in Odds 'Missed' outcome versus Drug Regimen

The first thing to note in attempting to make sense of the above graph is that all the Δexp(B) values are in the negative for all the 3 regimens, which is a very different scenario from all the other adherence outcomes i.e. reminded, wrong time and near-miss analysed in sections above. The reason lies in that, because of the accelerated SMS reminders from the Simpill server and subsequent follow-ups or visits by caregivers/health service providers, the probability of missing treatment altogether for any given medication day among the Simpill users tended to be extremely low. This would thus give rationale as to why the odds ratios for missing treatment (and subsequently the Δexp(B) values) were also low for the 'missed' adherence outcome with respect to drug Regimen.

However getting back to the interpretation of the graph, it is of interest to observe that Regimen 1 has a relatively higher %Δexp(B) value (-20.3) compared to Regimen 2 {%Δexp(B)= -39.5}, implying that the former presents relatively greater adherence difficulty than the latter under the

'missed' outcome. The argument on regimen complexity that has been consistent from previous outcomes analyses to an extent then loses weight in this instance. Another argument is thus proposed to attempt to explain this observation, and this is based on patients' individual factors (e.g. attitude towards treatment, self-efficacy and locus of control, fear-related factors, motivation etc). It is worth mentioning that patients on Regimen 2 are smear-positive retreatment patients, who would be returning for treatment after long periods of treatment interruption, relapse of illness as well as treatment failure. Such patients would therefore be unlikely to miss treatment altogether for any given medication day, since they would now be fully aware of the risk of treatment interruption, or are afraid that further treatment failures could lead to Multi-Drug Resistant forms of TB, which could prove to be fatal to them. Hence some higher level of 'fear' of the consequencies, based on their previous experiences could result in Regimen 2 patients not so easily missing treatment days, compared to Regimen 1 patients who would be taking anti-TB medication for the first time and do not have any experiences of treatment failure or relapse. In other words, under Regimen 2, patients'

- attitude towards treatment (e.g. *only not missing my treatment like last time could cure me of TB),*
- risk perception (e.g. *I cannot afford to miss treatment now or else I will relapse again*),
- self-efficacy (e.g. *I believe and am determined to take my treatment no matter how difficult it will be so that I do not relapse again*)
- (internal) Locus of Control (e.g. *to be able to finally rid myself of Tuberculosis and not repeat the relapse of last time would depend on me not missing my medications again no matter what challenges I face*),
- motivation-related factors (e.g. *I can have my health back to normal like XYZ if I do not miss my treatment this time*), and
- fear-related factors (e.g. *I might not be so lucky if I miss my treatment like last time, learning from XYZ's experience*) would cause them to have less likelihood of missing treatment altogether for any given medication day.

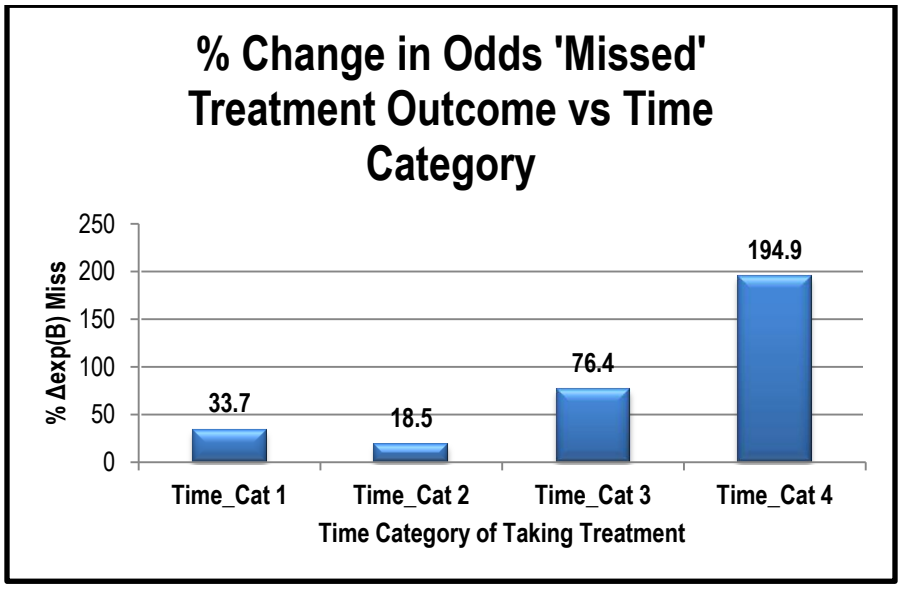
There seems therefore to be the existence of a prominent and complex interplay of individual-related factors (influenced by both personal and external/social sphere experiences) leading to variation in likelihood of missing treatment altogether for patients on both Regimen 2 and Regimen 1.

The result for drug Regimen 3 (paediatric cases) is consistent with what was observed for the other adherence outcomes in previous sections i.e. the responsibility of treatment management

for such category of patients lying in a parent, guardian or responsible older person. With high levels of care and support therefore, the patients would have very low likelihood to miss treatment i.e. as in this case with %Δexp(B) value of -76.3, representing the least adherence difficulty in this instance. It also needs to be reiterated how through the accelerated reminders, chances of patients missing treatment altogether for any given medication day is drastically diminished, particularly in cases where the treatment schedule is already the responsibility of a carer.

5.7.2 Time Categories

It was observed that a patient taking their anti-TB medication in Time Category 1 (between 5am-7.59am) was 33.7% (1.337-1) more likely to miss treatment altogether for any given medication day relative to taking it at the right time, all the other factors being constant. A patient taking their anti-TB drugs in Time Category 2 (8am-11.59am) was noted to be 18.5% (1.185-1) more likely to miss taking their treatment relative to taking it at the right time, all other factors being held constant. It was also observed from the study that a patient taking their anti-TB drugs in Time Category 3 (12noon-1.59pm) was 76.4% (1.764-1) more likely to miss taking their treatment relative to taking it at the right time, all other factors being held constant. Again it was observed that a patient taking their anti-TB drugs in Time Category 4 (2pm-5.59pm) was 194.9% (2.949-1) more likely to miss taking their treatment relative to taking it at the right time, all other factors being held constant. The graph below plots the % change in odds {Δexp (B)} of patients 'missing' taking their anti-TB drugs against the prescribed time categories of taking treatment.



Source: Author
Fig 5.10: Graph of % Change in Odds 'Missed' Outcome vs Time Category

The graph (Fig. 5.10) above shows a trend that confirms what was established for the other adherence outcomes when regressed across time categories - that patients generally found taking their anti-TB drugs a lot easier in the mornings (Time Categories 1 and 2). This would be for reasons earlier elaborated in sections *5.4.2* and *5.5.3* related to availability of treatment supporters in the mornings, a more conducive period when the socio-economic activities on the daily schedules would not have peaked, and also fairly less social interactions, which would most likely minimize risk of stigma and discrimination against patients on anti-TB treatment. This was noted to be in contrast with Time Categories 3 and 4 when daily routines seemed to present barriers towards treatment adherence, as earlier elaborated on {with %Δexp(B) values of 76.4 and 194.9 respectively}.

5.8 Relationship Between Gender (as a socio-cultural construct) and Adherence Outcomes

With there already having been concerns that most TB adherence studies have been undertaken in developed country settings, or at least not in situations of extreme prevalence and vulnerability such as Sub-Saharan Africa (see WHO, 2003), this thesis also took up issue with the way a number of reviewed previous studies used the variable 'sex' as meaning more or less the same as the variable 'gender'. Such conceptualisation, in the view of this author, became problematic particularly when conducting studies in contexts such as in Sub-Saharan Africa

where traditional and socio-cultural factors more strongly define roles, responsibilities and expections of one being male or female i.e. engendering of roles. In other words, the concern was that without strengthening the proxy for gender, the real effect of this variable would be unduly under-valued in studying treatment adherence as it apparently encompassed more than just one being merely male or female[53]. This research also noted that such reality was unfortunately even still not being given due recognition in the emerging body of adherence studies in developing country contexts. In order to avoid similar shortcomings, this study therefore intended to link patients' masculinity or femininity with their expected roles and responsibilities in the South African context, a typically patriachal[54] society[55], then link this with their respective adherence dynamics.

The point of departure, just like in previous studies, was to use the variable 'sex' i.e. a patient being male or female as a dummy coded regressor (having the code 0 for male and 1 for female) and as a predictor of adherence outcome in a regression process. After establishment of the relationship, thereafter an attempt was then made to link this with the socio-cultural context to bring out a stronger argument for the gender case. Now the Table 5.11 below shows the OLS regression undertaken between 'taking treatment at the right time' as the dependent variable and sex of patient as the predictor. It is important to note that patients in Age Category 1 (i.e. up to 14 years of age) were excluded from this analysis since as children they fell mainly under parental/guardian care and so were assumed to be least likely to take up much socially constructed roles and responsibilities to the extent of influencing treatment adherence outcomes.

[53] See http://www.who.int/gender/whatisgender/en/ (accessed 13/05/11)

[54] Patriarchy is a social system in which the father or eldest male is head of the household, having authority over women and children. Patriarchy also refers to a system of government by males, and to the dominance of men in social or cultural systems. ...(en.wikipedia.org/wiki/Patriarchal_society, accessed 13/05/11)

[55] See http://www.wikigender.org/index.php/Gender_Equality_in_South_Africa

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	.571	.008		71.765	.000
	Dummy_Sex_of_Patient	-.052	.012	-.052	-4.202	.000

a. Dependent Variable: Dummy variable for taking treatment at right time

Source: Author's Data analysis
Table 5.12: Regression of 'Right time' outcome by Sex of Patient

Basing on the above OLS regression output, the regression equation for taking treatment at the 'right time' with 'sex of patient' as the predictor is as below:-

Right Time = 0.571 + -0.052**[Sex_of_Patient]**

Assuming that a patient is male (coded value 0), then the estimation for the 'right time' parameter would thus be as below:

Right Time = 0.571 + -0.052**[0]**

= 0.571

If it is a female patient taking anti-TB medication (coded value 1), then the estimation for the Right Time parameter would be as below:

Right Time = 0.571 + -0.052**[1]**

= 0.519

As can be seen from the calculations therefore, the probability of taking anti-TB drugs at the right time diminishes if a patient is female. The rationale for this finding is socio-cultural, particularly in the South African patriarchial context where women bear most of the burden of domestic work and childcare over and above whatever livelihood activities they participate in. The chances therefore of females either postponing taking treatment or simply forgetting to take it because of engagement in domestic, childcare or other pre-occupations are relatively higher compared to their male counterparts. Further arguments are put across below with the regression of 'Missing Treatment' and Sex of Patient as the predictor variable.

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	.130	.006		23.499	.000
	Dummy_Sex_of_Patient	.022	.009	.031	2.549	.011

a. Dependent Variable: Dummy variable for missing treatment

Source: Author's data analysis
Table 5.13: Regression of 'Missing treatment' outcome by Sex of Patient

Based on the above analysis, the OLS regression equation for predicting the 'Missing Treatment' parameter with the regressor 'Sex of patient' will read as follows:

Missing Treatment = 0.130+0.022**[Sex_of_Patient]**

When the TB patient in question is male (coded value 0), the estimation of the Missing Treatment parameter will be as follows;

Missing Treatment = 0.130+0.022**[0]**

= 0.130

When the TB patient in question becomes female (coded value 1), then the parameter estimate for Missing Treatment will be as follows;

Missing Treatment = 0.130+0.022**[1]**

= 0.152

It is apparent that female patients tended to have greater probability to miss treatment compared to their male counterparts. This result, just as the one in the regression for the 'Right Time' outcome, was also linked to the gender notion of women having to take charge of virtually all domestic and childcare responsibilities, compared to their male counterparts, which could then result in them having a greater chance of forgetting to take treatment due to their overwhelming responsibilities. Furthermore, this study sought to substantiate the higher chances of non-adherence among women compared to men based on yet another socio-culturally constructed aspect of reproductive responsibilities.

It emerged from the pharmacological review under this study that one of the anti-TB drugs that is a component of all the Fixed Dose Combination (FDC) drugs used in treating the illness, Rifampicin, tends to decrease the efficacy of oral and injectable contraceptives by enhancing their metabolism. The implication here is that a female TB patient of reproductive age and already in marriage/partnership that included sexual relations, would be advised by a health service provider to switch to non-hormonal contraceptive alternatives, particularly the condom when no other alternative would be available (especially in resource poor settings). Now considering the socio-culturally based disempowerment of women with regards to negotiation for condom usage and other safe sex methods in patriarchal societies[56] (and yet they were still generally expected to ensure that there was no unwanted pregnancy in the relationship), it was argued in this study as being highly likely that a female patient might end up skipping certain medication days, especially after clearing of TB symptoms, so that they will not have to endure the very difficult task of convincing their partners to switch contraceptive methods (especially to the condom). In this way, they could also be avoiding the risks of domestic violence or being left by their partners since insisting on condom utilization (after a period of having used hormonal alternatives like pills) has been documented in developing country studies to be associated with infidelity and lack of trust in long-term relationships[57].

At the end of the day, this thesis argues that power relationships and gender among other socio-cultural constructs could end up creating complex barriers for patients (in this case women) to adhere to treatment. It could also even be the case that female carers/treatment supporters could be inhibited by gendered roles from effectively supporting patients on anti-TB treatment, thereby indirectly affecting adherence outcomes.

[56] Condom usage in long-term relationships and marriage has been noted by Williamson *et al* (2006) to be extremely low and an almost unacceptable contraceptive method from the male's perspective, especially in the African set-up.
[57] See Rio Gupta (2002), Muhwava (2004)

5.9 Effect of Taking Treatment during a Public Holiday on Adherence Outcomes

The study further took a keen interest on understanding what effects taking treatment on a public holiday had on patients, particularly with regards to their propensity towards adherence to the medication schedule. An Ordinary Least Squares (OLS) regression was run in order to establish the relationship, and the results follow as below:

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	.548	.005		104.335	.000
	public holiday	-.201	.041	-.051	-4.906	.000

a. Dependent Variable: dummy variable for taking treatment at right time

Source: Author's data analysis
Table 5.14: Regression of 'Right time' outcome by public holiday

Based on the above output, the estimated OLS regression equation for taking treatment at the right time can be written as below:

Right Time = 0.548+ -0.201**[Public Holiday]**

Assuming that a patient takes their anti-Tuberculosis drugs on a non-public holiday (coded as value 0), then the predicted value for Right Time would be:

Right Time = 0.548 + -0.201**[0]**
= 0.548

Now when the same patient takes treatment on a day that is a public holiday (coded as value 1), the equation would be as below:

Right Time = 0.548 + -0.201**[1]**
= 0.347

From the above, it is clear that taking treatment on a public holiday reduced the chances of a patient taking it at the right time.

The explanation for this kind of observation is based on the fact that public holidays result in general changes in routine for either patients or their carers e.g. changes in waking up time,

attending respective social gatherings/events being commemorated over the public holidays, and breaking from the usual occupational routines etc. This change in routine or participation in gatherings by patients might create scenarios not conducive for taking treatment e.g. the fear of being stigmatized at public events, leaving the medication behind at home or outrightly forgetting due to active engagements in social events. It could as well also be possible that carers who support treatment might have shifted from their usual non-holiday routines to attend to other activities, thereby increasing the probability of their not being present to support patients and ensure they take medication at the right time.

A further regression, this time based on 'Missing Treatment' as the dependent variable was also carried out and reported below, to seek to validate the argument raised above.

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	.153	.004		39.922	.000
	public holiday	.247	.030	.087	8.302	.000

a. Dependent Variable: dummy variable for missing treatment

Source: Author's data analysis
Table 5.15: Regression of 'Missing Treatment' by Public Holiday

Based on the above OLS output, the estimated regression equation for 'Missing Treatment' would be as below:

Missing Treatment = 0.153+0.247**[Public Holiday]**

Assuming that a patient takes their anti-Tuberculosis medication on a non-public holiday (coded as value 0), then the predicted value for Missing Treatment would be:

Missing Treatment = 0.153+0.247**[0]**

= 0.153

If the same patient takes their medication on a public holiday (coded as value 1), then the predicted value for 'Missing Treatment' would be:

Missing Treatment = 0.153+0.247**[1]**

= 0.4

It is clear therefore based on the above equations that taking anti-TB drugs on a public holiday increases the chances of a patient missing their treatment altogether. These results confirm and are in line with the argument of routine changes that was elaborated upon in the regression for 'Right Time' above.

5.10 Effect of Phase of Treatment on Adherence Dynamics

The study took further interest in also attempting to draw a relationship between the phase in which patients were taking their anti-Tuberculosis medication and their adherence outcomes, and the results from the OLS regression are as given below:

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	.554	.007		85.021	.000
	phase of treatment	-.027	.011	-.026	-2.517	.012

a. Dependent Variable: dummy variable for taking treatment at right time

Source: Author's data analysis
Table 5.16: Regression of 'right time' outcome by Phase of treatment

Based on the above output, the estimated OLS regression equation is as below

Right Time = 0.554 + -0.027**[Phase of Treatment]**

Assuming that a patient is taking their anti-Tuberculosis drugs in the intensive phase of treatment (coded as value 0), then the equation would be as below:

Right Time = 0.554 + -0.027**[0]**

= 0.554

If the patient is however taking their anti-Tuberculosis drugs in the continuation phase of treatment (coded as value 1), then the equation would be as follows

Right Time = 0.554 + -0.027**[1]**

= 0.527

These calculations therefore show evidence that a patient would generally have a slightly higher probability of taking treatment at the right time when they are in the intensive phase of treatment

compared to the continuation phase. Explanation for this can be found in the fact that within the intensive phase of treatment, the patient would still be visibly sick and still manifesting signs and symptoms of Tuberculosis illness, hence their higher motivation to adhere to treatment so that they can get better, clear off the symptoms and get back to their normal lives (without TB sickness). This is in contrast to when the patient now has to proceed with treatment in the continuation phase, yet the signs and symptoms of Tuberculosis infection/illness would have virtually cleared and the patient does not look or feel ill anymore. It is quite possible that as the patient moves to the continuation phase, their risk perception of Tuberculosis illness also diminishes since they do not feel sick anymore. It therefore implies that patient individual factors (e.g. attitude towards treatment, medication self-efficacy and disease risk perception, control beliefs etc.) would certainly play a key role in determining their medication adherence dynamics across the phases of treatment.

The table below shows the output from the regression between the 'missed' adherence outcome versus phase of treatment.

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	.138	.005		28.992	.000
	phase of treatment	.053	.008	.069	6.656	.000

a. Dependent Variable: dummy variable for missing treatment

Source: Author's data analysis
Table 5.17: Regression of 'Missing Treatment' outcome by Phase of Treatment

Based on the above output, the estimated OLS regression equation is as below

Missing Treatment = 0.138 + 0.053**[Phase of Treatment]**

Now assuming that a patient is taking their anti-Tuberculosis drugs in the intensive phase of treatment (coded as value 0), then the equation would be as below:

Missing Treatment = 0.138 + 0.053**[0]**
= 0.138

If the patient is however taking their anti-Tuberculosis drugs in the continuation phase of treatment (Coded as value 1), then the equation would be as follows

Missing Treatment = 0.138 + 0.053**[1]**
= 0.191

From the above calculations, there is evidence to support the argument that the probability of missing taking anti-TB treatment increases when a patient moves from the intensive phase to the continuation phase and this is confirmation of the same argument discussed earlier on. The implication is that after clearing of symptoms of TB and its ill-effects, patients apparently lose incentive/motivation to continue adhering to treatment; after all, they will be feeling 'normal' again and perhaps their disease risk perception and treatment self-efficacy lowers. Combining this with the social pressures (e.g. stigma and discrimination) associated with taking anti-Tuberculosis medication, a patient would rather stop taking medication or just continue do so intermittently so that they avoid these pressures too, particularly upon resumption of normal daily routines[58].

[58] This inference of course is with exception of paediatric cases who have been previously discussed not to be in control of their treatment schedules and so are likely to have consistent adherence patterns across phases of treatment

5.11 The Relationship between Age of Patient and Adherence Outcomes

Based on the categorization and characterization of the age variable done for this study, already discussed in section *4.2.2* of Chapter 4, the below findings emerged from the MNL modeling of adherence outcomes against age categories as the predictors:

5.11.1 Reminded Outcome

Parameter Estimates

Adherence Outcome[a]		B	Std. Error	Wald	df	Sig.	Exp(B)	95% Confidence Interval for Exp(B)	
								Lower Bound	Upper Bound
Reminded	Intercept	-3.045	.512	35.391	1	.000			
	[Age_Cat=1.00]	.390	.567	.473	1	.492	1.477	.486	4.485
	[Age_Cat=2.00]	2.148	.517	17.238	1	.000	8.571	3.109	23.633
	[Age_Cat=3.00]	1.869	.515	13.172	1	.000	6.481	2.362	17.783
	[Age_Cat=4.00]	1.369	.517	7.006	1	.008	3.932	1.427	10.835
	[Age_Cat=5.00]	1.820	.520	12.254	1	.000	6.169	2.227	17.089
	[Age_Cat=6.00]	0[b]	.	.	0	.	.	.	.

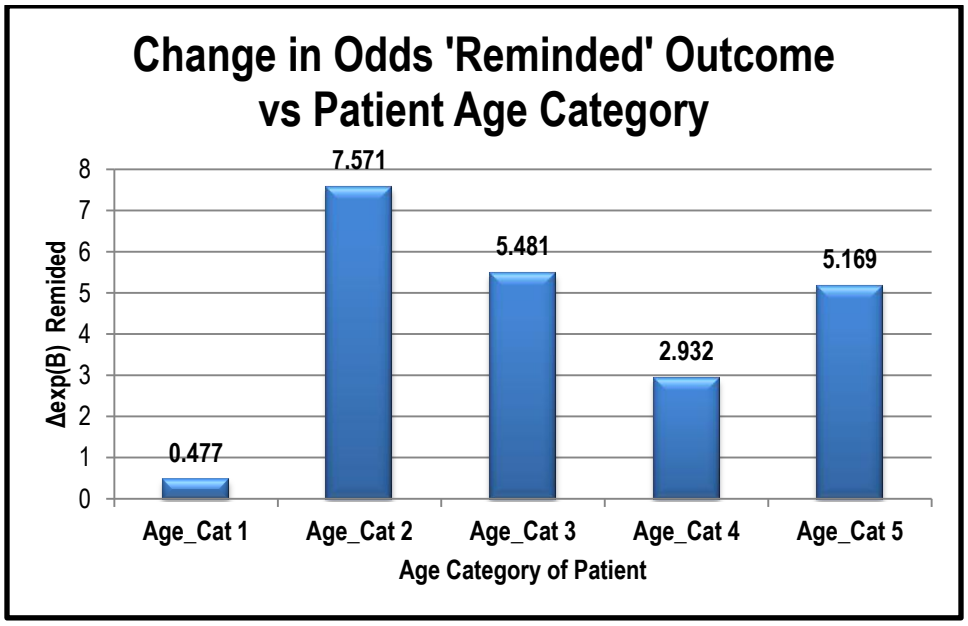
a. The reference category is: Right_time.

b. This parameter is set to zero because it is redundant.

Source: Author's data analysis
Table 5.18: Parameter estimates for 'Reminded' Outcome

A patient in Age Category 1 (i.e. between 8-14 years of age) was shown in the study to be 0.477 (1.477-1) times more likely to be in need of being reminded to take their anti-Tuberculosis medication relative to taking it at the right time, all other factors being held constant. A patient in Age Category 2 (15-21years) was shown in the study to be 7.571 (8.571-1) times more likely to be in need of being reminded to take their anti-Tuberculosis medication relative to taking it at the right time, all other factors being held constant. A patient in Age Category 3 (22-35years) was shown in the study to be 5.481 (6.481-1) times more likely to be in need of being reminded to take their anti-Tuberculosis medication relative to taking it at the right time, all other factors being held constant. A patient in Age Category 4 (36-49years) was shown in the study to be 2.932 (3.932-1) times more likely to be in need of being reminded to take their anti-Tuberculosis medication relative to taking it at the right time, all other factors being held constant. A patient in Age Category 5 (50-63 years) was shown in the study to be 5.169 (6.169-1) times more likely to be in need of being reminded to take their anti-Tuberculosis medication relative to taking it at the right time, all other factors being held constant. The graph below shows the change in odds

of patients needing to be reminded to take their anti-TB treatment based on their age categories.



Source: Author
Fig 5.11: Graph of Change in odds 'Reminded' outcome vs Patient Age Category

It is clear from the graph, Fig. 5.11 above that patients in Age Category 1 (8-14years) present the least need to be reminded to take anti-Tuberculosis treatment {Δexp(B)= 0.477}. This is primarily because patients in this category are virtually paediatric cases i.e. children, hence they do not necessarily self-medicate. A carer, whether parent, guardian or another older family member is therefore in charge of ensuring they take their treatment as scheduled. By implication, the level of care and support can have a positive or negative bearing on treatment adherence outcome, particularly for patients who can not self-medicate, as in this case of the paediatric patients.

The graph further shows that patients in Age Category 2 (15-21 years) interestingly had the greatest need of being reminded to take their treatment {Δexp(B)=7.571}. In other words, patients in this age category presented the greatest relative adherence difficulty and so required the most effort to get them to take their anti-Tuberculosis treatment. The most likely underlying reason for this finding could be in the growth and development stage of patients in this category. In this particular age group, as noted in already cited studies such as Pavis *et al* (1997),Varga (1999), Brook and Pahl (2006), Quadrel and Hartman (1990), when transition from being children to adulthood is happening, peer influence and opinions of significant others are bound

to play the greatest influence on health behaviour. Now considering the risk of stigma and discrimination by peers, associated with taking anti-Tuberculosis treatment, as noted earlier on in Chapter 2, a patient in this age group would choose to rather not take medication in the presence of his or her colleagues, lest they began to think that he/she was infectious and caused a serious health risk to them also, or was very sick or even had HIV/AIDS (due to the high association of TB with HIV/AIDS in the South African context) and hence shun them. Peer influence, the role of significant others and generally the need to maintain social reputation (in this case not being viewed as having an infectious illness) therefore become the most important determinants of adherence outcome in this instance.

Age Category 3 (22-35 years) and Age Category 4 (36-49 years) represent arguably the peak years of working and economic productivity in South Africa as already elaborated on in Chapter 4. Hence patients in these age categories might either forget to take treatment due to occupation-related schedules, might be forced to delay taking treatment due to unfavourable work schedules, or might wait until periods when they are secluded from colleagues, customers or employers whom they would otherwise not want to see that they are on anti-TB medication. Another issue could also be that patients might not appreciate having to possibly deal with medication side-effects such as nausea, vomiting, temporary visual blurring, painful joints[59] among others (depending on the type of regimen they are on) while they are at their place of work, hence maybe choosing to delay taking treatment until after critical working hours at least. So the relative adherence difficulties in these categories {Δexp(B) values of 5.481 and 2.932 respectively} could be explained based on a work-routine/occupation related argument.

The Δexp(B) value 5.169, for Age Category 5 (50-63 years), which represents the third highest adherence difficulty under the 'reminded' outcome, can be explained by three arguments. Firstly, with anti-TB drugs, the likelihood of serious side-effects such as drug-induced hepatitis increases the older the patient is (see UCT, 2003; GoSA, 2000). It may as well be the case that the much older patients therefore would encounter adherence difficulty due to this reason. Secondly, forgetfulness is also an issue with much older patients[60], and therefore greater efforts might be required in getting them to adhere to treatment. Thirdly, at older ages, it could also be that patients will also require high levels of care and support when they are on treatment, and so their adherence difficulties/ease might be explained by the levels of care and support around

[59] See Appendix 3 on side effects of anti-TB medication
[60] See http://www.slideshare.net/HELPLibrary/forgetfulness-old-age , accessed 14/05/11

them. It implies therefore that any or a combination of those factors could have resulted in the third-highest likelihood of needing to be reminded to take treatment being in this age group.

5.11.2 Wrong Time Outcome

Parameter Estimates

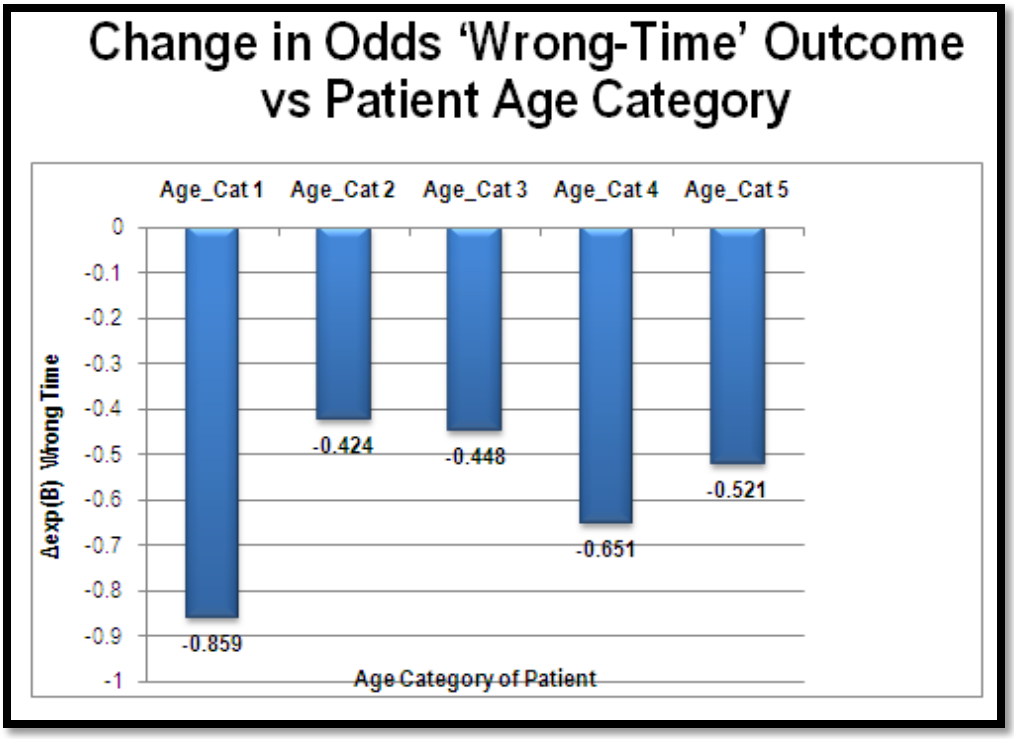
Adherence Outcome[a]		B	Std. Error	Wald	df	Sig.	Exp(B)	95% Confidence Interval for Exp(B)	
								Lower Bound	Upper Bound
Wrong_time	Intercept	-.875	.201	18.936	1	.000			
	[Age_Cat=1.00]	-1.962	.333	34.652	1	.000	.141	.073	.270
	[Age_Cat=2.00]	-.552	.222	6.196	1	.013	.576	.372	.889
	[Age_Cat=3.00]	-.594	.211	7.923	1	.005	.552	.365	.835
	[Age_Cat=4.00]	-1.052	.218	23.317	1	.000	.349	.228	.535
	[Age_Cat=5.00]	-.736	.228	10.455	1	.001	.479	.307	.748
	[Age_Cat=6.00]	0[b]	.	.	0	.	.	.	.

a. The reference category is: Right_time.

b. This parameter is set to zero because it is redundant.

Source: Author's data analysis
Table 5.19: Parameter estimates for 'Wrong time' outcome

It was shown from the results of the study that a patient in Age Category 1 (i.e. between 8-14 years of age) was 85.9% (0.141-1) less likely to take their anti-TB treatment at the wrong time relative to taking it at the right time, all other variables being kept constant. A patient in Age Category 2 (15-21years) was shown in the study to be 42.4% (0.576-1) less likely to take their anti-TB medication at the wrong time relative to taking it at the right time, all other variables being kept constant. A patient in Age Category 3 (22-35 years) was shown in the study to be 44.8% (0.552-1) less likely to take their anti-TB medication at the wrong time relative to taking it at the right time, all other variables being kept constant. A patient in Age Category 4 (36-49 years) was shown in the study to be 65.1%(0.349-1) less likely to take their anti-TB medication at the wrong time relative to taking it at the right time, all other variables being kept constant. A patient in Age Category 5 (50-63 years) was shown in the study to be 52.1% (0.479-1) less likely to take their anti-TB medication at the wrong time relative to taking it at the right time, all other variables being kept constant. The graph below shows the change in odds of patients taking their anti-TB treatment at the 'wrong time' based on their age categories.



Source: Author
Fig 5.12: Graph of change in odds 'Wrong time' outcome vs Patient Age Category

Consistent with the results for the 'Reminded' Outcome, patients in Age Category 1 (8-14 years) were the least likely to take treatment at the wrong time {Δexp(B)=-.859} and this can be explained once again by the fact that patients in this age category are paediatric cases and so management of their treatment schedule is by a parent, guardian or family member. Their adherence outcomes would then tend to be a function of the level of care and support around them, and in this case it also is evidently high, hence their having the least likelihood of taking medication at the wrong time. Speaking in relative terms, Age Category 2 (15-21 years) shows the highest likelihood of taking treatment at the wrong time {Δexp(B)=-0.424}, and this can also be explained by the effect of peer influence, social pressure and the role of significant others that is associated with teen and early adulthood lives, as already elaborated in *4.2.2* above. Age Categories 3 and 4 (between 22-49 years) represent the peak labour force/economic productivity years, and therefore the dynamics of taking treatment in these categories could be explained mostly by the type of work/occupation or means of livelihood a patient is engaged in, and to what extent it enables or inhibits taking treatment at certain time periods. The underlying cause for the observation of a Δexp(B) value of -0.521 for Age Category 5 would be based on the effects of forgetting to take medication by older patients, the level of care and support

around the elderly patient and some extent of adverse side effects (e.g. drug-induced hepatitis whose risk increases with age of patient).

5.11.3 Near-Miss Outcome

Parameter Estimates

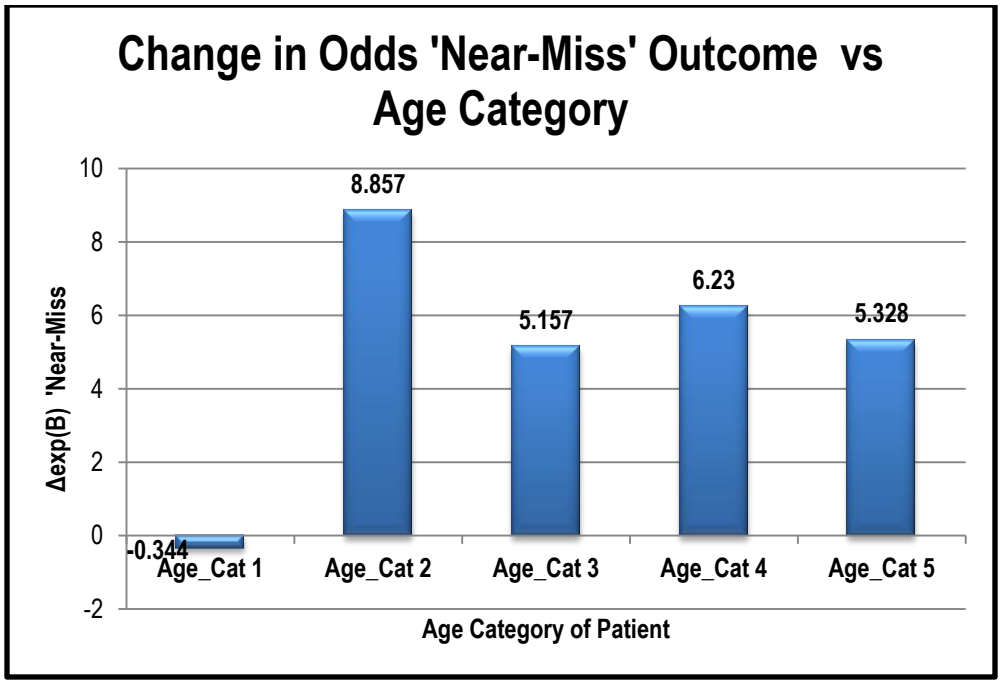
Adherence Outcome[a]		B	Std. Error	Wald	df	Sig.	Exp(B)	95% Confidence Interval for Exp(B)	
								Lower Bound	Upper Bound
Near-Miss	Intercept	-4.431	1.006	19.401	1	.000			
	[Age_Cat=1.00]	-.421	1.231	.117	1	.732	.656	.059	7.329
	[Age_Cat=2.00]	2.288	1.014	5.093	1	.024	9.857	1.351	71.916
	[Age_Cat=3.00]	1.818	1.012	3.229	1	.072	6.157	.848	44.711
	[Age_Cat=4.00]	1.978	1.011	3.825	1	.050	7.230	.996	52.493
	[Age_Cat=5.00]	1.845	1.019	3.277	1	.070	6.328	.858	46.644
	[Age_Cat=6.00]	0[b]	.	.	0	.	.	.	.

a. The reference category is: right_time.

b. This parameter is set to zero because it is redundant.

Source: Author's data analysis
Table 5.20: Parameter estimates for 'Near-miss' outcome

The study showed that a patient in Age Category 1 (i.e. between 8-14 years of age) was less likely to 'nearly-miss' taking their anti-TB medication by a factor of 0.344 (0.656-1) relative to taking it at the right time, all other factors being kept constant. A patient in Age Category 2 (15-21 years) was shown to be more likely to 'nearly-miss' taking their anti-TB drugs by a factor of 8.857 (9.857-1) relative to taking them at the right time, all other factors being kept constant. A patient in Age Category 3 (22-35 years) was shown to be more likely to 'nearly-miss' taking their anti-TB drugs by a factor of 5.157(6.157-1) relative to taking them at the right time, all other factors being held constant. A patient in Age Category 4 (36-49 years) was shown to be more likely to 'nearly-miss' taking their anti-TB drugs by a factor of 6.230 (7.230-1) relative to taking them at the right time, all other factors being held constant. A patient in Age Category 5 (50-63 years) was shown to be more likely to 'nearly-miss' taking their anti-TB drugs by a factor of 5.328 (6.328-1) relative to taking them at the right time, all other factors being held constant. The graph below shows the change in odds of patients 'nearly-missing' taking their anti-TB treatment based on the age categories they fell in.



Source: Author
Fig 5.13: Graph of Change in odds 'Near-miss' outcome vs Age Category

As with the same trends in the above outcomes, the least adherence difficulty (i.e. least likelihood of nearly missing treatment), was found to be in the Age Category 1 {Δexp(B)= -0.344}. This again finds explanation in the fact that adherence behaviour for patients in this age category is determined by the level of care and support around them, since they are paediatric cases. Age Category 2 (15-21years) is shown here to present the greatest adherence difficulty i.e. highest likelihood of 'nearly missing' treatment {Δexp(B)=8.857} because of the challenges of social pressures, peer influence and the role of significant others, elaborated in the other outcomes above. The Δexp(B) values for Age Categories 3 and 4 (5.157 and 6.23 respectively) that show the change in likelihood of nearly-missing treatment among patients between the ages of 22-49 years can be explained by work/occupation-related reasons as explained in earlier outcomes. For the much older patients in Age Category 5 (50-63years), the relatively high Δexp(B) value (5.328) can be explained by the level of care and support around the elderly patient, the patient merely forgetting to take treatment or enhanced side-effects of anti-TB treatment that come with old age. Furthermore it also needs to be generally noted that after Age Category 1, the likelihood values of 'nearly-missing' treatment are very high for the rest of the age groups. It could also be possible that patients under these categories would have the attitude of rather wanting to *'quickly taking the anti-TB medication, getting over with it* (for a particular medication event*) and moving on to other things'*, hence explaining these large odds

of taking treatment (erroneously) earlier than scheduled[61]. Such attitude by patients towards treatment tends to point towards a perceived inconvenience of taking medication, whether it might be from side-effects or from not wanting to be seen by significant others to be consuming medication (fear of being stigmatized).

5.11.4 'Missed' Outcome

Parameter Estimates

Adherence Outcome[a]		B	Std. Error	Wald	df	Sig.	Exp(B)	95% Confidence Interval for Exp(B)	
								Lower Bound	Upper Bound
Missed	Intercept	-.539	.180	8.991	1	.003			
	[Age_Cat=1.00]	-.929	.231	16.220	1	.000	.395	.251	.621
	[Age_Cat=2.00]	-.628	.199	9.998	1	.002	.534	.361	.788
	[Age_Cat=3.00]	-.857	.190	20.270	1	.000	.425	.292	.617
	[Age_Cat=4.00]	-1.012	.193	27.387	1	.000	.364	.249	.531
	[Age_Cat=5.00]	-.899	.205	19.203	1	.000	.407	.272	.608
	[Age_Cat=6.00]	0[b]	.	.	0	.	.	.	.

a. The reference category is: Right_time.

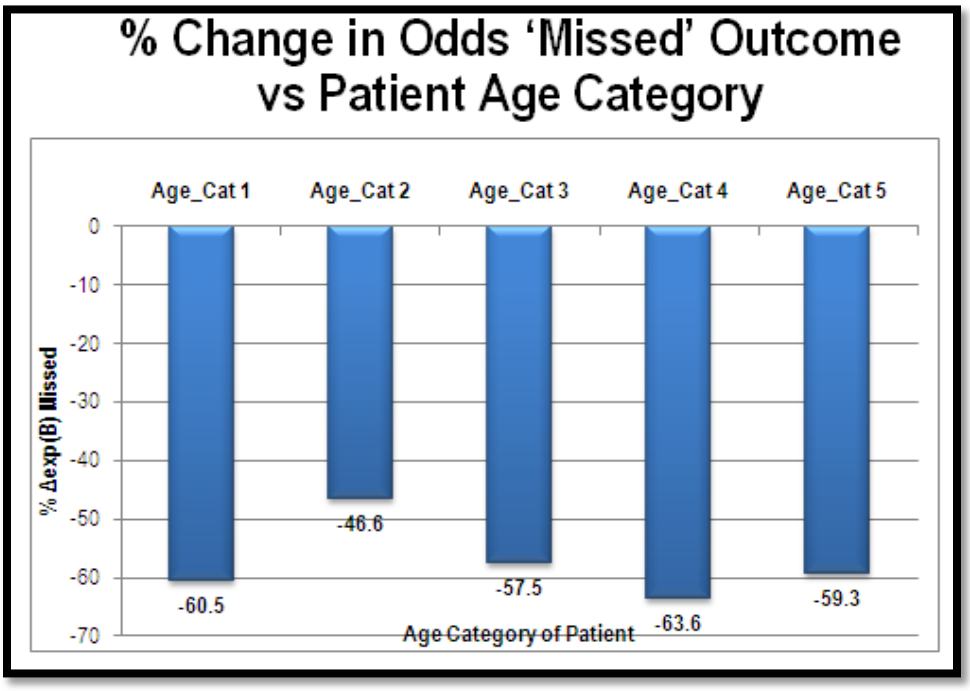
b. This parameter is set to zero because it is redundant.

Source: Author
Table 5.21: Parameter estimates for 'Missed' outcome

The study showed that a patient in Age Category 1(8-14years) was 60.5% (0.395-1) less likely to miss taking their anti-TB treatment altogether for any given medication day relative to taking it at the right time, all other variables being held constant. A patient in Age Category 2 (15-21years) was shown to be 46.6% (0.534-1) less likely to completely miss their anti-TB treatment for any given medication day relative to taking it at the right time, all the other variables being kept constant. A patient in Age Category 3 (22-35 years) was shown in the study to be 57.5% (0.425-1) less likely to miss taking their anti-TB treatment altogether for any given medication day relative to taking it at the right time, all other variables being kept constant. A patient in Age Category 4 (36-49 years) was shown in the study to be 63.6% (0.364-1) less likely to miss taking their anti-TB treatment altogether for any given medication day relative to taking it at the right time, all other factors being kept constant. A patient in Age Category 5 (50-63 years) was shown in the study to be 59.3% (0.407-1) less likely to miss taking their anti-TB treatment

[61] According to the Simpill definition of the Near-Miss category

altogether for any given medication day relative to taking it at the right time, all other factors being kept constant. The graph below shows the change in odds of patients 'missing' taking their anti-TB treatment based on their age categories.



Source: Author
Fig 5.14: Graph of % Change in odds 'Missed' outcome vs Patient Age Category

In analysing the 'missed' outcome graph of change in odds across age categories, the general trend of underlying explanations for adherence difficulty can, as in previous outcomes, more or less be observed as well i.e. Age Category 1 - care related factors, Age Category 2 - social pressure related factors, Age Categories 3 & 4 - work routine/occupation related factors, and Age Category 5 -forgetfulness due to old age, adverse side effects of treatment and care-related factors. It is also quite interesting to note that the Δexp(B) values fall on a very narrow range i.e. highest value -46.6%, lowest value -63.6% in comparison to previous adherence outcomes. This would be so because the likelihood of completely missing treatment altogether was noted to be severely diminished due to the rigorous follow-up that the Simpill system enabled (i.e. accelerated reminders, then follow up calls or visits by primary care-givers and/or health workers). The implication here would be that few patients would thus totally miss taking their treatment altogether for a given medication day. Section 5.12 below will seek to empirically validate the plausibility of this argument through interrogating the existence of comparative

benefits (if any) of using the Simpill system versus non-users among Tuberculosis patients, through analysis of treatment success rates between the 2 groups of patients.

5.12 Effects of Real-time Cue to Action on Adherence Outcomes: Comparison of Treatment Success Rates between Simpill and Conventional DOTS using Patients

As elaborated in the methodological section in section *4.10.2.2* of the previous chapter, this section endevoured to interrogate whether the Simpill device's real-time cue to action (i.e. the SMS reminders) had any effect on patient adherence behaviour. Again as earlier explained this was done through comparison of average treatment success (particularly cure rates[62]) between the Simpill using patients and those who had been medicating using the conventional DOTS method (control group). With the average treatment success rate for non-Simpill users being given as 71.9%[63], a one-sample ***t***-test was used to establish whether the mean success rates of the two groups had any significant difference or not. The results are as below:

One-Sample Statistics

	N	Mean	Std. Deviation	Std. Error Mean
Dummy Variable Cured Treatment Outcome	143	.9161	.27824	.02327

Table 5.22a: One-sample Statistics output for comparison of treatment success between Simpill and non-Simpill users

One-Sample Test

	Test Value = 0.719					
					95% Confidence Interval of the Difference	
	t	df	Sig. (2-tailed)	Mean Difference	Lower	Upper
Dummy Variable for Cured Treatment Outcome	8.470	142	.000	.19708	.1511	.2431

Table 5.22b: One-Sample T-test output for comparison of treatment success between Simpill and non-Simpill users

Source: Author's own data Analysis

[62] Cure rates henceforth considered as proxy for treatment success

[63] Because of ethical limitations in the study, the researcher only got access to an already calculated average treatment success rate for patients on DOTS (the control group), courtesy of Western Cape Provincial Government (200/07 Annual Health Report). This was still deemed adequate as a basis for comparison between Simpill and non-Simpill users.

Based on the 2 outputs above, it is evident that use of the SimPill device significantly gave improved TB treatment success rates (average 91.6%) compared to the conventional DOTS system (average 71.9%), with the difference between these mean treatment success rates having a p-value of 0.000, noted to be highly significant. This could be attributed to the fact that use of the Simpill indeed seems to overally reduce the number of patients who completely miss treatment altogether for any given medication day (as already expostulated in section *5.11.4),* since these patients are followed up on in real-time after the failure of accelerated reminders.

Also considering the great influence of the daily routine as a determinant of whether patients would postpone or forget taking treatment as earlier on discussed in above sections, the text messages from the Simpill system server, working as a real-time cue-to-action, would then tend to prompt (remind) the patient to take medication and so the continuation of these reminders throughout the treatment process also improves treatment persistence (i.e. prolonging the number of days a patient sustains the uptake of treatment) among the TB patients. It could also be argued that even if a patient had deliberately chosen not to take medication due to any manner of adherence hindering factor, the cue-to-action could also serve to re-alert the patient on the risk of not medicating, which would help in sustaining the right individual factors e.g. self-efficacy, locus of control and attitude towards treatment among other factors requisite for the maintenance of treatment adherence behaviour. It can then be reasoned out therefore that use of the Simpill device tends to skew patients towards the 'Right Time' and 'Reminded' outcomes, and particularly the least desirable 'Missed' adherence outcome is minimized.

5.13 Chapter Conclusive Remark

Indeed Chapter 5 was rigorous and very detailed in attempting to empirically ascertain the relationship between various treatment-scheduling variables and the polytomous variable 'Adherence Outcomes'. Upon validating the overall relationship, specific predictors were then explored using both Multinomial Logistic Modeling and Ordinary Least Squares regression methods. There was also successful verification of the efficacy of the real-time cue-to-action (i.e. the real-time SMS reminders from the Simpill system), in what the study argued to be the cue-to-action's role in enhancing treatment persistence among TB patients. Now the next chapter will discuss the findings from this chapter and interrogate what new concepts this study contributes, or at least what new perspectives it adds to already known concepts in the discourse on treatment adherence behaviour.

Chapter 6: Discussion of Findings, Conclusions and Development of Theoretical Model

6.1 Discussion of findings: what is 'old' and what is 'new'?

It is of great interest to observe that after rigorous analysis of the real-time and other treatment scheduling-related data from TB patients who were using the Simpill device, this study induced underlying determinants of adherence that could be categorized as below :-

- Drug Regimen-related factors
- Occupational schedule-related factors (including routine related factors)
- Role of significant others/social pressures
- Individual/patient-related factors
- Socio-cultural factors e.g. gender and power relationships
- Socio-demographic factors e.g. age of patient, and
- Care and support around patients

Now it is quite clear that these factors more or less resonate with previous studies on determinants of adherence already discussed in Chapter 2, and this is arguably so because the same phenomenon (i.e. treatment adherence) is ultimately being measured, even though this study was premised on real-time perspectives. Indeed factors such as regimen type and complexity, social pressures/role of significant others, socio-economic reasons, forgetting, behavioural factors such as attitude and motivation, level of care and support among other issues emerging from this particular study can easily be linked with previous works in this subject matter e.g. Jay *et al* (1984), Sukwa *et al* (1999), Cramm *et al* (2010), Shakya *et al* (2005) and WHO (2003), to mention but a few of the already alluded-to studies. One could then argue that in this regard, the findings could possibly be considered 'old', as in they are already well-known and well documented. The question then would be with respect to what new perspectives this study has brought in relating to further understanding of the issue of treatment adherence beyond what is already known? The answer indeed lies in a number of interesting issues that emerged from this study at the empirical and theoretical levels, which could in fact be considered as contributions to the existing body of knowledge in the treatment adherence discourse. These are as discussed in detail below:

6.2 Added Evidence from a Developing Country Context

Of course this study, being based on a Sub-Saharan Africa case, increases more insight particularly into TB treatment adherence dynamics in developing country contexts. This on its own contributes towards filling a knowledge gap already alluded to by the WHO (2003), whose main contention was that adherence studies had predominantly been conducted in developed countries, hence the need for more empirical evidence based on developing country realities. The importance of this, according to the same authors, lies in the imperative need to enrich understanding of context specificity as it pertains to its influence on adherence behaviour. In our case for instance, one immediate example on the benefits of building more appreciation of context-specificity has been the greater emphasis on the role of socio-cultural factors in influencing adherence dynamics. A particular case in point is in the way the etiological factor gender was analysed in this study, whereby the partriachal context of South Africa was put into consideration, and based on interrogation of the various socio-culturally defined roles, responsibilities and expectations of both males and females (with particular emphasis on the latter), the variation in risk of non-adherence was thus better understood. This without doubt added depth into the conceptualization of gender (in its actual form) as an etiological factor for treatment adherence, compared to the often-used practice of merely considering sex of respondent as proxy for the gender variable in prevous studies. Of course it also suffices to say that socio-culturally related factors influencing health behaviour (in this case treatment adherence) would tend to be more pronounced in third world country contexts where there is greater likelihood of entrenchment of traditional and culture-based stereotypes, norms and value systems as well as definitions of roles and responsibilities among societal members[64]. This study therefore becomes a significant contribution towards a deeper understanding of some of such socio-cultural dynamics and how they influence adherence behaviour.

6.3 Importance of Timing of Treatment

This study was adequately able to demonstrate that timing of treatment is without doubt a critical determinant of adherence behaviour among patients on anti-Tuberculosis treatment. Indeed it was empirically demonstrated how for instance the phase of taking treatment could moderate a patient's attitude and/or motivation towards taking their medication. Another scenario was shown where taking treatment on a public holiday had a negative effect on adherence because of the change in patients' or their carers' daily routines. The study also showed how in instances taking treatment in the mornings, afternoons or in the evenings also

[64] See Vlassoff (1994), UNDP (2003)

led to difference likelihoods of adhering to treatment among patients, depending of course on the patient's daily routine, among other cases where time-related variables had a bearing on adherence dynamics. Such findings certainly broaden understanding of etiological factors of non-adherence, especially with the added knowledge that timing of treatment interacts with and moderates other determinants of adherence behaviour among patients. To put this into perspective, we can consider scenarios raised in the previous chapter, where for instance, because a patient is taking treatment in the morning, chances of stigma and discrimination might be less than later in the day when he/she has more interaction with peers. It means then that even in a set-up with high stigma and discrimination as deterrents to adherence, the mere fact that the patient takes treatment at a time that minimises these deterrents (e.g. in the mornings) implies that adherence likelihood will be enhanced. In another example, given that a patient experiences side-effects from their anti-TB drug regimen, it follows then, that taking treatment during the day when they are at their place of employment might not be preferable, perhaps because the side-effects could affect their handling of mechanical or electrical equipment or other work-related procedures. In such case, the role of side-effects of medication thus becomes more amplified as a determinant of non-adherence, whereas if the same patient took treatment after working hours, they could perhaps lie down and rest as a means of managing the side-effects, thereby minimising the role of drug-induced side-effects as deterrent to treatment adherence. Interventions towards the improvement of treatment adherence would thus never be complete without consideration of whether the scheduled time of taking medication indeed optimises its uptake or not.

6.4 The Treatment Adherence Continuum

It also is very important to elaborate on the fact that the use of Multinomial Logistic (MNL) modeling in predicting adherence behaviour in this study was certainly novel, as it brought with it an opportunity to empirically prove that treatment adherence need not necessarily be viewed as a binary variable (i.e. as whether one adhered or not), but in fact as a multinomial continuum with at least 3 phases and points in-between adherence and non-adherence. The phases could be, as shown from the empirical analysis:-

- The exact time for taking treatment as scheduled i.e. the most optimal and ideal adherence outcome
- An acceptable window period (time range) for taking treatment, though not the exact prescribed time, but still considered an appropriate adherence outcome. This window

period depends on the medication being taken's half-life, optimal bio-availability rates etc, as earlier on alluded to in Chapter 5

- An increasingly risky time range, falling out of the acceptable window for adherence, which can be considered as wrong time for taking treatment. For a patient to take treatment in this range is not desirable and technically non-adherence begins in the same range
- A higher risk time range for taking treatment, which technically is as bad as missing treatment altogether. In this phase the classification of non-adherence is more pronounced
- The extreme end of non-adherence when a patient totally misses taking treatment for a scheduled medication event altogether.

Now appreciation of this polytomous nature of adherence outcomes would certainly be useful from a practitioner's viewpoint, as over-estimation of adherence can be avoided among patients where, say usage of pill counts or refill rates as measures of adherence might show treatment as having been taken 'according to schedule', yet it was being taken inappropriately, in other words in unacceptable time ranges. Risks such as drug resistance, toxicity and treatment failure which can arise as a result of taking treatment at wrong and inappropriate times (although maybe still on the same medication day, but more towards the non-adherence extreme) could thus be avoided if practitioners would have the capacity to monitor the real-time dynamics of patients' taking of treatment.

6.5 The Point of Medication

Now as the study was able to empirically demonstrate that predictors of adherence do determine adherence outcomes on an individual medication event basis, it implies therefore that outcomes at each medication event on the treatment schedule and their respective etiological factors can be viewed as a basic and complete unit of adherence measurement. This unit of measuring adherence, will henceforth be called the **'point of medication'** in this study i.e. that point in real-time when medication is taken, or is supposed to be taken, whose outcome is a function of the various etiological factors of adherence. The Point of Medication (POM) can be viewed as being independent of any other throughout the course of treatment since the etiologic factors (the various factors determining adherence) act on it at diffent intensities for each medication event, and hence could result in variable adherence outcomes.

Thus the sum total of these independent 'points of medication' should determine whether a patient can overally be classified as having successfully completed treatment or not at the end of the course, or at least can be used to locate a patient's general adherence behaviour on the treatment adherence continuum. Furthermore, it is important to mention that this concept of **'point of medication'** is most useful from a health intervention perspective; if the health delivery system is able to monitor a patient's treatment schedule on a 'point of medication' basis, it means there can be an immediate reaction when the patient for instance does not take treatment within the acceptable window period or misses it altogether e.g. through sending the patient a reminder, alerting a carer, nurse etc. This way, defaulters can thus be immediately identified and assisted, an improvement from the conventional methods in which detection of defaulters among patients could otherwise take days or even weeks (see section *2.10* of Chapter 2).

6.6 Interlinkage of Adherence Determinants

The study in many cases was also able to show how interconnected determinants of adherence were and how they did not necessarily exist or affect adherence outcomes independently of each other. One case in point would be the establishment of an apparent interconnection between Regimen 3 (the paediatric regimen of TB treatment) and level of care for such patients in ultimately determining adherence outcomes (see sections *5.4.1* and *5.5.1* of Chapter 5). Other arguments were raised where for example the fear of treatment side-effects (attitudinal and medicinal factors) would discourage someone at their place of work from taking treatment as they might not be able to operate certain types of machinery (occupational factors) or how a woman might end up forgetting to take treatment because of her overwhelming domestic and childcare responsibilities (gendered roles) to cite just a few cases. At the theoretical level, as noted in section *3.2* of Chapter 3, one of the main weaknesses noted in present theories used to study adherence, particularly the Health Belief Model, Social Cognitive Theory as well as the Information Motivation and Behavioural skills model lies in their failure to show inter-connectedness between the etiologic (causative) factors. The importance of these inter-linkages therefore are in being able to demonstrate that the etiological factors for adherence do in fact moderate each other's effect (i.e. one can have a bearing on the strength and effect of the other). Hence from an intervention perspective, practitioners would then opt for a more multi-perspective approach cutting across all causative factors as a means of responding to non-adherence. Such an approach is bound to produce greater results, as recommended by practitioners such as the WHO (2003). It is therefore of great interest that, looking at real-time

dynamics of treatment adherence actually led to a very apparent establishment of the inter-connection of multi-perspective etiological factors at the empirical level, and this certainly enriches conceptual understanding of the phenomenon of treatment adherence. This inter-connectedness will certainly be shown in the model that will follow the explanations of a few more emerging issues below.

6.7 The Role of the Real-Time Cue to Action

This study was also able to demonstrate that a sustained real-time cue-to-action can in fact improve adherence rates and ultimately treatment success rates among Tuberculosis patients. This could be so as a result of the prompting of would-be defaulters, thus reminding or encouraging them to take treatment. In cases where patients would be having other more complex problems causing them not to take treatment (apart from simply forgetting or needing a little prompting), a real-time cue-to-action to a carer would also mobilize support for the patient, which would facilitate the patient's taking of treatment or receiving further treatment support from the health service providers. In summary, the real-time cue-to-action would improve a patient's persistence in taking treatment i.e the duration of time from initiation to discontinuation of therapy, thereby improving their likelihood of treatment success.

6.8 Questioning the Notion of Rationality: Hypothesising on Socio-Cultural Normatives and Sub-Conscious Avertion to Treatment (SCATM)

As shown in Chapter 3, the challenge regarding too much assumption of rationality i.e. the state of having good sense and sound judgment among individuals taking medication, emerged as one of the major shortcomings from the critique of behavioural theories mostly used in studying treatment adherence. Indeed, assuming patients would make the most rational decisions concerning their health (in this case adhering to treatment) was evidently brought into doubt in this study in view of such factors as power relationships, social pressures, peer influence and occupational factors etc. For instance, scenarios were shown in the findings where a patient could possibly choose to delay taking treatment because he/she would be in the presence of peers, or at the workplace or attending public or other social events. The study also showed patients' probability of adherence dropping after the intensive period of treatment to add on to other already mentioned non-adherence scenarios, evidence which surely casts into doubt whether rationality in taking long-term treatment is in fact a tangible phenomenon among patients.

In other words, for all taking medication is worth, that is full recovery from TB and perhaps the avoidance of incapacitation (or even death) from TB illness, a question would arise as to why a patient would stop taking treatment because they now felt better after the intensive phase for instance, or choose their peers and to maintain social reputations (i.e. not being considered infectious in this case) ahead of their own health? While the findings also brought out the possibility of forgetting playing a crucial in adherence outcomes, this study also questions just how important taking medication becomes in the medium-to-long term for patients, bearing in mind that if it remained that much of a priority, the likelihood of forgetting would be minimal (except maybe in old-age induced cases). Even if the argument could be that indeed a patient might actually become so busy with other things during their day, be it with work, school or other social activities that they forget to take treatment, according to this thesis the issue would still remain. Looking at it from another perspective, would the same patient forget other important 'life-giving' activities like eating for example, whether they are at work, school or among their peers? If not, why then would the taking of medication for all it is worth, be forgotten still? Again it would be interesting to attempt to reasonably explain why a patient would rather choose to take their treatment earlier than scheduled to 'get it over and done with', yet there are apparent risks involved in that course of action, such as development of drug resistance, possible toxicity due to bio-accumulation of unmetabolised drugs in the system, risks the patient is made aware of at the beginning of treatment?

All these scenarios indeed demonstrate how rationality is indeed overrated among patients on long-term treatment, such as in this case for Tuberculosis treatment. The question of what actually happens to 'rationality' among the patients still remains unanswered though, and in a quest to provide possible perspectives, this study hypothesizes on two possible constructs that diminish rationality in patients, the first one being the Socio-Cultural Normatives and the other being the Sub-Conscious Avertion to Medication (SCATM). They are further explained below:

6.8.1 Socio-Cultural Normative Phenomenon

Under this phenomenon, this thesis argues that because of societal expectations emanating from traditionally and culturally defined norms and value systems, a patient might end up compromising on adherence to treatment out of the fear of being labeled non-conformant to generally accepted societal rules and regulations. For instance, in a society where adult men are expected to be breadwinners under any circumstances, an adult male patient might choose to deliberately not take medication so that perhaps he is not affected by side-effects or

stigmatized against as he works to feed his family. Another instance could be cases where a patient might rather choose to participate in social gatherings at the expense of taking their medication and resting at home, out of the fear of being seen as socially deviant from normal practice, in this case participating in social gatherings of community importance as and when expected to do so. Yet another scenario could be when say, a female patient, as a mother and because of socio-cultural expectations to take care of her family, might become too pre-occupied with domestic roles and childcare to take treatment as scheduled. It could even be possible that a female might choose to skip taking certain medications if they compromise her socio-culturally defined reproductive responsibilities e.g. the instance noted in this study where taking a type of drug might imply the need to switch contraceptive methods, which the male partner (who in partriachal contexts often has the final say even in reproductive matters) might not agree with in the long term. It is also important to emphasise at this point that socio-cultural normatives are also reinforced by the presence of influential others, in most cases custodians of a society's culture, and far-reaching platforms such as the media would also tend to play a key role in the entrenchment of these socio-cultural normatives.

As a result of this phenomenon therefore, as this study argues, even if a patient knew the 'right thing to do', that is adhere to treatment, they might end up having to compromise doing so due to the overwhelming socio-cultural expectations around them. In other words, a patient could therefore choose or be forced not to adhere to treatment as they seek to maintain reputation of being a pro-active societal member who participates in their defined roles and responsibilities. In such context and domain therefore can some of the irrationality among patients be explained.

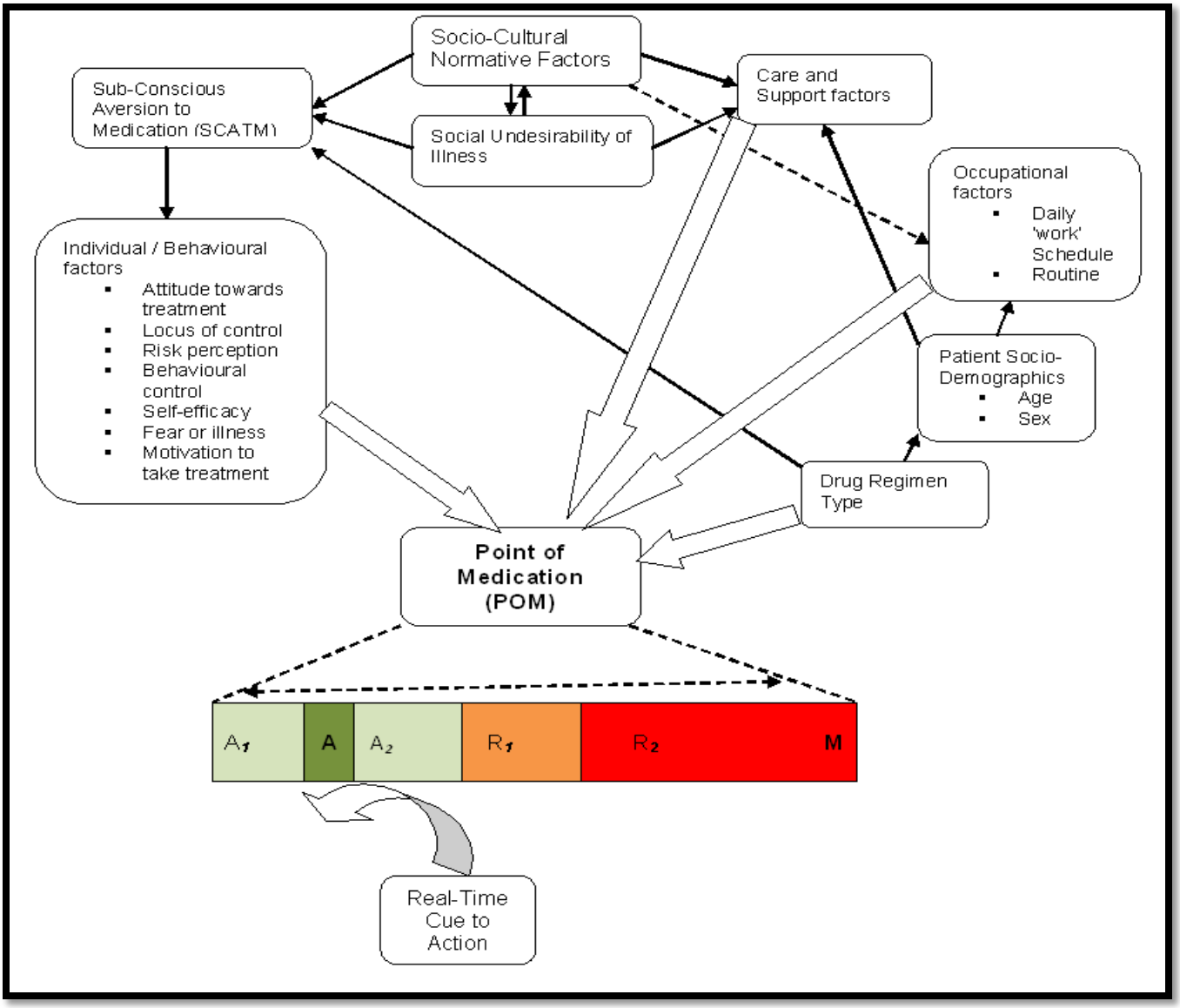
6.8.2 Sub-Conscious Aversion to Medication (SCATM)

In also attempting to rationalize particularly why patients would begin skipping treatment after a sense of feeling better, clearance of symptoms or in later stages of the treatment course and also trying to understand the thinking behind defaulting from treatment during public holidays or when in the presence of peers etc, this study proposes yet another hypothetical concept called Sub-Conscious Aversion to Medication (SCATM). The argument under this theoretical concept is that sub-consciously, human beings naturally do not want to take treatment, they consider taking medication as being un-natural, representing weakness, lack of well-being, perhaps even closeness to death, deviation from the ideal (good health) and in some cases look at it as a source of disturbance to normal life patterns e.g. eating patterns, dietary requirements, work and social routines etc. This is even made worse by side-effects given by the drugs (in

applicable cases). It means therefore that medication is most likely to be taken when it is absolutely necessary i.e. when there are visible signs of illness, apparent debilitation *etcetera* so as to clear such ill-health and return to normal health as quickly as possible. If treatment then becomes protracted into longer periods, for all taking medication is worth, patients start being erratic at adhering, in some cases even hoping (irrationally of course) that their bodies will naturally clear off the illness. Due to this Sub-Conscious Aversion to Medication as well, the taking of medication subsequently becomes a matter of convenience among patients, or at least when they remember to do so, in the medium-to-long term. While SCATM might partly have cognitive origins (within the individual patients themselves), it is arguably also 'nurtured' and reinforced by socio-cultural normatives and the social undesirability of illness within the society i.e. community members' perceptions of illness especially as regarding the negative consequencies illness causes to social systems based on previous societal experiences. It needs to be emphasized still, that this factor is a likely causative of irrationality among patients taking treatment and could have a negative bearing on adherence e.g. stopping treatment after feeling better or taking treatment sporadically in the medium-to-long term. Since the SCATM factor is arguably reinforced by exposure of one to notions of social undesirability of illness, it them becomes possible that the SCATM factor will differ by age of patients, as well their general exposure and life experiences within their respective societies.

6.9 Conclusion: Towards a Real-time Theoretical Perspective into Treatment Adherence.

Indeed this study seems to point towards interesting theoretical perspectives that could be useful in further understanding treatment adherence dynamics in real-time. These perspectives elaborated in the discussion above, can in fact be coined into a theoretical framework, which this author will call the Point of Medication Model. It is shown diagramatically as below:



Source: Author
Fig 6.1 Point of Medication (POM) Model

6.9.1 Theoretical Model Assumptions and Definition of Variables

- The Point of Medication Model assumes that the basic unit of understanding treatment is the Point of Medication (POM), which is a point in real-time in which the medication event (taking of medication or lack thereof) takes place.
- The POM is assumed to be an independent point in the treatment course of an illness and is exerted pressure upon by various etiologic factors that lead to its outcome falling in any of the positions on an adherence continuum

- The Adherence Continuum is a range of potential outcomes between adherence and non-adherence that demarcates acceptable and unacceptable time limits separating adherence or lack of it, and this continuum would differ according to the type of treatment being taken.

- As shown in figure 6.1 above, the demarcated section labelled **A** on the continuum, represents the optimum adherence time i.e. when a patient takes treatment at the recommended time. The time zones $\mathbf{A_1}$ and $\mathbf{A_2}$ represent acceptable window periods for taking medication before and after the scheduled time respectively, and the patient could still be considered to have been adherent if they took treatment in any of these window periods. The time zone $\mathbf{R_1}$ represents the first inappropriate (Risky) time zone for a patient to take treatment, such that even if treatment is taken, there is a risk of the medication event technically falling into the non-adherence category. This risk or inclination towards non-adherence increases in time zone $\mathbf{R_2}$, up to the worst extreme **M** on this 'non-adherent' part of the scale when treatment is missed altogether for a particular medication event.

- The model further assumes that 4 main categories of factors have a direct bearing on the Point of Medication (POM), and these are

    - **Drug Regimen Type** i.e. related to complexity of the drug regimen, side effects of the drugs etc. that could compromise treatment adherence outcomes at the Point of Medication.

    - **Occupational factors** i.e. related to what socio-economic activities make up the patient's day-to-day schedule and which times are allocated for taking treatment. This variable is also sensitive to changes in normal routines *vis a vis* how this can affect times for taking treatment etc.

    - **Care and Support factors** i.e. the quality and quantity of care and support given to patients taking treatment *vis a vis* the extent to which this affects their adherence behaviour

    - **Individual/Behavioural factors** of patient i.e. this concise category of variables includes aspects such as the patient's attitude towards treatment, self-efficacy, locus of control, behavioural control related factors, motivation to adhere etc.

- However, as the theoretical model further expostulates, these main factors are interconnected and moderated by other factors i.e.
    - Patient socio-demographics e.g. age and sex.
    - Socio-cultural normatives e.g. gendered roles, socio-culturally defined responsibilities and expectations (as reinforced by societal significant others)
    - Social undesirability of illness - origins of social pressures such as stigma and discrimination due to society's general discomfort with illness among some of its members, particularly if the illness is deemed infectious and risk and susceptibility perceptions are also high. It is also from this domain that general attitudes and beliefs about the illness being treated for emanate from.
    - **Sub-Conscious Aversion to Medication (SCATM)** - a hypothetical notion that people, at the back of their minds generally do not want to take medication because they consider it unnatural and interferes with 'normal' lifetsyles, hence only being tolerant of taking treatment in the short term, especially to clear off apparent signs and symptoms fo illness. If treatment has to be taken into the medium-to-long term, then adherence becomes more difficult to sustain.
- As a result of the interaction of these factors therefore, the concept of rationality is then diminished with respect to patients' taking of prescribed medication, leading to patients often 'unreasonably' defaulting on taking of treatment.
- Particularly, socio-cultural normative factors, social undesirability of illness and SCATM can be considered the domains in which the perceptions, attitudes, behavioural factors regarding adherence originate from, as well as being the domains where the role of significant others in determining health behaviour (in this case adherence) are clearly defined.
- As the theoretical model further contends, the presence of a real-time **Cue-to-Action** would be useful in enhancing treatment persistence among patients, through directly prompting and reminding them to take treatment or alerting primary (at the community level) and/or secondary carers (health service provider) to support the patients' adherence behaviour. From the model therefore, it is argued that the real-time cue-to-action 'pushes' patients toward more acceptable window periods of taking treatment

during the course of treatment i.e. through the prompts, reminders and follow-ups by carers.

6.10 Conclusive Remarks on the Theoretical Model

In conclusion, it needs to be mentioned that the proposed theoretical model, the Point of Medication Model, has indeed been developed in the backdrop of numerous other theoretical frameworks that have been employed in the quest to fully understand the age-old challenge of treatment adherence among patients on long-term treatment. As a composite theoretical model, it attempts to capture various domains with respect to the etiological factors of treatment adherence or lack thereof, i.e. biomedical, social, behavioural, routine-related factors and to an extent the socio-economic factors. Due to the model's multi-perspective nature, it certainly goes without saying that it will have stronger predictive power (at the hypothetical level at least) in estimating adherence behaviour dynamics compared to its counterpart theories. While scholars such as Munro (2008) have generally encouraged greater focus on working with existing theoretical frameworks in seeking to understand treatment adherence issues instead of developing new ones, again it becomes important to note the over-arching challenge in a number of these already existing theoretical frameworks i.e. not having been drawn from actual treatment adherence studies (e.g. some drawn from other medical activities such as exercises, dieting, breastfeeding etc. that have different dynamics to taking medication). This context has therefore led to the emergence of questions over appropriateness and relevance of these traditionally used theories in studying treatment adherence, thereby creating rationale and justification for the development of alternative theoretical perspectives based on actual observation of treatment adherence itself, such as the POM Model.

From an intervention point of view, the POM Model also finds comparative advantage in being multi-perspectival in nature i.e. cutting across various domains of etiologic factors for treatment adherence e.g. biomedical, socio-economic, socio-cultural and behavioural factors (as already alluded to), hence providing opportunities for conceptualization of inter-disciplinary interventions to curb non-adherence among chronic patients.

A general lack in developing country-context adherence studies (see WHO, 2003) has also over the years led to the underplaying of important issues such as socio-cultural contexts and how these have a very strong bearing on health behaviour in general and treatment adherence in particular. This is an aspect this study, and ultimately the theoretical model attempts to underscore on and contribute greater understanding towards. The POM model also dispels the

over-assumption of rationality that has notably been problematic in some of the main theories used in studying treatment adherence among patients. Moreover, through proposing and emphasizing on the important roles played by socio-cultural normative factors, social undesirability of illness and the Sub-Conscious Aversion to Medication (SCATM) as determinants of adherence behaviour, the POM Model adds greater insight into origins of health beliefs (as compared to the other conventionally used theories) both at individual and societal levels. It goes without saying then, that this critical advancement in theoretical appreciation of the origins of health beliefs has vast potential to strengthen the design of interventions aimed at curbing treatment non-adherence e.g. development of needs-based Information, Education and Communication (IEC) campaigns meant to dispel myths about TB illness and promote community care and support for patients, thereby creating a conducive environment for treatment adherence. The theoretical model also has a comparative advantage in that it identifies and interconnects factors that directly and indirectly affect adherence at the rudimentary level, also making it more pragmatically oriented in terms of development of adherence improving interventions i.e. focusing on optimizing factors that could increase the likelihood of treatment adherence at the point of medication and working at minimizing those that with the reverse effect.

Furthermore, with its origins and thrust being on improving and building on the success of already existing interventions (e.g. enhanced access to medication for illnesses of public health concern, such as TB under the DOTS programme in this case); this theoretical model is more of complementary as compared to being competitive to already existing efforts. It certainly is not exhaustive, neither is it conclusive, as it is the conviction of this author that with further research it can be fine-tuned, but it is without doubt a significant contribution towards more holistic appreciation of the age-long challenge of treatment adherence.

-The END-

APPENDIXES

Appendix 1: The Essential Anti-TB Drugs and the Treatment Regimens

These are the drugs, in Fixed Dose Combination (FDC) forms; make up the 3 drug regimens as detailed in the tables below

New smear positive and other serious pulmonary and extra-pulmonary tuberculosis

Regimen 1 (New Adult Patients)

4 Months Continuation phase (treatment given 5 times a week)	Patient under 50kg	Patient over 50kg
Combination tablet RH 150/100mg	3 tabs	
Combination tablet RH 300/150mg		2 tabs

If conditions do not allow for giving of treatment 5 times a week, treatment can also be given 3 times a week in the continuation phase, as below:

4 Months Continuation phase	**Patient under 50kg**	**Patient over 50kg**
(treatment given 3 times a week)		
Combination tablet	3 tabs	
RH 150/100mg		
H 100mg		
Combination tablet		2 tabs
RH 300/150 mg		
H 300mg		1 tab

R=Rifampicin : H= Isoniazid : Z=Pyrazinamide: E= Ethambutol : S=Streptomycin

***Ethambutol 225mg in combination is also acceptable**

Regimen 2 (re-treatment adult cases)

Smear positive retreatment cases (failure, relapse and return after interruption)

2 months initial Phase	**Patient under 50kg**	**Patient over 50kg**
(treatment given 5 times a week)		
RHZE	4 tabs	5 tabs
120/60/300/200mg*		
streptomycin	750mg	1000mg
3rd month (5 times a week)	**Patient under 50kg**	**Patient over 50kg**
RHZE	4 tabs	5 tabs

R=rifampicin: H=isoniazid (INH): Z=pyrazinamide: E=ethambutol: S=streptomycin

*Ethambutol 225mg in combination is also acceptable

5 months Continuation Phase	**Patient under 50kg**	**Patient over 50kg**
(5 times a week)		
RH 150/100mg	3 tabs	
E 400mg	2 tabs	
RH 300/150mg		2 tabs
E 400mg		3 tabs

5 months Continuation Phase	**Patient under 50kg**	**Patient over 50kg**
(3 times a week)		
RH 150/100mg	3 tabs	
H 100mg	1 tab	
E 400mg	2 tabs	
RH 300/150mg		2 tabs
H 300mg		1 tab
E 400mg		4 tabs

Note
Streptomycin should be reduced to 750mg/day to those older than 45 years and not be given to those over 65 years.It should also not be given during pregnancy
*Ethambutol 225mg in combination is also acceptable

Regimen 3 (Children with Tuberculosis)

Pretreatment body weight	**2 months initial phase (treatment given 5 times a week) RHZ 60/30/150mg**	**4 months continuation phase (treatment given 5 times a week) RH 60/30mg**
3-4kg	½ tab	½ tab
5-7kg	1 tab	1 tab
8-9kg	1 ½ tabs	1 ½ tab
10-14kg	2 tabs	2 tabs
15-19kg	3 tabs	3 tabs
20-24kg	4 tabs	4 tabs
25-29kg	5 tabs	5 tabs
30-35	6 tabs	6 tabs

R= Rifampicin: H= Isoniazid: Z= pyrazinamide

If conditions do not allow for giving treatment 5 times a week, it could also be given 3 times a week as shown below:-

Pretreatment body weight	**2 months initial phase (treatment given 5 times a week) RHZ 60/30/150mg**	**4 months continuation phase (treatment given 3 times a week) RH 60/60mg**
3-4kg	½ tab	½ tab
5-7kg	1 tab	1 tab
8-9kg	1 ½ tabs	1 ½ tabs
10-14kg	2 tabs	2 tabs
15-19kg	3 tabs	3 tabs

20-24kg	4 tabs	4 tabs
25-29kg	5 tabs	5 tabs
30-35kg	6 tabs	6 tabs

Note

Refer to weights before treatment for all regimes

Source: GoSA (2000)

Appendix 2: TB Patient Simpill Record

Simpill Device Number: **TB Patient Simpill Record**

Name Patient:	**TB Registration Number:**
Date treatment started:	**Regimen:**
TB Patient Cellphone Number:	**Other Drugs:**
Treatment Supporter Name:	**Treatment Supporter Cell Phone Number:**

Week	Date	Regimen 1	Repeat Sputum	Clinic visits	Simpill	Drugs	Date issue drugs & battery
1		Intensive Regimen 1 =		Clinic DOT		Daily at clinic	
2					Train patient & treatment supporter on Simpill	Daily at clinic	
3				Community DOT	Issue Simpill	Issue intensive phase drugs x 4 weeks	
4		Other drugs =					
5							
6							
7					Connect Simpill	Issue intensive phase drugs x 2 weeks	
8		Intensive Review compliance Weigh	x2 smears	x 3 (sputum x2 & Change to continuation phase)	Connect Simpill		
9		Continuation Regimen 1 = Other drugs =				Issue continuation phase drugs x 4 weeks	
10							
11							
12							
13						Issue continuation phase drugs x 4 weeks	
14							
15							
16							
17						Issue continuation phase drugs x 4 weeks	
18							
19							
20		Continuation (Review compliance	x2 smears	x2 (sputum x2)			
21		Continuation				Issue continuation phase drugs x 4 weeks	
22							
23							
24							
25				x1 (stop treatment discharge)	Return Simpill	Return unused drugs	

Appendix 3: Tuberculosis Treatment Side-effects and Management

Side Effects *Minor*	**Drug(s) Probably Responsible**	**Management** *Continue treatment*
anorexia, nausea, abdominal pain	rifampicin	give tablets last thing at night
joint pain	pyrazinamide	aspirin
burning sensation in feet	isoniazid	piridoxine 25 mg daily
orange/red urine	rifampicin	reassurance
Major		
skin itching/rash anaphylactic reaction	streptomycin	If a patient experiences any of these major side effects the drugs responsible should be immediately stopped and the patient referred to a specialist physician for an examination
deafness	streptomycin	
dizziness	streptomycin	
jaundice	most anti-TB drugs	
vomiting and confusion	most anti-TB drugs	
visual impairment	ethambutol	
generalised reaction, including shock and purpura	rifampicin	

Appendix 4: SIMPILL PROCEDURE

Week 1

- TB diagnosis needs to be confirmed, patient recalled and commenced on the appropriate treatment regimen.
- All patients are to receive daily clinic supervision for the first 2 weeks of TB treatment. Rationale for clinic treatment is three fold: educate the patient about his/her disease, monitor for side-effects and monitor compliance.
- Each newly diagnosed TB patient is to receive structured counselling sessions by TB staff on the following: nature of disease, compliance plan, spread TB, link between TB and HIV, side-effects
- Suitable community or workplace treatment supporter needs to be identified
- Enter patient details into TB register

Week 2

- Continue with daily clinic DOTS
- Appointment to be made to jointly counsel TB patient and treatment supporter on the use of the Simpill device
- Ascertain if treatment supporter and TB patient are in possession of their own private cellphones. Ensure direct ownership of cellphone, no shared cellphones acceptable for this project
- Complete TB patient Simpill patient record
- Pack intensive phase medication into Simpill device x 4 weeks

Week 3

- Arrange for patient and treatment supporter to jointly visit clinic
- Plot follow-up visits to clinic
- Provide treatment supporter and TB patient with follow-up dates
- Discuss time most suitable to treatment supporter and patient to take medication under supervision
- Issue Simpill device to treatment supporter
- Place a sticker with patient name on the side of the Simpill device
- Ascertain if both TB patient and treatment supporter understand the technology of the Simpill
- Explain Simpill will be connected to the network immediately
- Complete Simpill Device record
- Simpill technology will send messages to:
    - TB patient at predetermined time (1 hour after medication was agreed to be taken)
    - TB treatment supporter at pre-determined time (2 hours after medication was agreed to be taken)
    - TB Nurse at pre-determined time (14:00 every afternoon)
    - Fax Simpill device details through to Simpill for attention: to fax no: 021 710-2951

Week 3 – 6

- TB patient to have community or workplace supervision WITH Simpill connected to network

Week 6

- Pack intensive phase medication into pill holder device x 2 weeks

Week 7

- Arrange for treatment supporter to collect medication, swop medicine containers and exchange Simpill device battery
- Supply x2 sputum bottles for conversion sputum specimens

Week 8

- Ensure patient returns x2 consecutive early morning sputum specimens to clinic
- Arrange follow-up visit for TB patient to clinic
- Provide sputum results, weigh the patient, assess clinically if responding to treatment, check compliance on green card
- Change to continuation phase drugs

- Pack x4 week supply continuation phase drugs, swop pill containers and exchange Simpill battery
- Update TB register with conversion sputum results

Week 9-12

- TB patient to have community or workplace supervision WITH Simpill connected to network

Week 13

- Pack x4 week supply continuation phase drugs
- Arrange for treatment supporter to collect medication, swop pill containers and exchange Simpill battery
- Review compliance on green card

Week 13 - 16

- B patient to have community or workplace supervision WITH Simpill connected to network

Week 17

- Pack x4 week supply continuation phase drugs
- Arrange for treatment supporter to collect medication, swop pill containers and exchange Simpill battery
- Review compliance on green card
- Provide x2 sputum jars
- Arrange follow-up appointment to clinic at Week 20

Week 17- 20

- TB patient to have community or workplace supervision WITH Simpill connected to network

Week 20

- Ensure patient returns x2 consecutive early morning sputum specimens to clinic
- Arrange follow-up visit for TB patient to clinic

1) Provide sputum results, weigh the patient, assess clinically if responding to treatment, check compliance on green card
2) Pack x4 week supply continuation phase drugs, swop pill containers and exchange Simpill battery
3) Arrange for end treatment clinic visit
4) Update TB register with discharge sputum results

Week 20 -24

1) TB patient to have community or workplace supervision WITH Simpill connected to network

Week 25

1) Ensure patient returns to clinic for final assessment
2) Weigh the patient, assess clinically, check compliance on green card
3) Arrange for Simpill device and unused medication to be returned to clinic
4) Discharge patient from treatment
5) Discharge patient in TB register

Appendix 5: The Stop TB Strategy at a glance

The Stop TB Strategy at a glance

THE STOP TB STRATEGY

VISION	**A TB-free world**
GOAL	To dramatically reduce the global burden of TB by 2015 in line with the Millennium Development Goals and the Stop TB Partnership targets
OBJECTIVES	• Achieve universal access to high-quality care for all people with TB • Reduce the human suffering and socioeconomic burden associated with TB • Protect vulnerable populations from TB, TB/HIV and drug-resistant TB • Support development of new tools and enable their timely and effective use • Protect and promote human rights in TB prevention, care and control
TARGETS	• MDG 6, Target 6.c: Halt and begin to reverse the incidence of TB by 2015 • Targets linked to the MDGs and endorsed by the Stop TB Partnership: — 2015: reduce prevalence of and deaths due to TB by 50% compared with a baseline of 1990 — 2050: eliminate TB as a public health problem

COMPONENTS

1. **Pursue high-quality DOTS expansion and enhancement**
   a. Secure political commitment, with adequate and sustained financing
   b. Ensure early case detection, and diagnosis through quality-assured bacteriology
   c. Provide standardized treatment with supervision, and patient support
   d. Ensure effective drug supply and management
   e. Monitor and evaluate performance and impact
2. **Address TB/HIV, MDR-TB, and the needs of poor and vulnerable populations**
   a. Scale-up collaborative TB/HIV activities
   b. Scale-up prevention and management of multidrug-resistant TB (MDR-TB)
   c. Address the needs of TB contacts, and of poor and vulnerable populations
3. **Contribute to health system strengthening based on primary health care**
   a. Help improve health policies, human resource development, financing, supplies, service delivery, and information
   b. Strengthen infection control in health services, other congregate settings and households
   c. Upgrade laboratory networks, and implement the Practical Approach to Lung Health (PAL)
   d. Adapt successful approaches from other fields and sectors, and foster action on the social determinants of health
4. **Engage all care providers**
   a. Involve all public, voluntary, corporate and private providers through Public-Private Mix (PPM) approaches
   b. Promote use of the International Standards for Tuberculosis Care (ISTC)
5. **Empower people with TB, and communities through partnership**
   a. Pursue advocacy, communication and social mobilization
   b. Foster community participation in TB care, prevention and health promotion
   c. Promote use of the Patients' Charter for Tuberculosis Care
6. **Enable and promote research**
   a. Conduct programme-based operational research
   b. Advocate for and participate in research to develop new diagnostics, drugs and vaccines

Source: www.who.int ,13/05/11

Appendix 6: Millennium Development Goals Summary

Adopted by world leaders in the year 2000 and set to be achieved by 2015, the Millennium Development Goals (MDGs) provide concrete, numerical benchmarks for tackling extreme poverty in its many dimensions.

The MDGs also provide a framework for the entire international community to work together towards a common end – making sure that human development reaches everyone, everywhere. If these goals are achieved, world poverty will be cut by half, tens of millions of lives will be saved, and billions more people will have the opportunity to benefit from the global economy.

The eight MDGs break down into **21 quantifiable targets** that are measured by **60 indicators**.

- Goal 1: Eradicate extreme poverty and hunger
- Goal 2: Achieve universal primary education
- Goal 3: Promote gender equality and empower women
- Goal 4: Reduce child mortality
- Goal 5: Improve maternal health
- Goal 6: Combat HIV&AIDS, malaria and other diseases
- Goal 7: Ensure environmental sustainability
- Goal 8: Develop a Global Partnership for Development

Source: www.undp.org

Appendix 7: Case Processing Summary for variables in the MNL model

		N	Marginal Percentage
Adherence Outcome	right_time	3882	55.9%
	reminded	1028	14.8%
	wrong_time	759	10.9%
	near_miss	304	4.4%
	missed	977	14.1%
Regimen	1.00	5493	79.0%
	2.00	1189	17.1%
	3.00	197	2.8%
	99.00	71	1.0%
month into treatment	1	1899	27.3%
	2	2361	34.0%
	3	1539	22.1%
	4	671	9.7%
	5	317	4.6%
	6	129	1.9%
	7	24	.3%
	8	7	.1%
	9	3	.0%
Day of Taking Treatment	monday	1377	19.8%
	tuesday	1331	19.2%
	wednesday	1316	18.9%
	thursday	1441	20.7%
	friday	1450	20.9%
	saturday	20	.3%
	sunday	15	.2%
Categorised Times of treatment	5-7.983 hrs (first part of morning)	733	10.5%
	8-11.983 hrs (second part of morning)	4433	63.8%
	12-13.983 hrs (first part afternoon)	378	5.4%
	14-17.983 hrs (second part afternoon)	535	7.7%
	18-19.983 hrs (evening)	871	12.5%
phase of treatment variable	1.00	4655	67.0%
	2.00	2295	33.0%
Valid		6950	100.0%
Missing		2185	
Total		9135	

Appendix 8: BIBLIOGRAPHY

- **Ahasan,HN, Ayaz KFM, Hossain A, Rashid M and Chowdhury RA (2009):** *EXTENSIVELY DRUG-RESISTANT TUBERCULOSIS (XDR-TB), J MEDICINE;* 10 : 97-99
- **Ahlburg D A(2000):** *The economic impact of TB*. Ministerial Conference Amsterdam, WHO 2000.
- **Ailinger RL, Moore JB, Nguyen N, and Lasus H (2006).** *Adherence to latent tuberculosis infection therapy among Latino immigrants. Public Health Nursing*; 23(4):307–313. [PubMed: 16817801]
- **Ailinger RL**, **Black PL, Lima-Garcia N (2008):** Use of Electronic Monitoring in Clinical Nursing Research**.** *Clinical Nursing Research*. May: 17 (2): pp.89–97. doi: 10.1177/1054773808316941. NIH Public Access
- **Ajzen, I (2006):** *Theory of Planned Behaviour,* ***in*** http://www.km4dev.org/group/thehumanfactorinkm4dev, accessed 05/05/2011
- **Ajzen, I., & Fishbein, M. (1980):** *Understanding attitudes and predicting social behavior.* Englewood Cliffs, New Jersey, United States of America: Prentice-Hall. From http://www.cios.org/encyclopedia/persuasion/Gtheory_5references.htm
- **Anderson S., A. Auquier, W.W. Hauck, D. Oakes, W. Vandaele, and H.I. Weisberg (1980)**: *Statistical Methods for Comparative Studies*. New York, Wiley, 289 p. in **Wunsch G (2007):** *Confounding and control* .Demographic Research Vol. 16; Article 4, pp 97-120. DOI: 10.4054/DemRes.2007.16.4 on http://www.demographicresearch.org/Volumes/Vol16/4/
- **Armitage CJ and Conner M (2000):** *Social cognition models and health behaviour: A structured review.* Psychol Health, **15:**173-189. In **Munro,S Lewin,S ,Swart,T and Volmink J (2007)**: *A review of health behaviour theories: how useful are these for developing interventions to promote long-term medication adherence for TB and HIV/AIDS?* BMC Public Health 2007, **7**:104 doi:10.1186/1471-2458-7-104, BioMed Central Ltd,UK
- **Bandura A (1997):** *Self-efficacy: The exercise of control* New York: W. H. Freeman and Company; In **Munro,S Lewin,S ,Swart,T and Volmink J (2007)**: *A review of health behaviour theories: how useful are these for developing interventions to promote long-term medication adherence for TB and HIV/AIDS?* BMC Public Health 2007, **7**:104 doi:10.1186/1471-2458-7-104, BioMed Central Ltd,UK
- **Bandura A (2004):** *Health promotion by social cognitive means.* HealthEduc Behav, 31:143-164.
- **Bandura A (2000):** *Health promotion from the perspective of social cognitive theory.* In *Understanding and changing health behaviour: From health beliefs to self-regulation* Edited by: Norman P, Abraham C, Conner M. Amsterdam: Harwood Academic Publishers;:299-339.
- **BARNES P, F.& BARROW MS D. (1993):** *Tuberculosis in the 1990s*. Ann& of Internal Medicine, 119, 40&410.
- **Bates and Stead (1993):***The history of tuberculosis as a global epidemic.*Med Clin North Am. ; 77(6): 1205–1217.USA

- **Baussano I, Pivetta E., Vizzini L., Abbona F and Bugiani M (2008):***Predicting tuberculosis treatment outcome in a low-incidence area.* Int J Tuberc Lung Dis, 12(12):1441-8
- **Bayaga A (2010):** *Multinomial Logistic Regression:Usage and Application in Risk Analysis.*Journal of Applied Quantitative Methods.Vol 5. No. 2
- **Bello S. I. (2010):** *Challenges of DOTS implementation strategy in the treatment of tuberculosis in a tertiary health institution, Ilorin, Nigeria*. African Journal of Pharmacy and Pharmacology Vol. 4(4), pp. 158-164, April. ISSN 1996-0816. Academic Journals
- **Benyamini Y, Gozlan M and Kokia E(2004):** *On self-regulation of a health threat: Cognitions, coping and emotions among women undergoing treatment for fertility.* Cognit Ther Res, 28:577-592.
- **Berry M and Kon OM.(2009):** Multidrug- and extensively drug-resistant tuberculosis: an emerging threat. Eur Respir Rev. Dec 1;18(114):195-7.PMID: 20956144[PubMed]
- **Blackwell B (1992):** *Compliance.* Psychotherapy and psychosomatics, 58:161-169.In **Munro,S Lewin S,Swart T and Volmink J (2007)**: *A review of health behaviour theories: how useful are these for developing interventions to promote long-term medication adherence for TB and HIV/AIDS?* BMC Public Health 2007, **7**:104 doi:10.1186/1471-2458-7-104, BioMed Central Ltd,UK
- **Bo Hu, Mari Palta and Jun Shao (2006):** *Properties of R^2 for logistic regression.* STATISTICS IN MEDICINE Statist. Med. 2006; 25:1383–1395. Published online 29 July 2005 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/sim.2300
- **Borooah, V. (2001):** *Logit and Probit: Ordered and Multinomial Models,* SAGE Publications Inc, California
- **Brawley LR and Culos-Reed SN (2000):** *Studying adherence to therapeutic regimens: Overview, theories, recommendations.* Control Clin Trials, 21:156S-163S.
- **Brook, J.S., Pahl, K., and Ning, Y. (2006):** *Peer and parental influences on longitudinal trajectories of smoking among African Americans and Puerto Ricans.* Nicotine and Tobacco Research, 8, 639-651
- **Burney SMA (2008):** *INDUCTIVE & DEDUCTIVE RESEARCH APPROACH.* Department of Computer Science, University of Karachi. From http://www.drburney.net/INDUCTIVE%20&%20DEDUCTIVE%20RESEARCH%20APPROACH%2006032008.pdf , accessed 23/04/11
- **Chan Y H (2005):** *Biostatistics 305.Multinomial logistic regression.Statistics for doctors.* Singapore Med J; 46(6): 259
- **Chatterjee, S, Hadi, A.S., and Price, B (2000):** *Regression Analysis by Example* , 3rd edition, Wiley, New York, p104,
- **Corbett E. L., Watt C. J., Walker N., Maher D., Williams B. G., Raviglione M. C and Dye C(2003):***The Growing Burden of Tuberculosis: Global Trends and Interactions with the HIV Epidemic*. Archives of Internal Medicine. ;163:1009–21.[PubMed]
- **Council for International Organizations of Medical Sciences (CIOMS) and World Health Organization (WHO) (2002)** : *International Ethical Guidelines for Biomedical Research Involving Human Subjects*. Geneva, Switzerland

- **Cramer JA, Roy A, Burrell A, Fairchild CJ, Fuldeore MJ, Ollendorf DA and Wong PK (2008):** *Medication Compliance and Persistence:Terminology and Definitions*.Value in Health Volume 11 Number 1,International Society for Pharmacoeconomics and Outcomes Reseach (ISPOR)
- **Cramer, D. (2003):** *Advanced Quantitative Data Analysis.Understanding Social Research* (Bryman A -Ed.). Open University Press, Mcgraw-Hill Education, UK
- **Cramm JM, Finkenflügel HJ, Møller V and Nieboer AP(2010):** *TB treatment initiation and adherence in a South African community influenced more by perceptions than by knowledge of tuberculosis.* BMC Public Health, 10:72
- **Daniel TM (2006):** *The history of tuberculosis*. Respir Med. Nov; 100(11):1862-70. Epub 2006 Sep 1. PMID:16949809,USA
- **Daniel, T (2006):** *The history of tuberculosis.* Respiratory Medicine - November 2006 (Vol. 100, Issue 11, Pages 1862-1870, DOI: 10.1016/j.rmed.2006.08.006).Elsevier Inc.
- **Dick J, van der Walt H, Hoogendoorn L, Tobias B (1996):** *Development of a health education booklet to enhance adherence to tuberculosis treatment*. Tuber Lung Dis 77: 173-177.
- **Dick, J. and Lombard, C (1997):** *Shared vision – a health education project designed to enhance adherence to anti-tuberculosis treatment*. International Journal of Tuberculosis and Lung Diseases 1, pp. 181–186.
- **Dictionary of Health Services Management (1982**). Thomas Timmreck (Ed). Owings Mills, Md. : National Health
- **Diwan VK, Thorson A (1999):** *Sex, gender and tuberculosis*. Lancet 353: 1000-1001.
- **Doetsch R,(1978):** *Benjamin Marten and His "New Theory of Consumptions".* MICROBIOLOGICAL REVIEWS, Sept., p. 521-528, Vol. 42, No. 3. American Society for Microbiology,USA
- **Dorak MT(2010):** *Bias and Confounding*, *from* http://www.dorak.info/epi, accessed 20/03/11
- **Dorland's Medical Dictionary for Health Consumers (2007)** by Saunders, an imprint of Elsevier, Inc.
- **Draper NR and Smith H (1998):** *Applied Regression Analysis (3rd edn).* Wiley: New York,
- **Dubanoski, J. P. and Cohen, H. I. (1998):** *Tuberculosis chemoprophylaxis: Measuring adherence to the regimen.* Psychology, Health & Medicine, 3: 2,181-192
- **Dunbar JM, Marshall GD, Hovell MF (1979):** *Behavioural strategies for improving compliance.* In Compliance in health care Edited by: Haynes RB, Taylor DW, Sackett DL. Baltimore: Johns Hopkins University Press: 174-190.
- **Eccles M, Grimshaw J, Walker A, Johnston M and Pitts N (2005)**: *Changing the behavior of healthcare professionals: The use of theory in promoting the uptake of research findings*. J Clin Epidemiol, 58:107-112.
- **Eccles, J. S. (2005):** *Subjective task value and the Eccles et al. model of achievement-related choices.* In A. J. Elliot & C. S. Dweck, Handbook of competence and motivation (pp. 105-121). New York, NY: The Guilford Press

- **Edgar KA, Skinner TC (2003):** *Illness representations and coping as predictors of emotional wellbeing in adolescents with Type I diabetes***.** J Pediatr Psychol, 28:485-493.
- **Elizaga, Jorge; Friedland, Jon S(1997):** *Monitoring Compliance With Antituberculosis Treatment by Detection of Isoniazid in Urine (Research Letter).* Lancet (10/25/97) Vol. 350, No. 9086, P. 1225 .AEGIS, Information, Inc., Bethesda*, MD*
- **Elwood J.M. (1988):** *Causal Relationships in Medicine*. Oxford, Oxford University Press, 332 p
- en.wikipedia.org/wiki/Patriarchal_society, accessed 13/05/11)
- **Farmer P (1997):** *Social scientists and the new tuberculosis.* Soc Sci Med 44: 347-358.
- **Feinn R, Tennen H, Cramer J and Kranzler HR(2003):** *Measurement and prediction of medication compliance in problem drinkers*. Alcoholism: Clinical & Experimental Research; 27(8):1286–1292.
- **Feinstein AR (1990):**On white coat effects and the electronic monitoring of compliance. Arch Intern Med;150:1377–8.
- **FELTON C, P. and SHAH H, P. (1996):** *Isoniazid clinical use and toxicity.* In: W.N. ROM & S.M. GARAY (Eds),***Tuberculosis*** (pp. **773-778).** Boston: Little Brown.
- **Fisher JD, Fisher WA, Amico KR, Harman JJ(2006)**: *An information-motivation-behavioral skills model of adherence to antiretroviral therapy.* Health Psychol, 25**:**462-73. In **Munro,S Lewin,S ,Swart,T and Volmink J (2007)**: *A review of health behaviour theories: how useful are these for developing interventions to promote long-term medication adherence for TB and HIV/AIDS?* BMC Public Health 2007, **7**:104 doi:10.1186/1471-2458-7-104, BioMed Central Ltd,UK
- **Gebhardt WA and Maes S (2001):** *Integrating social-psychological frameworks for health behaviour research. Am J Health Beh*, 25:528-536.
- **Gebremariam MK, Bjune GA and Frich JC (2010):** *Barriers and facilitators of adherence to TB treatment in patients on concomitant TB and HIV treatment: a qualitative study.*BMC Public Health,10:651 from **http://www.biomedcentral.com/1471-2458/10/651**
- **Glynn JR, Caraël M, Auvert B, Kahindo M, Chege J, Musonda R, Kaona F and Buvé A (2001):** *Why do young women have a much higher prevalence of HIV than young men? A study in Kisumu, Kenya and Ndola, Zambia*. AIDS. ; 15:S51–60. For the Study Group on Heterogeneity of HIV Epidemics in African Cities
- **Gordis, L (1979):** *Conceptual and methodological problems in measuring patient compliance*. In: *Compliance in Health Care* (Haynes R.B., Taylor D.W. & Sackett D.L., eds.). Baltimore: Johns Hopkins University Press.
- **Gourieroux C. (2000):** *Econometrics of Qualitative Dependent Variables*. Translated by Klassen P. B, Cambridge
- **Government of South Africa (2006):***Provincial Government of the Western Cape department of Health Annual Report*, Cape Town, South Africa
- **Government of South Africa (2007):** *Provincial Government of the Western Cape department of Health Annual Report*, Cape Town, South Africa
- **Government of South Africa (2007):** *TUBERCULOSIS STRATEGIC PLAN FOR SOUTH AFRICA, 2007-2011.*Department of Health, Pretoria, South Africa

- **Government of South Africa (2000):***The South African Tuberculosis Control Programme Practical Guidelines.Department of Health*, Republic of South Africa
- **Grange JM and Zumla A (2002**)**:** *The global emergency of tuberculosis: what is the cause?* Perspectives in Public Health June vol. 122 no. 2 78-81.UK
- **Green, D (2011),** *personal communication,*28/01/11
- **Guillaume Wunsch G.(2007):** *Confounding and control. DEMOGRAPHIC RESEARCH,* VOLUME 16, ARTICLE 4, PAGES 97-120 Feb. DOI: 10.4054/DemRes..16.4 *from* http://www.demographic-research.org/Volumes/Vol16/4/
- **Haas DW, Des Prez RM (1994):** *Tuberculosis and acquired immunodeficiency syndrome: a historical perspective on recent developments*. *Am J Med.*May;96(5):439–450.
- **Harrell F.E. Jnr (2001):** *Regression Modeling Strategies-with applications to linear models, logistic regression and survival analysis*. Springer-Verlag, New York Inc. USA
- **Haynes R.B (1982):** *Strategies for enhancing patient compliance*. Drug Therapy*; Jan:33*-40.In **Jay S, Litt I and Durant H (1984):***Compliance with Therapeutic Regimens.Journal of Adolescent Health Care;*5:124-136. Elsevier Science Publishing Co. New York.
- **Haynes RB (1979):** *Determinants of compliance: The disease and the mechanics of treatment.* Baltimore MD, Johns Hopkins University Press,
- **Haynes RB, McDonald H, Garg AX and Montague P (2002): *Interventions for helping patients to follow prescriptions for medications.*** Cochrane Database Syst Rev: CD000011.
- **Haynes RB, Taylor DW, Sackett DL, Gibson ES, Bernholz CD and Mukherjee J(1980):** *Can simple clinical measurements detect patient noncompliance?* Hypertension. Nov–Dec; 2(6):757–764.
- **Helland IS (1987):** *On the interpretation and use of R^2 in regression analysis*. Biometrics 1987; 43:61–69 Stamford, Connecticut.
- **Hollis S and Campbell F (1999):** *What is meant by intention to treat analysis? Survey of published randomised controlled trials.* BMJ. ;319:670–674. (11 November.) PubMed
- **Hosmer, D.W and Lemeshow S (2000):** *Applied Logistic Regression*. *2^{nd} Ed.* Wiley Series in Probability and Statistics.John Wiles&Sons Inc. Canada
- http://psych.unl.edu/psycrs/971/altreg/logistic1.pdf, accessed 28/04/11
- http://www.ats.ucla.edu/stat/spss/output/mlogit.htm, accessed 15/10/11)
- http://www.ats.ucla.edu/stat/spss/output/mlogit.htm, accessed 15/10/11)
- http://www.ats.ucla.edu/stat/stata/webbooks/reg/chapter2/statareg2.htm,(accessed 11/05/11)
- http://www.bridges.org/case_studies/137 , (accessed 11/05.2011
- http://www.finddiagnostics.org , (accessed 11/04/11)
- (http://www.ist.massey.ac.nz/dstirlin/CAST/CAST/HdiagnosticsTwo/diagnosticsTwo4.html , (accessed 15/05/11)
- http://www.slideshare.net/HELPLibrary/forgetfulness-old-age , (accessed 14/05/11)
- http://www.snv.jussieu.fr/~wensgen/Doc/scilab-2.6/internals/node18.html, (11/05/11)
- http://www.soc.iastate.edu/sapp/soc401FAM.html,(accessed 20/02/11)

- http://www.tbalert.org/news_press/TBHistoricalTimeline.htm ,30/03/11
- http://www.vetmed.wsu.edu/courses-jmgay/glossclinstudy.htm, accessed 25/03/11
- http://www.who.int/gender/whatisgender/en/ (accessed 13/05/11)
- http://www.who.int/tb/dots/en/ , (accessed 11/04/05)
- http://www.who.int/tb/topics/en/, (accessed 13/04/2011)
- http://www.who.int/whosis/indicators/compendium/2008/4tsr/en/index.html, (13/05/11)
- http://www.wikigender.org/index.php/Gender_Equality_in_South_Africa , 13/05/11
- http://www.xycoon.com/ (accessed 11/05/11),
- http://www.ist.massey.ac.nz/dstirlin/CAST/CAST/HdiagnosticsTwo/diagnosticsTwo4.html (accessed 15/05/11)
- **Hu B, Palta M, and Shao J (2006):** *Properties of R^2 statistics for logistic regression*. Statistics in Medicine, 25, 1383-1395.
- **Huitt, W. and Hummel, J. (1998):** *Cognitive development. Educational Psychology Interactive.* Valdosta, GA: Valdosta State University. http://chiron.valdosta.edu/whuitt/col/cogsys/piaget.html , accessed 02/05/11
- **Jaggarajamma K, Sudha G., Chandrasekaran V., Nirupa C., Thomas A., Santha T, Muniyandi M and Narayanan P.R(2006):** *Reasons for Non-Compliance among Patients Treated Under Revised National Tuberculosis Control Programme (RNTCP),Tiruvallur District, South India*. Indian J Tuberc 2007; 54:130-13
- **Jay S, Litt I and Durant H (1984):** *Compliance with Therapeutic Regimens.Journal of Adolescent Health Care;* 5:124-136. Elsevier Science Publishing Co. New York.
- **Jin BW et al (1993):** The impact of intensified supervisory activities on tuberculosis treatment. *Tubercle & Lung Disease,* 74:267–272.
- **Kaona, FAD, Tuba M, Siziya S, and Sikaona L (2004)**: *An assessment of factors contributing to treatment adherence and knowledge of TB transmission among patients on TB treatment*. BMC Public Health. ; 4**: 68.** Published online December 29. doi: 10.1186/1471-2458-4-68.PMCID: PMC545081
- **Krishnaswami KV et al (1981):** *A randomised study of two policies for managing default in out-patients collecting supplies of drugs for pulmonary tuberculosis in a large city in South India. Tubercle,* 62:103–112.
- **Last, J. (Ed.). (2001):** *International epidemiological association. A dictionary of epidemiology (4th ed.)*. New York: Oxford University Press.
- **Leventhal H and Cameron L (1987):** *Behavioural theories and the problem of compliance.* Patient Educ Couns, 10:117-138.In **Munro,S Lewin,S ,Swart,T and Volmink J (2007)**: *A review of health behaviour theories: how useful are these for developing interventions to promote long-term medication adherence for TB and HIV/AIDS?* BMC Public Health 2007, **7**:104 doi:10.1186/1471-2458-7-104, BioMed Central Ltd,UK
- **Leventhal H, Leventhal EA and Schaefer PM (1992):** Vigilant coping and health behaviour. In *Aging health and behaviour* Edited by: Ory MG, Abeles RD, Lipman PD. Newbury Park: Sage;:109-140. . In **Munro,S Lewin,S ,Swart,T and Volmink J (2007)**: *A review of health behaviour theories: how useful are these for developing interventions*

to promote long-term medication adherence for TB and HIV/AIDS? BMC Public Health 2007, 7:104 doi:10.1186/1471-2458-7-104, BioMed Central Ltd,UK

- **Leventhal H, Meyer D and Nerenz D (1980):** *The common sense representation of illness danger.* In *Contributions to medical psychology Volume 2*. Edited by: Rachman S. Oxford: Pergamon Press;:7-30. ; In **Munro,S Lewin,S ,Swart,T and Volmink J (2007)**: *A review of health behaviour theories: how useful are these for developing interventions to promote long-term medication adherence for TB and HIV/AIDS?* BMC Public Health 2007, **7**:104 doi:10.1186/1471-2458-7-104, BioMed Central Ltd,UK
- **Lewin SA, Skea ZC, Entwistle V, Zwarenstein M and Dick J (2001):** *Interventions for providers to promote a patient centred approach in clinical consultations*. Cochrane Database of Systematic.Reviews, Issue 4. Art. No.: CD003267. DOI: 10.1002/14651858.CD00326
- **Ley P (1988):** Communicating with patients: Improving communication, satisfaction and compliance. New York: Chapman and Hall Croom Helm, London In **World Health Organisation (2003):** Adherence to long-term therapies: Evidence for action.WHO Press, Geneva, Switzerland.
- **Liefooghe R *et al* (1999):** *A randomised trial of the impact of counselling on treatment adherence of tuberculosis patients in Sialkot, Pakistan*. International Journal of Tuberculosis & Lung Disease, 3:1073–1080.
- **Litt IF and Cuskey WR (1980):** *Compliance with medical regimens during adolescents*.Pediatr Clin North Am; 27:3-15. In **Jay S, Litt I and Durant H (1984):** *Compliance with Therapeutic Regimens*.Journal of Adolescent Health Care; 5:124-136. Elsevier Science Publishing Co. New York.
- **Lumley T (2005):** *Confounding and effect modification*. *From* http://courses.washington.edu/b570/handouts/confounding.pdf
- **Mackenzie JF & Jurs JL (1993).** *Theory of reasoned action/theory of planned behavior*, University of South Florida,USA
- **Mannheimer SB, Morse E, Matts JP, Andrews L, Child C, Schmetter B and Friedland GH (2006):** *Sustained benefit from a long-term antiretroviral adherence intervention: results of a large randomized clinical trial.* J Acquir Immune Defic Syndr 43(Suppl 1):S41-S47. Dec 1
- **Marshall L A (2007):***Simpill Adherence Management Pilot Western Cape Report July 2006-April 2007*,Cape Town, South Africa
- **Mateus-Solarte JC and Carval-Barona R (2008):** *Factors predictive of adherence to tuberculosis treatment.Valle del Cauca, Colombia. INT J TUBERC LUNG DIS 12(5):520-526*.The Union, Colombia
- **McDonald, M (2002):** *A Teaching Note on Cook's Distance – A Guideline*. Res. Lett. Inf. Math. Sci. , 127-128. http://www.massey.ac.nz/~wwiims/research/letters/ .Auckland, N.Z.
- **McFadden D (1974):** *Conditional logit analysis of qualitative choice behaviour. In P. Zarembka,* Ed, *Frontiers in Econometrics*, pages 105–142. Academic Press, New York,

- **McGraw-Hill Concise Dictionary of Modern Medicine (2002)** by The McGraw-Hill Companies, Inc.
- **Meichebaum. D and Turk D, C. (1987).** *Facilitating treatment adherence: apractitioner's handbook.* New York: Plenum Press.In **Dubanoski, J. P. and Cohen, H. I.(1998):***Tuberculosis chemoprophylaxis: Measuring adherence to the regimen,* Psychology, Health & Medicine, 3: 2,181-192
- **Michie S and Abraham C (2004):** *Interventions to change health behaviours: Evidence-based or evidence-inspired?* Psychol Health, 19:29-49.
- Michie S, Johnston M, Abraham C, Lawton R, Parker D and Walker A (2005): **Making psychological theory useful for implementing evidence based practice: A consensus approach.** *Qual Saf Health Care*, **14:**26-33.
- **Michie, S and Abraham, C. (2004):** *Interventions to change health behaviours: Evidence-based or evidence inspired?* Psychology and Health, 19, 29-49.
- **Mittlboeck M, Schemper M (1996**): *Explained variation for logistic regression. Statistics in Medicine 1996;* 15: 1987–1997.
- **Montori VM and Guyatt GH (2001):** *Intention-to-treat principle*. CMAJ. Nov 13; 165(10):1339-41. PMID: 11760981. PubMed
- **Mosby's Medical Dictionary (2009),**8th edition, Elsevier
- **Mothlake MP (2005):***Noncompliance among TB Patients at Moreteletsi Hospital.Masters thesis,* University of Pretoria,South Africa
- **MSF-Operational Center Amsterdam MSF-OCA (2007)**: *TB and HIV-The Time to Act.* Plantage Middenlaan 14, Amsterdam, The Netherlands
- **Muhwava W (2004):** *Condom Use within Marriage and Consensual Unions in the Era of HIV/AIDS in Zimbabwe.* African Population Studies vol. 19 n°1/Etude de la population africaine vol. 19 n° 1
- **Mullen PD, Hersey JC and Iverson DC (1987):** *Health behavior models compared.Soc Sci Med*, 24:973-981. In Munro,S Lewin,S ,Swart,T and Volmink J (2007): A review of health behaviour theories: how useful are these for developing interventions to promote long-term medication adherence for TB and HIV/AIDS? BMC Public Health 2007, 7:104 doi:10.1186/1471-2458-7-104, BioMed Central Ltd,UK
- **Munro, S(2008):***Theoretical models to support long term adherence in TB and HIV.* 3rd International Conference on ARV treatment adherence, March 17-18, Jersey City, New Jersey, USA
- **Munro,S Lewin,S ,Swart,T and Volmink J (2007)**: *A review of health behaviour theories: how useful are these for developing interventions to promote long-term medication adherence for TB and HIV/AIDS?* BMC Public Health 2007, **7**:104 doi:10.1186/1471-2458-7-104, BioMed Central Ltd,UK
- **National Income Dynamics Study-NIDS (2009)**: *Labour Market: Analysis of the NIDS Wave 1 Dataset Discussion Paper no. 12* .Vimal Ranchod Southern African Labour & Development Research Unit, South Africa
- **O'Donnel, C.J., Connor, D.H. (1996):** *Predicting the severity of Motor vehicle accident injuries using models of ordered multiple choice*,Accident Analysis and Prevention Vol. 28, No.6, 739-753

- **Odusanya OO, and Babafeni O J (2004):** *Patterns of delays among pulmonary tuberculosis patients in Lagos, Nigeria.*BMC Public Health*, 4*:17.
- **Paramasivan R, Parthasarathy R and Rajasekaran S (1993):** *Short course chemotherapy: A controlled study of indirect defaulter retrieval method.* Indian Journal of Tuberculosis, 40:185–190.
- **Pavis S, Cunningham-Burley S and Amos A (1997):** *Alcohol consumption and young people: exploring meaning and social context.* HEALTH EDUCATION RESEARCH Vol.12 no.3 Theory & Practice Pages 311–322.Oxford University Press
- **Pilote L *et al* (1996):***Tuberculosis prophylaxis in the homeless.A trial to improve adherence to referral*. Archives of Internal Medicine*;*156:161–165.
- **Polit D. (1996) :** *Data Analysis and Statistics for Nursing Research*. Appleton & Lange,
- **Ponyk RM, Makhubele MB, Hargreaves JR, Tollman SM and Hausler HP(2001):** *Assessing health seeking behaviour among tuberculosis patients in South Africa.*Int J Tuberc Lung Dis *,* 5(7)**:**619-627
- Pozsikc, .J. **(1993).** Compliance with tuberculosis therapy. ***Medical Clinics of North America,*** 77, **1289-1301.**In Dubanoski, J. P. and Cohen, H. I.(1998):Tuberculosis chemoprophylaxis: Measuring adherence to the regimen, Psychology, Health & Medicine, 3: 2,181-192
- **Prochaka. JO, and DI Clemente, C.C. (1992).** *Stages of change in the modification of problem behaviors.* In: M.HERSEN,R .M. EISLER& P.M. MILLER (Eds), ***progress in behaviour modification*** Volume 28 (pp. 184-218). Sycamore, IL Sycamore Publishing Company.
- **Prochaska JO and DiClemente CC(1983):** *Stages and processes of self-change of smoking: Toward an integrative model of change.* Journal of Consult Clin Psychol, 51:390-395. In **Munro,S Lewin,S,Swart,T and Volmink J (2007)**: *A review of health behaviour theories: how useful are these for developing interventions to promote long-term medication adherence for TB and HIV/AIDS?* BMC Public Health 2007, **7**:104 doi:10.1186/1471-2458-7-104, BioMed Central Ltd,UK
- **Prochaska JO, DiClemente CC, Norcross JC (1992):** *In search of how people change: Applications to addictive behaviours.* Am Psychol 47**:**1102-1114.
- **Pryanishnikov I and Zigova K (2003):** *Multinomial Logit Models for the Austrian Labor Market.* AUSTRIAN JOURNAL OF STATISTICS Volume 32, Number 4, 267–282
- **Rand CS (1993):** *Measuring adherence with therapy for chronic diseases: implications for the treatment of heterozygous familial hypercholesterolemia.* American Journal of Cardiology, 72:68D-74D.
- **Rand, C.S. (1990).** *Issues in the measurement of adherence.* In: S. A. Shumakere SA, SCHRONJ B. Ockenec K,Parker T, Probste JL and Wolle DJM(Eds), *The handbook of health behaviour change* (pp. 102-1 10). New York Springer.
- **Rao C.R, Miller J.P and Rao D. C (2008):***Epidemiology and Medical Statistics.*Handbook of statistics 27. North-Holland (Elsevier B.V), The Netherlands
- **Rao Gupta, G. (2002):***How men's power over women fuels the HIV epidemic*, *BMJ* 324: 183–4.

- **Raviglione M, Snider D and Kochi A(1995):** *Global epidemiology of tuberculosis:Morbidity and mortality of a worldwide epidemic.* J AmMed Assoc, 273:220-226.
- **Redding CA, Rossi JS, Rossi SR, Velicer WF and Prochaska JO (2000):** *Health behaviour models.*International Electronic Journal of Health Education,3:180-193 [http://www.oiiq.org/SanteCoeur/docs/redding_iejhe_vol3_nospecial_2000.pdf].
- **Redding, C.A., J.S. Rossi, S.R. Rossi, W.F. Velicer, and J.O. Prochaska (2000):** *Health Behavior Models.* The International Electronic Journal of Health Education, 3 (Special Issue):180-193.
- **Rogers RW (1975):** *A protection motivation theory of fear appeals and attitude change.* J Psychol 1975, 91:93-114. In **Munro,S Lewin,S ,Swart,T and Volmink J (2007***: A review of health behaviour theories: how useful are these for developing interventions to promote long-term medication adherence for TB and HIV/AIDS?* BMC Public Health 2007, **7**:104 doi:10.1186/1471-2458-7-104, BioMed Central Ltd,UK
- **Rosenstock I., Strecher, V and Becker, M. (1994):** *The Health Belief Model and HIV risk behavior change*. In **R.J. DiClemente, and J.L. Peterson (Eds.),** Preventing AIDS: Theories and Methods of Behavioral Interventions (pp. 5-24). New York: Plenum Press.
- **Ross E, Deverell A (2004):** *Psychosocial approaches to health, illness and disability: A reader for health care professionals* Pretoria: Van Schaik;
- **Rothman KJ, Greenland S and Lash TL (2008):** *Types of epidemiologic studies.* In *Modern Epidemiology*, 3rd edn, **Rothman KJ, Greenland S, Lash TL (eds)** pp 95–97; Philadelphia: Lippincott, Williams & Wilkins
- **Sackett D.L. and Snow, J.C. (1979).** *The magnitude **of** compliance and noncompliance.* In: R.B. Haynes RB, Taylor DW & Sackett DL(Eds), *Compliance in health cure (pp. 11-22)*. Baltimore: Johns Hopkins University Press
- **Salleras SL et al (1993).** *Evaluation of the efficacy of health education on the compliance with antituberculosis chemoprophylaxis in school children. A randomized clinical trial.* Tubercle & Lung Disease, 74:28–31
- **Schoenstadt A, (2008):** An Introduction to the History of Tuberculosis. Clinaero Inc, *from* http://tuberculosis.emedtv.com/tuberculosis/tuberculosis-history.html
- **Shakya R, Rao BS and Shrestha B (2005):** *Management of antitubercular drugs-induced hepatotoxicity and therapy reintroduction strategy in a TB clinic of Nepal.* Kathmandu University Medical Journal Vol. 3, No. 1, Issue 9, 45-49
- **Shargie, E. B and Lindtjørn, B (2007):** *Determinants of Treatment Adherence Among Smear-Positive Pulmonary Tuberculosis Patients in Southern Ethiopia*. PLoS Med; 4(2): e37, http://dx.doi.org/10.1371/journal.pmed.0040037
- **Shrestha-Kuwahara R, Wilce RM, Joseph H.A., Carey J.W., Plank R., and Sumartojo E. (2004):** *Tuberculosis Research and Control. In Encyclopedia of Medical Anthropology: Health and Illness in the World's Cultures.* Carol R. Ember and Melvin Ember, eds. Pp.528-542. New York: Kluwer Academic.
- **Skinner BF (1938):** *The behavior of organisms.* New York, Appleton-Century-Crofts.In **World Health Organisation (2003):** Adherence to long-term therapies: Evidence for action.WHO Press, Geneva, Switzerland.

- **Skinner BF (1988):** *Science and human behavior.* New York, Free Press-Macmillan, 1953:23–42.
- **Smith, I. (1999):***STOP TB :IS DOTS THE ANSWER?* Indian. Journal on Tuberculosis. 46, 8, India
- **Snider DE and La Montagne JR(1994):** *The neglected global tuberculosis problem: a report of the 1992 World Congress on Tuberculosis*. J Infect Disn; 169: 1189-96
- **Spencer (1999):** *The White Death - A History of Tuberculosis.* The British Journal of Antimicrobial. Chemotherapy,44(3): 423 doi:10.1093/jac/44.3.423
- **SPSS Inc (2008):** *SPSS 17.0 Regression Models*. Upper saddle River, NJ:Prentice-Hall, USA
- **St Claire L(2003):** *Rival Truths: Common sense and social psychological explanations in health and illness* Hove: Psychology Press; In **Munro,S Lewin,S ,Swart,T and Volmink J (2007)**: *A review of health behaviour theories: how useful are these for developing interventions to promote long-term medication adherence for TB and HIV/AIDS?* BMC Public Health 2007, **7**:104 doi:10.1186/1471-2458-7-104, BioMed Central Ltd,UK
- **Statistics South Africa (2010):***Mid-year population estimates*.Pretoria, South Africa
- **Stone D (1999)**: *Social Cognitive Theory.* In **Munro,S Lewin,S ,Swart,T and Volmink J (2007)**: *A review of health behaviour theories: how useful are these for developing interventions to promote long-term medication adherence for TB and HIV/AIDS?* BMC Public Health 2007, **7**:104 doi:10.1186/1471-2458-7-104, BioMed Central Ltd,UK
- **Stroebe W (2000):** *Social psychology and health* 2nd edition. Buckingham: Open University Press;
- **Suarez PG et al (2001):***The dynamics of tuberculosis in response to 10 years of intensive control effort in Peru*. *The Journal of Infectious Diseases,* ,184:473–478.
- **Sukwa TY, Kaona ADF and Musonda MR(1991)**: *Preliminary Report on Multicentre Study on Factors Determining Deferential Spread of HIV in African Towns (Ndola site)*. Ndola Tropical Diseases Research Centre. Zambia
- **Sumartojo E (1993).** *When tuberculosis treatment fails: a social behavioural account of patient adherence.* American Review of Respiratory Disease, 147, 1311-1320.
- **Sutton S (1997):** *Theory of planned behaviour***.** In *Cambridge handbook of psychology, health and medicine* Edited by: Baum A, Newman S, Weinman J, West R, McManus C. Cambridge: Cambridge University Press;177-179.
- **Sutton S(2000):** *A critical review of the transtheoretical model applied to smoking cessation.* In *Understanding and changing health behaviour: From health beliefs to self-regulation* Edited by: Norman P, Abraham C, Conner M. Amsterdam: Harwood Academic Publishers;:207-225.
- **Tanguis HG et al. (2000):** *Factors predicting non-completion of tuberculosis treatment among HIV-infected patients in Barcelona.* International Journal of Tuberculosis and Lung Disease, 4(1):55–60
- **Tanke ED, Martinez CM and Leirer VO (1997):** *Use of automated reminders for tuberculin skin test return.* American Journal of Preventive Medicine;13:189–192.

- **TB Alliance-Global Alliance for TB Drug Development (2010):** *More than Ever-It's time for a Faster Cure.2010 Annual Report*, *from* www.tballiance.org
- **Tellumat South Africa(2007):***Simpill Solution for TB.Press Release, March 02 2007*
- **The American Heritage Medical Dictionary Copyright (2007)** by Houghton Mifflin Company.
- **The American Heritage Medical Dictionary Copyright (2004**) by Houghton Mifflin Company.
- **Vlassoff C (1994)**: Gender inequalities in health in the third world: uncharted ground. *Soc Sci Med.*pp;39:1249–59. [PubMed]
- **World Health Organization (2006):** *The Global Plan to Stop TB, 2006–2015- Actions for life towards a world free of tuberculosis* .Geneva, (WHO/HTM/STB/2006.35).
- **The Lancet (1996*): Results of directly observed short-course chemotherapy in 112,842 Chinese patients with smear-positive tuberculosis*. China Tuberculosis Control Collaboration. *Lancet,* 347:358–362.
- **United Nations Development Programme (2010):** *Millennium Development Goals Report 2010*. New York, USA
- **United Nations Development Programme Human Development Report (2003):***Millennium Development Goals: A compact among nations to end human poverty.*Oxford University Press, New York
- **University of Cape Town (2003):**SAMF-South Africa Medicines Formulary 5th edition. Division of Clinical Pharmacology. Health and Medical Publishing Group, South African Medical Association
- **Urquhart J (1992):** *Ascertaining how much compliance is enough with outpatient anti-biotic regimens.* Postgraduate Medical Journal*,* 68:49–59.
- **Urquhart J(1996):** *Patient non-compliance with drug regimens:measurement,clinical correlates, economic impact*. European Heart Journal*,* 17 (Suppl A):8–15.
- **Varga, C. (1999):** *South African People's Sexual Dynamics: Implications for Behavioral Response to HIV/AIDS.* p13-24 in John Caldwell et al (Ed) *Resistance to Behavioral Change to Reduce HIV/AIDS Infection in Predominately Heterosexual Epidemics in Third World Countries* .Canberra Health Transition Center
- **Volmink J and Garner P(2000):** *Interventions for promoting adherence to tuberculosis management.* Cochrane Database of Systematic Reviews, (4):CD000010.
- **Volmink J and Garner P (2001):** *Directly observed therapy for treating tuberculosis.* Cochrane Database of Systematic Reviews*.* 2001 (4):CD003343.
- **Washington, S.P., Karlaftis, M.G., Mannering, F.l. (2003):** *Statistical and Econometric Methods for Transportation Data Analysis*, Chapman & Hall, USA.
- **Wedagama, Priyantha, D.M and Dissanayake, Dilum (2001):** *Analysing Motorcycle Injuries on Arterial Roads in Bali using a Multinomial Logit Model.* Journal of the Eastern Asia Society for Transportation Studies, Vol.8, 2009
- **Williamson NE, Liku J, McLoughlin K, Nyamongo IK and Nakayima F (2006):** *A Qualitative Study of Condom Use among Married Couples in Kampala, Uganda.Reproductive Health Matters* ;14(28):89–98 .Elsevier, UK
- **World Health Organisation (1994):** *TB A Global Emergency*. Geneve, WHO/TB/94.177

- **World Health Organisation (2010).***Global TB Control report*. WHO/HTM/TB/2010.7, Geneva,Switzerland
- **World Health Organisation (2010):** *Global tuberculosis Control Report.* WHO/HTM/TB/2010.7. WHO Press,Geneva, Switzerland
- **World Health Organisation (2003):** Adherence *to long-term therapies: Evidence for action.*WHO Press, Geneva, Switzerland.
- **World Health Organisation (2006):** *The Global Plan to Stop TB 2011-2015 – Transforming the fight, towards elimination of TB*. WHO/HTM/STB/2006.35. WHO Press,Geneva
- **World Health Organisation (2006):** THE *STOP TB STRATEGY- Building on and enhancing DOTS to meet the TB-related Millennium Development Goals.* WHO/HTM/TB/2006.368. WHO Press,Geneva
- **World Health Organisation (2010)***: The Global Plan to Stop TB, 2011–2015.* Geneva, World Health Organization.(WHO/HTM/STB/2010.2).
- **World Health Organisation (1993).** *A review of current epidemiological data and estimation of future tuberculosis incidence and mortality.* WHO/TB/93,173 Geneva
- **Wunsch G (2007):** *Confounding and control*. Demographic Research Vol. 16; Article 4, pp 97-120. DOI: 10.4054/DemRes.2007.16.4 on http://www.demographicresearch.org/Volumes/Vol16/4/
- www.simpill.com ,2009
- www.tbalert.org, 30/03/11
- **www.undp.org/mdg** (accessed 05/04/11)
- **www.undp.org/mdg** (accessed 05/04/11)
- www.utexas.edu (20/12/10), *Multinomial Logistic Regression Basic Relationships. Lecture SW388R7-Data Analysis & Computers II*
- http://www.vetmed.wsu.edu/courses-jmgay/glossclinstudy.htm, accessed 25/03/11
- **Yadollahi M, Paim LH, Othman M and Suandi T (2009):** *Family Economic Status (FES) Among Households Kerman City*. European Journal of Social Sciences. Volume 11, Number 4