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The ethics of smart pills in South Africa

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THE ETHICS OF SMART PILLS IN SOUTH AFRICA

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A research report submitted to the Faculty of Health Sciences, University of Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree Master of Science in Medicine (MScMed) in Bioethics & Health Law

Johannesburg, 2019

DECLARATION

I, Gary Mark Sopher, declare that this Research Report is my own, unaided work. It is being submitted for the Degree of Master of Science in Medicine (MScMed) in Bioethics and Health Law at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.



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Signature of candidate

18 December 2019

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Date

Sandton

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Place

In memory of my father

Joel Sopher

1948-2016

ABSTRACT

Smart pills are a new form of medical device technology that combines traditional pharmaceutical tablets and capsules with digital microchips. The primary function of smart pills is to detect medication ingestion events and monitor adherence. After ingestion, the smart pill sends a signal to a receiving device which collects data such as the medicine name, type, dosage and time of consumption. Objective adherence monitoring leads to improvements in adherence parameters and clinical outcomes in diseases such as diabetes, hypertension, TB and HIV. Reduced wastage of medicines and better healthcare resource utilization are additional benefits. Clinical trials have demonstrated the efficacy, safety, convenience and cost-effectiveness of smart pills.

Smart pills may enable a new standard of digital adherence monitoring in TB treatment programs, where wirelessly observed therapy (WOT) could replace the current mandatory approach of directly observed therapy (DOT). The ethical issues of smart pills include patient privacy concerns due to pervasive surveillance, confidentiality and data management and trust relationships between clinicians, patients and payers. Affordability and access to smart pills are important considerations in poorer communities.

Smart pills are ethically justified in South Africa, when viewed from a bioethical principle-based perspective. The principles of respect for autonomy, beneficence, non-maleficence and justice can be upheld with appropriate oversight of smart pill technology. The opportunity to improve clinical outcomes and reduce wastage is particularly appealing from a utilitarian point of view. Local ubuntu communitarian culture may also support smart pills, because of the emphasis on community well-being rather than individual autonomy.

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NOMENCLATURE

AI	Artificial Intelligence
APM	Adhesive Personal Monitor
CBA	Cost-Benefit Analysis
CEA	Cost-Effectiveness Analysis
DFE	Discounted Future Earnings
DOT	Directly Observed Therapy
EHR	Electronic Health Records
EULA	End User License Agreement
FDA	Food and Drug Administration
HCP	Healthcare Professional
HIPAA	Health Insurance Portability and Accountability Act
HITECHA	Health Information Technology for Economic and Clinical Health Act
IEM	Ingestible Event Marker
IoT	Internet of Things
LMIC	Low and Middle-Income Country
mHealth	Mobile Health
PAIA	Promotion of Access to Information Act
PDA	Positive Detection Accuracy
POPIA	Protection of Personal Information Act
QALY	Quality-Adjusted Life Year
RBA	Risk-Benefit Analysis
SAHPRA	South African Health Products Regulatory Authority
SMS	Short Message Service
WHO	World Health Organization
WOT	Wirelessly Observed Therapy
WTP	Willingness to Pay

CHAPTER 1: INTRODUCTION

1.1 The Internet of Things

In the world today there are an increasing number of internet-connected devices, including smart phones like the Apple iPhone™ and Samsung Galaxy™. Many of us own fitness trackers like Fitbit™, and wear a smart watch like Garmin™ and Apple Watch™ (Elenko et al., 2015). Many of the latest home and kitchen appliances, from doorbells to dishwashers, can connect to the internet. Smart televisions and smart speakers have digital voice assistants like Siri™ and Alexa™, who act as virtual butlers, searching online for our favorite songs, news updates and weather information.

The term “Internet of Things” was coined in 1999 by Kevin Ashton, to describe the connection of devices to each other via the internet, and the ability of the devices to automatically share data without relying on human input (Achituv and Haiman, 2016; Ashton, 2009). An Internet of Things (IoT) device is any device which is able to connect to other devices via the internet (Achituv and Haiman, 2016). In 2010, more than 12.5 billion connected devices were sold globally and about 25 billion smart phones were in use in 2015 (Elenko et al., 2015).

This technology is penetrating the medical field. Medical devices are becoming internet-connected devices, including medical implants which measure glucose levels, monitor heart rate and rhythm, and pills or capsules with ingestible sensors and cameras (Vayena et al., 2018; Elenko et al., 2015; Montgomery, 2016; Morgan, 2014). Pills are available, or are being developed, that deliver semi-permanent or permanent devices into our digestive tract, our bloodstream and into our tissues (Montgomery, 2016). These pills, called smart or digital pills (Klugman et al., 2018; University of Illinois at Chicago, 2018) connect to smart devices such as smart phones and to the internet. They record and analyze data and display information via applications or apps. This information may then be shared via the internet.

The first smart pill, combining a tiny microchip to a pill capsule, was announced by researchers at the University of Florida in March 2010 (Gagnon et al., 2013). It would take 4 more years of clinical research before the United States’ regulatory agency,

the Food and Drug Administration (FDA), approved the Abilify MyCite™ smart pill towards the end of 2017 (Klugman et al., 2018). Defined as true medical products, smart pills must undergo thorough testing in clinical trials and directly affect the course of a medical condition (Elenko et al., 2015).

The smart pill's primary function is to measure medication consumption and thus objectively measure patients' adherence to medical treatment (Frias et al., 2017; Hafezi et al., 2015; Klugman et al., 2018). The tiny, digital microchip sensor in Abilify MyCite™ smart pills, called Proteus™, "was designed specifically to provide feedback for medication taking and other health behaviors to both patients and providers" (Frias et al., 2017, p.2). Additional potential benefits of smart pills include remote monitoring of patients, remote disease management, self-tracking, self-care and digital phenotyping (Klugman et al., 2018).

1.2 Digital Health Landscape

Smart pills are part of an expanding digital health landscape, which includes digital wearable, implantable and ingestible devices, electronic health records (EHRs), mobile health (mHealth) applications, online communities, telemedicine, artificial intelligence (AI) and big data collections (Elenko et al., 2015; Hafezi et al., 2015; Klugman et al., 2018; Vayena et al., 2018). The World Health Organization (WHO) defines mHealth as those medical and public health initiatives that are based on wireless devices such as cellphones, patient monitoring devices and other personal digital devices (Ojo, 2018).

Because they are ingested and incorporated into our bodies, smart pills may be considered to hold a particular digital intimacy and allude to a future of mankind combining with machines as cybernetic organisms or cyborgs. In a more immediate sense, Elenko et al (2015) describe the "connected patient" (p.459) generating and sharing physiological, behavioral and medical data with other connected patients, in a digital health community. Indeed, it is the generation of patient level data, shared in a big, continuous healthcare dataset, that is the fundamental feature of smart pills and other digital health initiatives (Vayena et al., 2018).

1.3 Digital Health Initiatives in Southern Africa

Since smart pills are not yet approved by the South African Health Products Regulatory Authority (SAHPRA), they are not yet available in South Africa, but the technology can be expected to penetrate our healthcare sector in the foreseeable future. Mobile technology is rapidly spreading across the developing world, with South Africa having one of the highest cellphone penetration rates on earth (Ojo, 2018). More than half of the world's mobile phone subscriptions are in Asia and almost two-thirds of Sub-Saharan African homes had at least one mobile phone in 2013 (Ndlovu et al., 2014). Botswana, with 95% of its population already using its mobile phone network, is increasing its network penetration into rural areas (Littman-Quinn et al., 2013; Ndlovu et al., 2014).

Africa's cellular infrastructure provides a fertile environment for digital health and mHealth initiatives, with approximately 100 mHealth initiatives ongoing in 2018 in South Africa (Labrique et al., 2018; Ojo, 2018). One of the most successful projects is the MomConnect short message service (SMS) information sharing program for pregnant mothers (Labrique et al., 2018). MomConnect originated as a public-private partnership and rapidly grew into a large National Department of Health program, with over 1.5 million pregnant mothers registered and receiving helpful information about their pregnancy, in any of the eleven national languages (ibid.). Other South African programs, which have earned international recognition, include Cell-Life MAMA SMS for expecting mothers, Project Masiluleke for patients with HIV/AIDS and SIMPiL, which assists with medication adherence (Ojo, 2018).

Botswana has piloted at least four telemedicine and mobile learning initiatives, which help to improve healthcare delivery in rural areas (Littman-Quinn et al., 2013). Healthcare professionals (HCPs), at the point of care in far flung rural areas, send images and other clinical information to specialists in main centers in country and internationally, who provide advice on further management (ibid.). This has worked for interventions such as cervical cancer screening, radiology, dermatology, oral health and pathology (ibid.). Medical schools in Botswana have used mobile technology to collaborate with universities in the USA, on training, mentorships and information sharing projects (ibid.).

These examples of successful digital health initiatives in Southern Africa, demonstrate the potential for further digital, mHealth and technological initiatives, such as smart pills, to improve the provision of healthcare in the region.

1.4 Research Rationale and Research Question

Smart pills are expected to deliver numerous healthcare benefits to individual patients and broader society, including enhanced medication adherence, improved healthcare monitoring, data gathering, better clinical outcomes and reduced medicine wastage. As a new and emerging medical technology, smart pills are generating new ethical concerns relating to patient autonomy, digital surveillance, privacy rights, confidentiality, data protection, changes in the trust relationships between HCPs and patients, discrimination, access and affordability (Klugman et al., 2018). It is important to understand the ethical implications of smart pills and whether the expected benefits justify the risks of these new devices, in the resource restricted environment of South Africa.

I therefore pose the research question: are smart pills are ethically justified in South Africa?

1.5 Thesis Statement

I will argue that smart pills are ethically justified in South Africa, from a bioethical principle-based perspective, from a utilitarian perspective and from an ubuntu perspective.

1.6 Research Aim and Objectives

The aim of this research is to investigate whether smart pills are ethically justified in South Africa.

The research objective is to highlight the ethical concerns generated by smart pills and normatively review these using a bioethical principle-based approach, a utilitarian approach and the local cultural practice of ubuntu.

1.7 Research Method and Report Structure

This is a purely desktop and library-based research report which reviews the key scientific, medical (and on occasion, legal) literature relating to smart pills, digital health, adherence and relevant bioethical references. There is no empirical component, therefore the findings in this report may require further real-world observation and study in the South African environment. The research received ethics clearance from the Wits HREC (medical); clearance reference number W-CBP-191104-2 which is attached as Appendix B.

In Chapter 2, I review the literature which describes the mechanisms of action, capabilities, benefits, efficacy and safety of smart pills. The key benefit of smart pills at this time is enhanced medical adherence monitoring. I review the issue of medication adherence and how smart pills can enhance this important driver of healthcare outcomes at individual patient and societal levels. I review the published clinical trials of smart pills, which have been conducted across a range of communicable and non-communicable diseases such as HIV, tuberculosis (TB), diabetes, hypertension and chronic mental disorders. Studies demonstrate smart pill systems to be accurate, safe and convenient. I provide a tabulated summary of the published clinical trials in Appendix A.

In Chapter 3, I describe the ethical issues generated by smart pill technology, which primarily relate to the ethical management, oversight and governance of patients' data. Digital surveillance may reduce personal autonomy and threaten rights to privacy and confidentiality. The trust relationships between clinician and patients may be affected. Funders and payers may use adherence data to discriminate against patients who have low levels of medication adherence. Affordability and access to smart pill technology in lower socio-economic patient groups are important considerations.

In Chapter 4, I introduce the principle-based approach in bioethics and the four key bioethical principles of autonomy, non-maleficence, beneficence and justice. I review smart pills' ethical issues using these principles. In Chapter 5, I introduce the consequentialist ethical theory of utilitarianism and I consider smart pills from an outcomes-based perspective. In Chapter 6 I briefly discuss ubuntu and how this local

ethical practice may relate to smart pills. I conclude by summarizing my findings in chapter 7.

1.8 Argumentative Strategy

My argumentative strategy is as follows:

There are large HIV and treatment programs in South Africa. Patients' levels of adherence to treatment are too low, which leads to poor health outcomes and wastage of medicines and other resources. Smart pills are accurate, medically safe and can improve patients' adherence to treatment. The potential benefits to South African patients and society include improved healthcare outcomes, reduced wastage and more cost-effective adherence monitoring.

The ethical issues relate to data management and include reduced autonomy, overbearing surveillance, privacy intrusions, confidentiality breaches and affordability concerns. By using a bioethical principle-based approach I argue that smart pills' benefits are impressive and the harms can be minimized. Various theories of justice support smart pills. Using a utilitarian approach, I argue that the consequences of smart pills for society, when balanced against the potential harms, are beneficial for society and justify the use of smart pills in South Africa. Additionally, the local ethical practice of ubuntu, an African, communitarian ethical approach, which values community considerations and shared decision making over individual autonomy, may be expected to support smart pill technology in South African communities.

CHAPTER 2: LITERATURE REVIEW OF THE MECHANISM OF ACTION, CAPABILITIES, BENEFITS, EFFICACY AND SAFETY OF SMART PILLS

2.1 Introducing Smart Pills

In this chapter, I discuss the smart pill device's components, how smart pill systems work and the medical benefits, efficacy and safety. I cover medication adherence in this chapter, as this is the key benefit of smart pills. I review the published clinical trials in detail here and I summarize these studies in the table in Appendix A.

In November 2017 the world's first smart pill, called Abilify MyCite™, was approved by the United States' regulatory agency, the Food and Drug Administration (FDA). (Klugman et al., 2018). This smart pill is a drug-device combination. It contains the active pharmaceutical ingredient aripiprazole, a dopamine partial agonist initially approved in 2002 by the FDA for the treatment of psychiatric diseases like schizophrenia and bipolar mood disorder (BMD) (www.abilify.com), combined with an ingestible sensor which was developed by Proteus (www.proteus.com) and approved in a separate review pathway by the FDA in 2012 (Plowman et al., 2018).

2.2 The Smart Pill System

The ingestible sensor is known as an Ingestible Event Marker (IEM) (ibid.). The IEM is a tiny device, called an integrated-circuit microsensor, which measures 1.0 mm x 1.0 mm x (0.30 to) 0.45 mm (Eisenberger et al., 2013), which is similar in size to a grain of sand (Hafezi et al., 2015) or a poppy seed (Naik et al., 2017) and is produced in a microfabrication process (Hafezi et al., 2015). The device consists of a tiny microcircuit, or microchip, covered with microscopic (~10 μm) layers of copper and magnesium, embedded in a 5 mm disc composed of edible cellulose (Eisenberger et al., 2013).

The IEM can be integrated with pharmaceutical oral formulations including tablets and capsules (Hafezi et al., 2015). Three methods are used during manufacturing: the devices are incorporated into tablets during tablet compression; fixed to the surface of tablets or capsules with adhesive; or placed inside capsules during filling (ibid.). The IEM is considered safe to ingest and non-toxic: the levels of copper,

magnesium and other minerals are far below usual dietary levels (Au-Yeung et al., 2011).

Within a few minutes after ingestion, the electrolytes in the stomach interact with the copper and magnesium layers of the IEM. These copper and magnesium molecules act as a “biogalvanic battery” (ibid. p 249) and power a temporary electric signal that travels through the body tissues to the surface of the skin. (ibid.) This unique identifying signal is detected by an adhesive patch worn on the chest or abdomen, called an Adhesive Personal Monitor (APM) (Eisenberger et al., 2013; Kane et al., 2013).

This process of electrical signal promulgation is similar to the mechanism used by electrocardiogram (ECG) machines to detect and analyze heart beats and rhythm (Au-Yeung et al., 2011; Kane et al., 2013). This conducive mechanism of signal transmission confines the signal to the patient’s body, which can only be detected by a directly in-contact sensor, such as the APM (Belknap et al., 2013; Kane et al., 2013). The signal produced by the IEM lasts for approximately 7 minutes, after which it becomes inactive, passes through the gastrointestinal tract (GIT) and is eliminated in the faeces (Au-Yeung et al., 2011; Belknap et al., 2013).

The APM is a flexible, adhesive patch measuring 5 cm x 11 cm x 1 cm (Au-Yeung et al., 2011). It is worn on the skin of the torso like an adhesive bandage. This wearable sensor patch is intended to be worn around the clock, including during activities, exercise and sleep and is changed every 7 days (Noble et al., 2016). The APM performs 2 main functions: firstly, it detects and records the unique signals from IEMs, capturing the specific name of the medicine taken, amount, dosage and the time. The APM also measures physiological parameters like heart rate, respiratory rate, step counts, activity levels, body position, sleep duration, quality, circadian rhythm and wearing compliance (ibid.).

The system is capable of detecting multiple, different IEMs ingested at the same time (Belknap et al., 2013). A wireless, Bluetooth-based transmitter in the APM sends the stored, encrypted data to a Bluetooth enabled smart phone, where it can be displayed and analyzed in applications (apps) and sent to secure, cloud based data storage servers, via the cellular data network (Au-Yeung et al., 2011; Eisenberger et

al., 2013; Kane et al., 2013). The server level data can then be securely accessed and analysed via the web on a computer, tablet or smart phone (Au-Yeung et al., 2011). The patient may provide permission for other designated people to view the data, e.g. family, caregivers and healthcare professionals (ibid.). The data can be added to big data systems with other forms of electronic records such as EHRs. The smart pill ingestibe event marker (IEM), plus the adhesive personal monitor (APM), plus the smart phone or tablet apps and server data or data cloud are called a digital health feedback system (Noble et al., 2016). In this report, I will use the phrase 'smart pill system' when referring to the smart pill digital health feedback system.

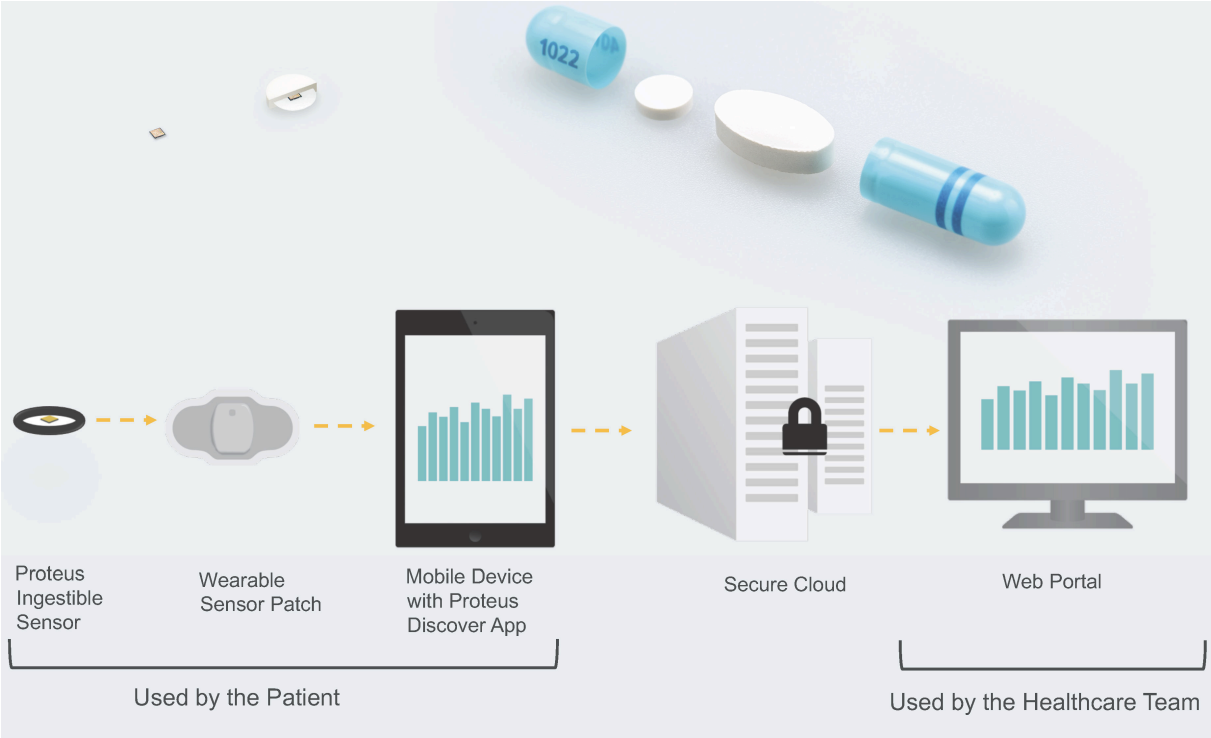


Figure 2.1 Smart Pill System (Frias et al., 2017, p.3)

Smart pills with IEMs are primarily designed to monitor adherence to oral treatment regimens, for patients suffering chronic, serious medical conditions (Hafezi et al., 2015). The Abilify MyCite™ smart pill is indicated for the management of serious mental disorders such as schizophrenia and bipolar mood disorder (BMD) (Batra et al., 2017; Kane et al., 2013; Peters-Strickland et al., 2016).

In addition to measuring ingestion events, ingestible sensors can detect various chemical parameters, e.g. gastric pH, presence of blood and levels of digestive enzymes (Hafezi et al., 2015). They could be modified to start their activities in

specific parts of the gastrointestinal (GI) tract and measure GI electrical activity, acidity, transit times, hydration and body fat content (ibid.). In the future, smart drugs may have the ability to adjust certain pharmacokinetic and pharmacodynamic parameters, and target specific areas in the patient, in response to specific conditions (ibid.). Ingestible sensors may be attached to certain foodstuffs to assist with dietary monitoring in athletes, and in patients with eating disorders like obesity, anorexia and bulimia nervosa (ibid.). Smart pills will provide toxicologists with precise information, in poisoned patients in the future (Chai et al., 2015).

Capsules containing endoscopic cameras have been in clinical use for longer than IEMs and are becoming increasingly reliable as non-invasive alternatives to regular colonoscopy for screening and diagnostic applications in gastrointestinal diseases (Adler and Metzger, 2011; Kuo et al., 2007; Montgomery, 2016).

2.3 Medication Adherence Monitoring

> "Digital medicine…represents a new and rapidly evolving paradigm in healthcare. Continuous measurement of physiological metrics and rapid sharing of data between patients and caregivers offers unprecedented opportunities for diagnosing disease, tailoring treatment to individual patient physiology and behavior, and responding to new information with little or no delay. These capabilities can provide solutions to some of the most elusive and intractable challenges in healthcare. Medication nonadherence is one such problem." (Hafezi et al., 2015, p.99)

The WHO defines adherence in healthcare as "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" (Sabaté and World Health Organization, 2003, p.3). In the setting of prescribed medication, adherence to pharmacological treatment is defined by how closely a patient follows their physician's prescribed medicine regimen, in terms of dosage, frequency and timing of ingestion (Osterberg and Blaschke, 2005). The term 'adherence' is preferred to another commonly used term, 'compliance', as it denotes a more empowered patient, who is an active member of a therapeutic relationship with the prescriber (ibid.).

Many chronic, medical conditions e.g. hypertension, diabetes, TB, schizophrenia and HIV are managed by long-term medication regimens. It is important that patients maintain high levels of adherence, in order to maximize clinical benefit (ibid.). The treatment plans may be complex, requiring patients to take a variety of medicines, multiple times a day (Granger and Bosworth, 2011). Additionally, patients should adhere to rules regarding timings and restrictions regarding concurrent ingestion with food, drink or other medicines. These restrictions are necessary to prevent interactions which may lead to toxicity or reduced efficacy of the medicines. Poor adherence leads to worsening of disease, increased mortality and increased healthcare costs (Iuga and McGuire, 2014; Osterberg and Blaschke, 2005; Viswanathan et al., 2012).

In the treatment of HIV, high levels of adherence to therapy are necessary to maintain pharmacologic effectiveness and prevent resistance (B. Nachega et al., 2011). In the management of TB, poor adherence is one of the factors that has greatly assisted the development of multidrug resistant forms of the disease. The routine application of directly observed therapy (DOT) has been the required international standard in TB management for decades (Metcalfe et al., 2015). DOT is when a witness is required to observe the patient taking their medicine. It is well established that poor adherence leads to poor patient outcomes (Iuga and McGuire, 2014).

Despite the importance of adherence, a significant proportion of patients are poorly adherent (DiMatteo, 2004; Iuga and McGuire, 2014; Osterberg and Blaschke, 2005; Viswanathan et al., 2012). In clinical trials, where high adherence rates may be expected, adherence ranges from 43% to 78% (Osterberg and Blaschke, 2005). A meta-analysis of over 500 clinical trials showed an average adherence rate of 75% (DiMatteo, 2004). This is below the generally accepted level for adequate adherence of 80% for most disorders, and well below the expected level of at least 95% in HIV (Osterberg and Blaschke, 2005). Outside of clinical trials, adherence levels are even lower. In the general population, adherence rates to chronic treatment are at a dismal 50% (Haynes et al., 2008; Iuga and McGuire, 2014; Osterberg and Blaschke, 2005; Viswanathan et al., 2012).

The financial costs to society of poor adherence are significant. Poor adherence leads to avoidable hospitalizations, wasted hospital visits for unnecessary diagnostics, wasted medicines and ineffective pharmacy spend, and increased health system resource utilization (Iuga and McGuire, 2014). In the USA, the estimated annual cost associated with poor adherence is reported to be as high as $300 billion, which may be as much as 10% of the entire American healthcare budget (Iuga and McGuire, 2014; Viswanathan et al., 2012). The significance of the adherence problem was outlined in the 2003 report by the WHO (Sabaté and World Health Organization, 2003), which noted the need for improvements in patient-level support and the need for new methods of adherence monitoring. The WHO suggested that improving adherence would have a major effect on the outcomes of chronic diseases in the human population, both in terms of clinical and health outcomes, and in terms of cost savings and better healthcare resource utilization (ibid.).

Monitoring of patients' adherence to medication has been conducted for centuries, using a variety of direct and indirect techniques (Osterberg and Blaschke, 2005). Indirect methods include patient self-reporting, medication diaries, questionnaires, pill counts, prescription refill rates and clinical response (ibid.). These methods are relatively cheap, and commonly used, but are susceptible to inaccurate reporting, distortion and bias (ibid.). Electronic lids for pill and medicine bottles, which have been in limited use for years, detect and record when the lid is opened, but do not directly measure if the medicine was actually ingested or applied (ibid.)

Direct methods, which tend to be more costly and difficult to implement, include DOT where patients are watched as they consume their tablets, and measurement of blood and urine drug and metabolite levels (ibid.). DOT is the standard method of improving adherence to TB treatment, and is intended to assist the prevention of emergent multidrug resistant TB (Metcalfe et al., 2015). Even DOT is not foolproof, as patients may hide tablets in their mouth and not actually swallow them (Osterberg and Blaschke, 2005).

Technology is being employed more frequently in the field of adherence monitoring. SMS text message reminder systems and electronic pill bottles and eye drop dispensers have been in use for some years already, but have had limited impact on improving adherence (Granger and Bosworth, 2011). Large analyses of the effect of

various interventions on medication adherence, conducted by The Cochrane Collaboration (Haynes et al., 2008; Nieuwlaat et al., 2014), have demonstrated a wide variety of results. Only a small number of randomized controlled trials (RCTs) have demonstrated improvements in both adherence and clinical outcomes (ibid.). These results indicate the need for more objective methods of adherence monitoring (ibid.).

Smart pills with IEMs provide “low cost” (Chai et al., 2015, p.440) opportunities to improve objective adherence monitoring (Chai et al., 2015). As a direct form of adherence monitoring, IEMs provide real-time, accurate information on ingestion events, without the need for directly observed ingestion, or measurement of blood levels (ibid.). As a component of a multi-device, mHealth-based ecosystem, which is deployed in support of traditional, low-tech adherence support methods, smart pills have the potential to improve treatment adherence in clinical studies and in the control of chronic diseases in the wider population (ibid.).

Clinical trials of smart pills, which are covered in detail in section 2.3, demonstrate the potential for Wirelessly Observed Therapy (WOT) to replace DOT in TB management (Au-Yeung et al., 2011; Belknap et al., 2013; Browne et al., 2015b), with the additional potential benefit of cost savings (Au-Yeung and DiCarlo, 2012). Other disease areas which may benefit from enhanced adherence monitoring include: HIV therapy, chronic cardiac disease, management of drug addiction and dependency, acute and chronic pain management, hypertension, diabetes, and severe mental illness (Au-Yeung et al., 2011; Chai et al., 2015; Kane et al., 2013).

The smart pill system delivers an enhanced form of adherence monitoring in numerous ways (Chai et al., 2015):

1) Providing direct, real time evidence of medicine ingestion. This reduces recall bias and distortion.

2) Allowing longitudinal adherence observation in real time. This helps to detect patterns and trends, which can be detected early, before adverse clinical outcomes.

3) The detection of subtle and early behavior associated with adherence patterns. Behavioral and physiological inputs, e.g. heart rate, temperature and

gastric pH detected by the APM and IEM can provide additional data to assist with understanding adherence patterns.

4) Performance feedback in real time and real time reminders. The smart pill system can provide reminders and alerts to patients to take their medication. Forgetful patients or those with memory and psychiatric disorders can share information with their caregivers which can help prevent missed medication or overdosing.

5) Improvements in managing drug overdoses. For toxicologists, IEMs would help identify the precise compounds and timing of ingestion, in poisoned patients.

South Africa has a high burden of HIV with large treatment programs (Barth et al., 2010). In HIV therapy, it is well established that very high rates of medication adherence, of at least 95%, are required to keep viral load adequately suppressed, and improve the outcome of patients (Georgette et al., 2016; B. Nachega et al., 2011; Omonaiye et al., 2018). A meta-analysis of 27 studies in Sub-Sahara Africa showed adherence levels of 77% (Mills et al., 2006), although the majority of trials used patient self-reporting as the method of adherence monitoring, which may have overestimated adherence levels. A large review of 89 studies in Sub-Sahara Africa showed viral suppression rates of only 67% at 2 years (Barth et al., 2010). It is clear from these data that adherence to antiretroviral therapy (ARV) is not high enough and improvements in adherence support are required (Georgette et al., 2016; B. Nachega et al., 2011; Omonaiye et al., 2018; Sabaté and World Health Organization, 2003).

Studies in Sub-Sahara African countries, including South Africa, have proven the general effectiveness and acceptability of digital interventions like SMS adherence reminders (Georgette et al., 2016) and electronic medication container bottle cap systems e.g. MEMS™ and Wisepill™, that record the time and date of medication bottle opening (Campbell et al., 2018).

Smart pills may provide further adherence improvements across a wide variety of treatment programs in South Africa, including HIV, TB and non-communicable diseases like hypertension and diabetes. With the potential for reduced medicine wastage and more prudent utilization of healthcare services and resources, improved

adherence monitoring with smart pills may provide meaningful financial savings to the South African healthcare system, provided the acquisition costs of smart pills are not too high. The cost of the smart pill Abilify MyCite™ is reported to be double that of the regular version (Klugman et al., 2018).

2.4 Published Clinical Trials

In order to review the ethical issues of smart pills in later chapters, it is important to gather sufficient and appropriate scientific evidence of their medical functionality. The quality and quantity of clinical evidence is considered a crucial component of ethical decision making in medical research and practice (Vayena and Ienca, 2018). Good clinical evidence contributes to a robust informed consent process and enhances patient autonomy by providing sufficient factual information to assist with medical decisions (ibid.). I therefore review the clinical trial data of smart pills in this section. A tabulated summary of the published clinical trials is found in Appendix A.

Various types of clinical trials, assessing a variety of parameters, have been conducted in healthy volunteers (Chai et al., 2019; DiCarlo et al., 2012; Ibrahim et al., 2018; Flores et al., 2016) and across a wide range of medical conditions, including diabetes (Browne et al., 2015a; Frias et al., 2017), cardiovascular disease (Thompson et al., 2017), heart failure (Au-Yeung et al., 2011) hypertension (Au-Yeung et al., 2011; Frias et al., 2017; Naik et al., 2017; Noble et al., 2016), kidney transplantation (Eisenberger et al., 2013), opioid ingestion patterns (Chai et al., 2017a, 2017b), tuberculosis (Au-Yeung et al., 2011; Belknap et al., 2013; Browne et al., 2015b) and bioequivalence studies with antiretroviral (ARV) therapies (Chai et al., 2019; Ibrahim et al., 2018). Trials are underway in cancer and the results are expected to read out in 2021 (Brodwin, 2019). In 2016, over 500 patients had consumed at least 20’000 ingestible sensors (Noble et al., 2016); by early 2019, the number of sensors ingested had jumped to over 177’000 (Brodwin, 2019).

Perhaps due to technical difficulties in designing blinded studies, the evidence base of smart pills does not include large, randomized trials, with well-designed placebos and APM dummies. In the future, smart watches or bracelets like the Apple Watch™, and Fitbit™ will perform the function of the APM. This should improve the comfort and usability for patients and alleviate the need to design dummy APMs for trials. This

could enable improved clinical trial designs, with patients and investigators being blinded to the active and control groups.

2.5 Clinical Efficacy

Published clinical trials of smart pills are relatively small, with patient numbers ranging from 5 (Browne et al., 2015a) to 167 (Naik et al., 2017). In 2011, the results of an early feasibility study, funded and conducted by Proteus Biomedical Inc., were published (Au-Yeung et al., 2011). This short-term study of 111 participants, included 4 cohorts: healthy volunteers, patients with active TB, stable heart failure and stable hypertensives.

Firstly, the system was shown to be safe and well tolerated: the commonest adverse event was mild skin irritation associated with the adhesive patches, or APMs (ibid.). Secondly, it produced accurate ingestion detection results: a high level of positive detection accuracy (PDA) of 97% was proven (ibid.). PDA is the number of IEMs detected (by the APM), divided by the number of IEMs administered, and confirmed by directly observed ingestion. Participants' body mass indices (BMI) did not affect the PDA results.

The system was also able to detect multiple, different IEMs from different smart medicines, taken at the same time, during unsupervised, take-at-home portions of the study. The system was perfectly able to detect the variety of medicines ingested, with 100% identification accuracy (ibid.). However, the study was limited, with small sample sizes and short duration of participation, up to 42 days. Long term usability across a wide patient population was not proven in this study (ibid.).

Other studies have shown similarly high levels of PDA and identification accuracy, in healthy volunteers (DiCarlo et al., 2012; Flores et al., 2016), in patients with active tuberculosis (Belknap et al., 2013; Browne et al., 2015b), kidney transplantation (Eisenberger et al., 2013), and in patients with schizophrenia and bipolar mood disorder (BMD) (Kane et al., 2013).

Two bioequivalence studies have been performed with antiretroviral medications, one proving pharmacokinetic (PK) bioequivalence with the standard formulations for

tenofovir and emtricitabine co-encapsulated with the Proteus™ IEM (Ibrahim et al., 2018), and the other demonstrating bioequivalence of tenofovir, over-encapsulated with the ID Cap™ IEM, with the standard, non-digital form of tenofovir (Chai et al., 2019).

Studies have shown a large gap between self-reported ingestion and smart pill detected measured ingestion. The smart pill was able to detect differences between measured ingestion and self-reported ingestion in cardiovascular disease (Thompson et al., 2017). Additionally, the smart pill may have boosted adherence levels in certain studies, above the standard figure of 50% (Haynes et al., 2008) in the literature: in one study of over 100 participants with hypertension and Type 2 diabetes, measured adherence was at least 80% while using the smart pill system (Frias et al., 2017); a study of 28 participants with schizophrenia or bipolar mood disorder (BMD) showed an adherence rate of 74% (Kane et al., 2013). However, the studies did not have control arms and were not designed to detect differences in adherence rates between smart pills and conventional pills. Nonetheless, they provide some evidence of adherence improvements, with measurements that are higher than the historically reported figure of 50%, for adherence to chronic oral medication (Frias et al., 2017; Haynes et al., 2008).

In addition to improvements in adherence monitoring, some of the studies provide evidence of improved clinical outcomes. The randomized study of 107 patients with poorly controlled hypertension and diabetes by Frias et al. (2017) showed improvements in objective disease markers, such as systolic blood pressure (SBP), glycated haemoglobin (HbA1c) and low-density lipoprotein-cholesterol (LDL-C), for smart pill groups versus usual care (ibid.). A community-based study of 39 hypertensive patients by Noble et al. (2016) was able to determine the cause of poor BP control in all patients, with almost 1/3 of participants (32%) falling below the predefined 80% adherence rate. In this study, systolic and diastolic BP decreased among the study participants (ibid.). The authors noted that improved adherence in this study may have been partly due to the Hawthorne effect (ibid.), which is when trial subjects modify their behavior, merely because they are being studied.

A larger registry study of 167 hypertensive patients identified almost one third of study participants who had inadequate use of their prescribed treatment and were

able to control their BP with no increase in therapy (Naik et al., 2017). Mean systolic and diastolic blood pressure measurements also decreased over the course of the study (ibid.). Most patients found the wearable patches to be comfortable and the ingestible smart pills to be convenient (ibid.).

Two studies of smart pills have been conducted in patients with serious mental conditions, schizophrenia and bipolar mood disorder (BMD) (Batra et al., 2017; Kane et al., 2013; Peters-Strickland et al., 2016). In an 8-week prospective trial, investigators assessed 49 schizophrenic patients' abilities with the tasks of applying the adhesive, wearable sensor (APM) and pairing with a smartphone (Peters-Strickland et al., 2016). More than 80% of participants managed to complete the tasks with little or no help (ibid.). A separate study of 28 mentally ill patients showed a high completion rate of 96% (Batra et al., 2017; Kane et al., 2013) and 70% of patients found the smart pill and APM concept easy to understand (Kane et al., 2013). Similarly, high levels of usability and acceptability for participants, are reported in many of the studies in non-psychiatric patients (Belknap et al., 2013; Frias et al., 2017; Naik et al., 2017; Noble et al., 2016; Peters-Strickland et al., 2016; Thompson et al., 2017).

Initial feasibility studies of smart pills in TB, demonstrate the potential for a new form of treatment adherence monitoring, called wirelessly observed therapy (WOT) (Belknap et al., 2013; Browne et al., 2015b). In one study, WOT was compared with DOT in 14 active TB patients and the system was able to wirelessly detect 98% of observed ingestions, and led to more daily doses ingested than DOT (Browne et al., 2015b). The over-encapsulated IEM was safe and bioequivalent to the standard TB treatments (ibid.). Belknap et al. (2013) published additional results from the active TB patient cohort described above (Au-Yeung et al., 2011). This feasibility study demonstrated the ability of the smart pill system to accurately detect medication ingestion, with 95% positive detection accuracy (PDA) of WOT compared with DOT in patients with active TB (Belknap et al., 2013). There was no difference in accuracy for patients with different body mass indices (BMIs) (ibid.). The smart pill was well tolerated in these active TB patients (ibid.). The authors conclude that WOT has the potential to improve TB treatment adherence, with reduced demand on personnel and resources (ibid.).

An economic model developed by Proteus researchers, Au-Yeung and DiCarlo (2012), demonstrated cost savings for WOT versus DOT in TB treatment. Proteus also demonstrated cost offsets for smart pills in those patients suffering concurrent diabetes, hypertension and hypercholesterolemia (Kim et al., 2015).

2.6 Safety and Tolerability

All the trials which report on the safety of the IEM and APM, report very high levels of safety and tolerability, with minimal adverse events. Plowman et al. (2018) published a review of the safety of smart pills with IEMs. They describe the safety of the technology, which has been demonstrated in 13 years of study in over 120 clinical trials (ibid.). In the research setting, about 500 volunteers varying in age from 21 years to 85 years, have ingested more than 20'000 IEMs and represent over 6'400 days of patch use (ibid.). Less than 1% of these patients experienced nausea or vomiting, and approximately 12% experienced mild skin irritation at the site of adhesive sensor (APM) placement (ibid.). It is notable that there have been no serious adverse events reported (ibid.). Continuing real world use confirms "extremely high patient satisfaction and usability ratings" (ibid. p.851).

2.7 Conclusions

Smart pills are accurate, with the ability to detect medication ingestion events and objectively measure medication adherence, with minimal device-related toxicity. Safety results from clinical trials and real-world use are reassuring, with no serious adverse events due to smart pills. Clinical trials show high levels of patient and healthcare professional satisfaction, engagement and comfort.

Studies demonstrate improvements in medication adherence parameters, and improved clinical and healthcare outcomes in diseases such as hypertension, tuberculosis, HIV and schizophrenia. Cost effectiveness studies of smart pills have demonstrated cost effectiveness (Au-Yeung and DiCarlo, 2012; Kim et al., 2015). Cost savings can be expected when smart pill enabled WOT is compared with DOT, in the management of patients with TB (Au-Yeung and DiCarlo, 2012).

Notable weaknesses of these studies are that they are mostly small pilot studies and feasibility studies of short duration, usually funded and/or otherwise assisted by the smart pill manufacturer. There are few randomized, controlled trials demonstrating sustained improvements in long-term adherence to medication. Studies in cancer are underway (Brodwin, 2019) and should provide more insights into the long term benefits of smart pills.

CHAPTER 3: ETHICAL ISSUES OF SMART PILLS

3.1 Introducing the Ethical Issues

New technologies, especially in the healthcare field, can be expected to generate ethical discussion. The ethical issues relating to smart pills have been posited in the mainstream media (Belluck, 2017) and in the scientific (Campbell et al., 2016; Campbell, 2016; Klugman et al., 2018; Vayena et al., 2018) and legal (Montgomery, 2016) literature. Some of the ethical issues are not new, and relate to medication adherence in general, patient monitoring and surveillance, and to biomedical and 'big' data generation and governance (Campbell et al., 2016; Klugman et al., 2018; Montgomery, 2016; Vayena and Ienca, 2018).

In the New York Times in 2017, various physicians reportedly raised their concerns for the potential of smart pills to become a "biomedical big brother" (Belluck, 2017, p.4) and a "tattletale" (ibid. p.2) type of technology, with the ability to intrude on patients' privacy, and perhaps to pressurize or coerce patients to take medication, in 'view' of their healthcare providers (Belluck, 2017).

In a seminal publication, which generated robust ethical debate and comment, Klugman and colleagues (2018) allude to the foreboding metaphor of the "digital medicine panopticon" (Klugman et al., 2018, p.45). The potential for patients to be constantly monitored by many connected IoT devices, of which smart pills are one type, raises concerns that patients' freedom and autonomy may be eroded (ibid.). Due to their "intimate" (ibid. p.38) nature - these are medical devices that are ingested and thus internalized in the body - smart pills deserve particular ethical consideration and review (Klugman et al., 2018). The authors frame the ethical issues into those affecting individual patients, those affecting healthcare providers, and the ethical issues at societal level (ibid.).

Issues affecting individual patients include autonomy, privacy, confidentiality, consent, therapeutic misconception, data management, external influences and device dependability (ibid.) Provider level issues include trust and the clinician-patient relationship, monitoring of clinicians and increased expectations and liability risk (ibid.). Societal issues are those of affordability and equitable access to the

technology, discrimination, pressure by payers or insurers, and transparency with technological and data policy (ibid.).

As part of his PhD research into electronic adherence monitoring of HIV patients in Uganda, Jeffrey Campbell highlights four ethical issues, aligned with those defined above, relating to electronic adherence monitoring: Autonomy, privacy, trust and ancillary care obligations (Campbell, 2016; Campbell et al., 2016, 2018). In their review of the ethics of personalized health monitoring, Mittelstadt and colleagues identified five ethical themes: privacy, autonomy, obtrusiveness and visibility, stigma, identity and social isolation (Mittelstadt et al., 2014). Of these, they describe autonomy as the central ethical theme (ibid.).

Despite slightly different approaches in the literature, there is also much convergence and overlap of ideas. It is clear that the emerging ethical issues of smart pills have a strong foundation in the bioethical principles of patient autonomy and justice, and how these principles relate to data usage and protection. For the purposes of discussion in this research report, I will loosely group these related ethical themes into the following categories:

- Autonomy and informed consent
- Privacy and surveillance
- Confidentiality and data management
- Trust relationships
- Access and availability

3.2 Autonomy

Mittlestadt (2014) describes the principle of autonomy as the central ethical theme of electronic adherence monitoring. The word *autonomy* derives from the Greek language and means *self-rule* (Beauchamp and Childress, 2013). The bioethical principle of respect for autonomy is one of the four bioethical principles popularized by Beauchamp and Childress (2013). The other three principles are non-maleficence, beneficence and justice (ibid.). These bioethical principles are well established as the core bioethical principles in modern clinical medicine and research and are also known as the Georgetown Mantra. Beauchamp and Childress (2013) provide a clear summary of the concept of personal autonomy:

> "At a minimum, personal autonomy encompasses self-rule that is free from both controlling interference by others and limitations that prevent meaningful choice, such as inadequate understanding." (ibid. p.101).

Two conditions are described as critical for autonomy: *liberty*, which is the freedom from external, controlling influences and *agency*, which is the capacity for intentional action (ibid. p.102). The moral rules, or rights and (positive or negative) obligations, which are derived from the principle of respect for autonomy, include rights to liberty and privacy, obligations of truthfulness, obligations to maintain confidentiality, and the obligation for researchers to obtain informed consent before conducting certain invasive or dangerous interventions with patients .

Adherence monitoring may reduce patients' autonomy by limiting their liberty or freedom to be non-adherent (Campbell et al., 2016). However, it can be argued that the potential outcomes of being non-adherent, i.e. remaining ill, deteriorating, or spreading a dangerous, infectious disease to others in the community are not valuable for patients nor for society, but rather they are harmful and therefore minor limitations of autonomy can be justified (ibid.). Respect for an individual's autonomy in the medical setting is usually considered a relative moral principle, with only prima facie value (Beauchamp and Childress, 2013). Due to the competing interests of individual patient care, public health or population-based healthcare initiatives, and scarce resource allocation, individual autonomy may be justifiably limited to ensure balanced and reasonable outcomes for a healthcare system (ibid.).

If a patient voluntarily chooses to use an adherence monitoring system, this further strengthens the case that the user wishes to improve their adherence, and the use of the technology thereby enables the patient to exercise their autonomous intention (ibid.). Additionally, if the adherence monitoring system enables the patient to be discharged from hospital to be monitored in their home, this is an improvement in freedom of movement and autonomy (Mittelstadt et al., 2014). As described previously in section 2.2, severe infectious diseases like HIV and TB require high levels of medication adherence to be successfully managed, and to prevent communal spread (Osterberg and Blaschke, 2005). In these circumstances, patients who are offered electronic monitoring devices may have little choice but to use them

(Campbell et al., 2016). This implies that the challenge to autonomy does not stem from the technology itself, but from the lack of better alternatives to increase adherence (ibid.).

3.3 Informed Consent and User Agreements

> "At a bare minimum, respect for persons requires clear and comprehensible information available to patients on what is being done with the patient data and who, if anyone, has the right to view those data." (Klugman et al., 2018, p.42)

The use of informed consent procedures is the standard method for preserving patient's autonomy in research (Campbell et al., 2016), and enables patients' voluntary agreement or disagreement to participate in invasive diagnostic, therapeutic and research procedures (Klugman et al., 2018). The informed consent process could be adapted for use with smart pill systems, although this may create barriers to smart pill use in busy clinical settings (Campbell et al., 2016). Smart pills introduce another complication, as the use of these digital devices may be subject to user agreements (Klugman et al., 2018), or EULAs (end user license agreements). Patients could therefore be faced with 2 different types of contracts, which may affect their understanding and thus their autonomy (ibid.).

Informed consent is usually a face to face process, between healthcare provider or researcher and patient, and is intended to benefit the patient (ibid.). A user agreement, however, is designed to benefit the company and is typically a long, non-negotiable contract written up by legal experts (ibid.). They are often complicated documents which do not sufficiently, nor understandably (comprehensibly) for patients, describe the information gathering and data collection activities that the smart pill system is conducting, both in the present time, and what the data may be used for in the future (Montgomery, 2016). If the potential user does not know what the precise risks are, their autonomy to make informed decisions is significantly reduced (ibid.).

Patients cannot use the technology unless they agree, so they may feel they have no choice but to accept the terms and conditions of the user agreements, which

diminishes their autonomy (Klugman et al., 2018). Patients may not fully understand the scope of the EULA, which may include the need for periodic updates and maintenance and even access to patient data, to maintain the system (ibid.). The EULAs should be clear about intended and unintended future data use, and the levels of deidentification, coding and protection that will be applied to the data (ibid.). Patients should be given appropriate opportunities to understand any technological, pharmacological and data management changes and to re-consent or withdraw their consent.

Dynamic consenting processes, providing patients with clear and informed opportunities to opt in, or opt out, of using smart pills at all times during their treatment journey, should help preserve personal autonomy for smart pill users (Beauchamp and Childress, 2013; Campbell et al., 2016; Klugman et al., 2018). In a recent publication addressing digital health data governance in low- and middle-income countries (LMICs), Tiffin and colleagues (2019) list five important points that should be incorporated into the design of the informed consent process for digital data gathering:

1) Intended data use:
Who may use the data, when, and over what time period, should be clearly indicated. Primary and secondary data use must be clearly defined, and separate consent obtained for future data uses. Information about potential or actual monetization or commercialization of the data and third-party access must be included.
2) Anonymization methods:
How the data may be anonymized, deidentified and coded, should be explained.
3) Data storage and protection:
The measures that will be taken for data storage and protection must be explained.
4) Risks and benefits:
The potential risks and benefits of the digital data collection activities must be explained.
5) Contact information:

Patients should be provided with contact details of the relevant healthcare professionals (and perhaps the manufacturers should set up support helpdesks) to resolve questions, concerns and requests to amend or update the informed consent.

3.4 Privacy and Surveillance

Linked to the principle of autonomy, is the duty of healthcare providers to preserve patient privacy and the confidentiality of patients' information and their data (Beauchamp and Childress, 2013). Privacy can be defined as a state of limited access to an agent's body, information, space, choices, property and relations (ibid.). The corresponding right to privacy describes an agent's ability to control access to their private matters (ibid.). Privacy breaches relate to the gaining of information and data of patients, which are not part of the technology's intended purpose, but which may be inadvertently gathered by the system (Campbell et al., 2016). In relation to smart pills, privacy rights should be upheld so that patients do not to have any personal information or data, other than what is necessary and required for adherence monitoring, acquired, stored or shared with anyone else.

With digital adherence technologies, in addition to monitoring patients' adherence patterns and influencing adherence related behavior, there may be a more general impact on other aspects of patients' lives (ibid.). The constant monitoring "gaze" (Campbell et al., 2016, p.338) of clinicians and researchers could infringe on their privacy to behave in ways that may be unconventional or even "embarrassing" (ibid.). Patients may feel that they are being constantly watched by healthcare service providers who may learn about their personal habits, including their sleep and wake patterns, their eating and drinking preferences, exercise and activity levels, sexual behaviors and other private matters (ibid. p.339). This concept of digital surveillance applies to the various smart, wearable, implantable and ingestible devices technologies that we interact with every day, which have the ability to store and share data.

The use and interpretation of these data allow patients to be observed and monitored from a distance and thus smart pills are a form of surveillance technology (Mittelstadt et al., 2014). The terms "überveillance" (Gagnon et al., 2013, p.60) and "digital

medicine panopticon" (Klugman et al., 2018, p.45) arise as a result of these digital technologies pervading almost all aspects of peoples' lives. Überveillance can refer to always-on monitoring devices that continuously measure and track behavior and physiology in real time (Gagnon et al., 2013). They can be permanent (implanted in the body e.g. cardiac pacemakers) or semi-permanent (wearable patches and blood glucose monitors), or temporary, as is the case with ingestible smart pills (ibid.).

The term "digital medicine panopticon" (Klugman et al., 2018, p.45) is derived from the modern, French philosopher Michel Foucault's "concepts of governmentality and bio-power" (Gagnon et al., 2013, p.61), wherein Foucault used the term *panopticon* to describe the surveillance and disciplinary power that is present in public health systems (ibid. p.62). The word panopticon originates from the Greek language and means *everything*, *place of full sight*, or *all-seeing*. It is used as an architectural descriptor of a building, typically a prison, that has a central point from which all other persons in the building can be observed (ibid.). Interestingly, this concept is influenced by Jeremy Bentham's approach to prison architecture and design in Britain in the 18th century (ibid.). Jeremy Bentham was an English judge and philosopher, who is credited with the founding of modern utilitarian theory (Crimmins, 2019; Rachels and Rachels, 2015).

Firstly, the panoptical design of prisons facilitated the continuous surveillance of every incarcerated individual by prison guards. Secondly, it proved that constant surveillance lead to increased discipline of the prison population (Gagnon et al., 2013). The prisoners experienced the disciplinary effect of constant surveillance and many came to self-discipline themselves, merely because they knew that they were under constant observation by the authorities (ibid.). This physical panopticon serves as a metaphor for the constant digital exposure of patients, that may eventualize with the numerous digital monitoring devices entering the environment. It may occur that the combined surveillance pressure of these devices could become unacceptable to patients, despite each individual device being acceptable on its own (Klugman et al., 2018). Additionally, critics argue that the healthcare surveillance systems require high levels of ethical oversight and governance – "*quis custodiet ipsos custodes*?" (Guta et al., 2018, p.63) which means 'who will watch the watchmen' or 'who will guard the guards themselves.'

The extent to which people accept loss of privacy may be culturally relative (Campbell, 2016). Studies conducted in HIV patients show different patterns of concern amongst patients in different countries (ibid.). Patients in Malawi, India and the USA raised concerns that smart pill bottles, which look different to regular pill bottles, may cause suspicions among their friends or family members (ibid.). However, patients in Uganda, Tanzania and South Africa were less concerned (ibid.). Campbell et al. (2018) conducted a study of 60 Ugandans with HIV, who were undergoing electronic monitoring of ARV adherence. The study showed that despite some patients acknowledging a sense of pressure to adhere, this was viewed as a helpful and desirable effect (ibid.). The patients were pleased to have an intervention which helped them to adhere to their treatment and ultimately achieve their own health goals (ibid.).

3.5 Confidentiality and Data Management

> "Medical information is unique in that it is both highly personal to patients and valuable to businesses." (Montgomery, 2016, p.170)

Smart pill systems collect patients' behavioral, physiological and ingestion event data which are stored and analyzed. This is done at the individual patient level, to monitor adherence patterns, to help identify issues related to poor adherence and to provide opportunities to optimize a patient's adherence to treatment. The data can also be fed into large healthcare data platforms, which are collecting vast amounts of data from electronic health records (EHRs), claims databases, pharmacy records and other systems (Cohen et al., 2014). These large, real-time datasets are commonly termed 'big data' (ibid.). These big data can be used to develop predictive analytical models which can determine health risks, predict clinical outcomes, identify opportunities to improve healthcare delivery, and lower the costs of healthcare delivery (ibid.).

Big data require careful protection because they are more susceptible to re-identification, even if they have been anonymized (Ballantyne, 2018). Due to the huge number of data points gathered on an individual, the standard methods of de-identification are failing to completely anonymize big data (ibid.) and data scientists

have indicated that it is possible to reidentify databases using updated computer technology (Montgomery, 2016).

Confidentiality is a type of “informational privacy” (Beauchamp and Childress, 2013, p.316) which prevents the sharing of a person’s information outside of a trust-based, and usually professional relationship, without the appropriate consent. With smart pill systems, confidentiality relates to the appropriate protection of, and limitation of access to, personal health and adherence data that the system intentionally gathers, that may be shared with a variety of external stakeholders (Campbell et al., 2016). Patients can choose who is able to receive or view their adherence data. This includes their physicians, other HCPs, family, friends and caregivers, and may also extend to the manufacturers, insurers and other stakeholders (Klugman et al., 2018).

Maintaining strict confidentiality is the duty of healthcare professionals, who must not reveal any patient’s personal health, disease and treatment information to anyone who is not authorized to know such information. Patients have high expectations of confidentiality and privacy, based on law, professionalism and ethics (ibid.). Maintaining confidentiality is a vital part of the therapeutic relationship between the healthcare professional (HCP) and the patient. Patients confide in their HCPs when explaining their symptoms and sharing private information as part of the consultation process. HCPs, who require this information to make the correct clinical decisions, keep this information secret and do not share it with anyone, except other HCPs who are part of the treatment team. In addition, HCPs are bound by laws and regulations which compel them to maintain the confidentiality and privacy of patients’ information.

This model will likely work for smart pills and the professional medical team, but if the adherence data can be shared with other persons, e.g. family members and friends, it is important to consider what levels of confidentiality can be expected from non-professionals (ibid.). Family and friends of patients who receive adherence data may be required to be educated about the importance of confidentiality and commit to such in writing. The collection and use of data by third parties, for example manufacturers and insurers, should be governed by dynamic informed consent processes and data use agreements (Cohen et al., 2014; Klugman et al., 2018; Tiffin et al., 2019; Vayena et al., 2018).

A significant risk of smart pill systems is that patients' personal health information may be unintentionally disclosed. This has particular relevance in the treatment of stigmatized diseases, such as HIV, where unintended disclosure may be undesirable and damaging to the patient (Klugman et al., 2018). It is clear that suitable protection of such sensitive data is necessary. Ownership of the data generated by smart pills will depend on numerous factors including deidentification, jurisdiction (ibid.) and any informed consent or user agreements.

In the USA, Electronic data generated by smart pills will enjoy some protection under the Health Insurance Portability and Accountability Act (HIPAA) and other legislative instruments which govern data breaches (Campbell et al., 2016; Klugman et al., 2018; Montgomery, 2016). However despite this legislation, data breaches still occur and it is uncertain how the HIPAA law will specifically apply to smart pills (Campbell et al., 2016). Data protection is less developed in many developing countries (ibid.) and South Africa has yet to fully adopt the Protection of Personal Information Act 4 of 2013 (POPIA) although this is expected soon (Tiffin et al., 2019).

In addition to legal gaps which may impact privacy and confidentiality, smart pills themselves may be technologically more susceptible to data breaches than many other devices in the medical field (Montgomery, 2016). The small size (form factor) of smart pill devices provides convenience for consumers but makes them more difficult to secure (ibid.). It is technologically challenging to include the battery and processing power to enable robust anti-hacking and encryption functions (ibid.). Despite this, it is argued that it is in the manufacturing companies' best interests to ensure data security as a cornerstone of their businesses' viability, as data breaches are reported to be more costly and damaging to the companies, than to the individual consumers (ibid.).

Klugman and colleagues (2018) mention that "best practices" (p. 41) in digital medicine products and data management are required. Smart pill users should be fully informed in terms of who has access to, and what is being, or will be, done with the data (ibid.). Users should have clear opportunities to adjust or retract their consent about data usage at any time (ibid.).

Nicki Tiffin et al. (2019) describe four key digital data governance principles, based on their experience with digital healthcare programs in India and South Africa, which may “ensure health benefit and participant protection for vulnerable populations in LMICs.” (p.2). The first principle is to establish a suitable and ethical informed consent process, with identification of vulnerable populations and their particular resource requirements for data protection. A tiered consent process with clear descriptions of primary, secondary and other data usage is recommended. The consents should contain detailed information on data anonymization methods, storage, protection, backup and retention periods. Options to withdraw and delete data should be easily available and the responsible parties for data management must be clearly identified and contact details provided. Any third party access to the data must be explained (ibid.).

The second principle is data access control, which can be managed at two levels: procedural oversight and structural (or technological) protection (ibid.). Procedural control should include standard operating procedures (SOPs) which clearly document the processes required to access the datasets. A data access committee or similar governance board could be set up to review, authorize and document data access requests (ibid.). When reviewing data access requests, the data access committee should consider the geographic locations and legal jurisdictions of the dataset, computer servers and the requestor. Different countries have different laws governing data use and transfer which must be considered. The intended use of the data must be considered, and the expected benefits balanced with potential risks (e.g. data breaches) to ensure equitable and ethical data access and reduce “predatory data acquisition” (Tiffin et al., 2019, p.6).

In addition to suitable data protection processes and procedures, the structural and technological protection of data is also necessary (Tiffin et al., 2019). The basic software applications such as firewalls, encryption and password protection are a minimum requirement to control access to the system and data (ibid.). Databases can be designed to protect patients, by physically separating the storage of identifying data e.g. biometrics, from clinical data, e.g. adherence data. A special linkage key is required to match the separate data, which reduces the risk of breaking confidentiality. Together with a suitable data access policy, this database

design can enable data access to only the minimal data required by the requestor for the intended (and consented) purpose (ibid.).

The third principle of digital data governance in LMICs is sustainability (ibid.). It is recommended that a formal sustainability plan is drawn up, to ensure the data governance is maintained for as long as necessary into the future. This plan should aim to maximize the benefits of the data collection over time, to ensure the best use of funding, and to demonstrate respect to those patients that have provided their data (ibid.). Lack of sustainability planning has led to the proliferation of large numbers of small, fragmented and short-lived digital health programs in LMICs, which has been called “pilotitis” (ibid. p.6). The government of Uganda has even restricted new digital app development in the healthcare environment, to avoid duplication and diversion of scarce resources. Digital health monitoring programs should be integrated into the core healthcare services of LMICs, to ensure maximum reach, cost effectiveness and long-term viability (ibid.). Sustainability also requires long term data storage, backup and retrieval. Tiffin et al. (2019) describe the FAIR principles which are required for data stewardship: data should be Findable, Accessible, Interoperable and Reusable (if appropriate consent is in place). Budgeting and resource allocation should be part of sustainability planning to ensure long term usability and protection of datasets (ibid.).

The fourth principle for data governance in LMICs is development of, and compliance with, the legal framework. Laws to protect personal, private and health information are being developed and refined in many countries (ibid.). As mentioned previously, the United States has federal laws that regulate the privacy of health information, particularly the Health Insurance Portability and Accountability Act (HIPAA) which was instituted in 2000 and then later supported by the Health Information Technology for Economic and Clinical Health Act (HITECHA), which was legislated in 2009 (Montgomery, 2016). Exactly how these statutes will affect smart pill systems is not entirely clear (Campbell et al., 2016). Instead of being pre-emptive, laws tend to be reactive to new technological challenges, and it is difficult for legislators to foresee all potential risks with new technologies (Tiffin et al., 2019). It is also important that new regulations are supportive of technological progress and do not unnecessarily stifle the emergence and application of digital health technologies (Montgomery, 2016).

In South Africa, POPIA is in the process of implementation, but is not yet ratified (Tiffin et al., 2019). POPIA specifically addresses health data which it classifies as 'special' data, requiring strict regulations for use and reuse (ibid.). Additionally, the National Health Act 61 of 2003 of South Africa (NHA) describes the confidentiality requirements between the clinician and patient and protects sensitive health data. The Promotion of Access to Information Act 2 of 2000 (PAIA) ensures that patients have the right to access data about them, and to know how their data have been shared and utilized (ibid.).

These principles of data governance require oversight by data access committees and ethics committees, and enforcement by governmental regulators (ibid.). In South Africa, a large mobile health program which provides information via SMS to pregnant mothers, called MomConnect, is overseen by a dedicated governmental task force and full-time advisor (Ojo, 2018; Labrique et al., 2018; Tiffin et al., 2019). The scope of this task force could be expanded to cover other digital health programs, including smart pill adherence monitoring systems. To support the POPI legislation roll-out in South Africa, a POPI regulator has been developed to support consumers and companies to legally and ethically manage data use (Tiffin et al., 2019). Due to the sensitive nature of healthcare and digital health data, the scope and expertise of the Institutional Review Boards (IRBs) and ethics committees must expand to accommodate digital health and data considerations. IRB members should keep abreast of digital health trends and understand data management, so they can provide adequate protection to patients in the evolving area of digital health programs (ibid.), such as smart pill monitoring.

3.6 Trust Relationships

Trust is a key element of the relationship between HCP (clinician or researcher) and patient (Campbell et al., 2016; Klugman et al., 2018). Patients trust their physicians to care for them and keep their personal and health information confidential (Klugman et al., 2018). Physicians trust their patients to comply with their prescribed treatment (ibid.). Smart pills provide objective measures of medication adherence which may differ from self-reported adherence data. This may damage the trust relationship between physician and patient as patients may be made to feel that they are untrustworthy or deceitful (Campbell et al., 2016; Klugman et al., 2018). They

may feel embarrassed if their measured adherence is lower than they report. Some patients may prefer to remain non-adherent to their treatment and smart pills limit their ability to deceive their HCPs (Klugman et al., 2018).

However, it is argued that remaining poorly adherent is detrimental to individual health and to the population and therefore some erosion of trust is acceptable, if increasing adherence is the outcome (Campbell et al., 2016). Further, if validated data on adherence form smart pills is available for review by HCP and patient, this may bolster the trust relationship between HCP and patient by providing a factual basis for further clinical discussion (Klugman et al., 2018). If there is concordance between self-reported adherence and smart pill measured data, this will enable the clinician to focus on reasons other than poor adherence for any untoward effects in the patient. Unambiguous information about their medication consumption and adherence may empower patients to comply with their own health and treatment goals (Campbell et al., 2016).

Another potential effect of smart pills on the trust relationship between HCP and patient may be due to a therapeutic misconception (Klugman et al., 2018). The therapeutic misconception is a term coined by renowned American psychiatrist, ethicist and researcher, Paul Applebaum in 1982, when describing the results of a study of informed consent in psychiatric patients (Appelbaum et al., 1982, 2004; Lidz et al., 2015). The study clearly demonstrated that patients did not fully understand that as participants in a clinical trial, they may receive treatment that is experimental and potentially harmful, or that they may be assigned to an ineffective treatment arm, as is the case with placebo treatment (ibid.). In the case of smart pill systems, patients may believe that their healthcare team is keeping a closer watch on their health and adherence parameters than they actually are (Klugman et al., 2018). Patients may not fully understand the abilities and limitations of the smart pill system and the responsibilities and duties of the healthcare team to review their data. This may lull patients into a false sense of security about their health, especially if they are not alerted by the system when monitored parameters fall out of desired ranges (ibid.).

Another trust relationship that may be affected is that between HCPs and medical insurers, funders (Klugman et al., 2018) and even regulators. Medical insurance

companies, medical aids and other similar funding organizations may be able to monitor clinicians with smart pill systems: what treatments they prescribe, how often they log into smart pill monitoring databases, how they react to system alerts and whether they help their patients to improve adherence (ibid.). Some of this clinician monitoring may be necessary to maintain the system and deliver updates to improve it, but there may be undesirable or unnecessary invasion of clinicians' professional independence and autonomy (ibid.). Increasing the oversight monitoring by insurers and payers over HCPs may limit the uptake of smart pill systems by prescribers (ibid.). HCPs may be concerned about increased liability should they now have access to further patient data like adherence data and expectations to act on these data (ibid.).

The third trust relationship that may be affected by smart pills is the relationship between manufacturers or developers and society. As is the case with regular, non-smart medicines, patients will be required to trust the smart pill manufacturers that their products and systems are safe to use (ibid.). The potential for failure of any electronic device exists and any problems such as hacking, data breaches and device vulnerability or unreliability must be declared to the public and remedied (ibid.). As smart pill systems will contribute data to the "big data ecosystem" (Vayena et al., 2018, p.4), there should be high levels of public trust in these systems. Without high levels of public trust, large data gathering programs are likely to fail (ibid.). In addition to privacy protection, other elements of data management stewardship are required to maintain public trust (ibid.). These include clear information about data ownership, access and control, transparency, accountability and benefit sharing (ibid.). Manufacturers should therefore include transparency policies in their user agreements (Klugman et al., 2018).

3.7 Access and Availability

Smart pills may cost more than the conventional non-digital form of medicines, and this will inevitably put affordability pressure on payers and patients, particularly those in developing countries like South Africa. While smart pills are not yet available for sale in South Africa, the cost of the Abilify MyCite™ smart pill in the USA is almost double that of the regular Abilify™ pill (Klugman et al., 2018). Additionally, smart pills

require the use of smart mobile phones with internet connectivity to upload data to cloud based servers.

While mobile phone penetration levels are high in Sub-Sahara Africa countries, with almost two thirds of households owning a mobile phone (Ndlovu et al., 2014) and even higher penetration levels in South African households (Ojo, 2018), the proportion of mobile phones that are smart and internet-connected is probably much lower. Mobile data costs are high, and many people do not have reliable internet connectivity. Even in the United states, smart phone ownership in the lower socio-economic groups is only at about 64% (Klugman et al., 2018).

Cohen et al (2014) analyzed the ethical impact of big data and predictive analytics and highlighted the concern that these technologies may further widen the gap in healthcare between the rich and the poor. Economically disadvantaged patients, with diminished levels of access to health care, may become worse off because their needs are not being measured and addressed by these new devices. While mHealth (mobile health) programs are becoming increasingly popular in Southern Africa (Ndlovu et al., 2014; Ojo, 2018), most of these are based on relatively low-tech, SMS-type communications which work with cheap, non-smart, mobile phones.

It is imperative that access to the benefits of smart pills should not be limited by socioeconomic status (Klugman et al., 2018). In order to enable equitable access to smart pill systems, manufacturers should take steps to bridge the “digital divide” (ibid. p.45) by providing access to smart phones for patients through loan programs, subsidization, and designing smart pill systems to work with the cheapest and most basic forms of smart phones (ibid.).

Over time, the cost of digital technologies is actually decreasing (Vayena et al., 2018). Developing countries are rolling out increasing numbers of mHealth, telehealth, EHRs, big data and other digital health initiatives (ibid.). Smart pill technology, like other forms of digital and mobile health programs, should not be limited to affluent countries or affluent members of developing countries. The potential health benefits and cost savings are significant and developing countries like South Africa could benefit immensely from digitized TB, HIV and hypertension treatment programs. Higher adherence levels and cost-effective wireless patient

monitoring should result in cost-effective use of healthcare resources, reduced wastage of medication, improved health outcomes and reduced transmission of serious infectious diseases.

CHAPTER 4: A PRINCIPLE-BASED APPROACH

4.1 Introduction

In this chapter I will introduce the principle-based approach of bioethical reasoning, with a focus on the four bioethical principles popularized by Tom Beauchamp and James Childress, at Georgetown University in the USA in the 1970's. I will then review the ethical issues of smart pills introduced in Chapter 3 using these bioethical principles.

Principles and rules are "general moral norms" (Childress, 2009 p.67) or "action guides" (ibid.) which help guide our moral reasoning when deducing what actions are required, allowed or forbidden, in the particular circumstances (Childress, 2009). These moral norms are derived from what Beauchamp and Childress call the common morality. The common morality is a universally acceptable collection of norms that are relevant to all moral people and are not relative to culture (Beauchamp and Childress, 2013). Some examples of norms within the common morality are obligations such as telling the truth, not committing murder, preventing harm to others, keeping promises and not stealing (ibid.). The common morality also proposes character traits or virtues such as honesty, kindness, nonmalevolence and trustworthiness (ibid.). These norms and characteristics are applicable to all persons, regardless of culture, group or religion (ibid.).

Biomedical ethics draws its moral norms from the common morality and the classical ethical theories usually include these principles in some way (ibid.). Principle based approaches can be deontological, consequential, or a combination of both (Childress, 2009). The principle of respect for persons is one of the core principles of deontological theories such as Kantian deontology. Utilitarianism, a consequentialist theory, is based on the principle of utility (ibid.). The principle of distributive justice is expressed in some form in a variety of theories e.g. utilitarian, libertarian, communitarian, egalitarian, well-being and capabilities theories (Beauchamp and Childress, 2013).

While principles are general norms which provide an overarching ethical framework, rules are derived from principles and are more specific (Childress, 2009). For

example, the principle of respect for autonomy is effected by the rule of informed consent in clinical trials, which ensures the provision of necessary information required by potential trial participants to make an informed and therefore autonomous decision to participate (ibid.).

There are a variety of principle-based approaches in the literature, which generally orientate around moral obligations to: not cause harm or kill (nonmaleficence), respect other people (respect for autonomy), help others (beneficence), deliver a balance of benefits over harms (justice), tell the truth and disclose information, keep promises and adhere to contracts (fidelity), and to respect privacy and confidentiality (Childress, 2009). In 1981, Robert Veatch emphasized the principles of beneficence, fidelity, autonomy, honesty, not killing and justice, as well as the rule of informed consent (ibid.). In 1995, Engelhardt distilled the principles into only two: principles of permission (similar to autonomy), and beneficence (ibid.).

Beauchamp and Childress (2013) describe four primary principles:

- Respect for autonomy
- Nonmaleficence
- Beneficence (which includes the principle of utility)
- Justice

Secondary rules derived from these principles include truth-telling (veracity), confidentiality, privacy and obtaining informed consent (Childress, 2009).

When applying these principles to a particular case, for example, analyzing smart pills, we may encounter conflicting principles or ambiguous outcomes. For example, potential data privacy breaches may diminish personal autonomy, but improved health outcomes are beneficent. In order to resolve potential conflicts, cases are analyzed using the techniques of specification and balancing (ibid.). Specification is when details, such as who, what, when and where, are applied to a principle in a particular case (ibid.). For example, it is a universally acceptable principle not to lie. However, it may be appropriate in certain circumstances to intentionally deceive in order to prevent harm or deliver benefit. For example, if an unjust, racist government refused to provide funding for medical treatment of people of a certain religion, race

or group, it may be justified for a physician to falsely identify her patient as not belonging to that religion, race or group.

Balancing is when the relative weights or strengths of conflicting principles are assessed and ranked (ibid.). On the one hand, absolutists believe that certain principles and rules are always binding, regardless of the situation or case (ibid.). It is difficult to apply an absolutist approach to positive obligations, e.g. if we were always to help others by giving charity, we may eventually become bankrupt and unable to help even ourselves. The absolutist approach probably applies best to certain negative obligations, for example, the rule against rape (ibid.). On the other hand, act utilitarians only recognize one principle, that of utility; all other principles and rules are merely advisory (ibid.).

Beauchamp and Childress provide an intermediate approach, by arguing that their four primary principles, and the rules derived thereof, are prima facie binding (ibid.). This means that they are binding "at first impression unless outweighed or overridden" (Childress, 2009 p.72) by other principles or rules. This aligns with W.D. Ross' argument that our obligations and rights are prima facie rather than actual (Beauchamp and Childress, 2013). Obligations must be fulfilled unless a stronger obligation emerges (ibid.). Rights must be fulfilled, unless a stronger right emerges (ibid.). The four principles are prescriptive and moral agents may only depart from any of the principles by demonstrating that another principle has more weight (ibid.).

Unlike the singular focus on the principle of utility in act utilitarianism, all four principles and the relevant rules are weighed and balanced when assessing a situation (Childress, 2009). Critics argue that this approach is "excessively intuitive" (ibid. p.73). In order to improve objectivity and reasoning when balancing the principles, Beauchamp and Childress (2013) provide six conditions which must be met to justify the infringement of a prima facie norm:

1) Good reasons are provided to override the norm
2) The objective justifying the infringement is likely to be achieved
3) There are no morally better alternatives
4) The lowest level of infringement required is chosen
5) The negative effects of infringement are minimized

6) All persons affected have been treated impartially

Despite these balancing attempts, critics of principlism denounce:

> "the tiresome invocation of the mantra of principles…which tempts novices to suppose that they have become experts in ethics because they can chant the mantra" (Childress, 2009 p.74).

Despite these criticisms, supporters of the principle-based approach argue for its usefulness and accept the need to reflect and improve on its weaknesses (Childress, 2009).

4.2 Respect for Autonomy

The principle of autonomy and the associated issues of informed consent, user agreements, confidentiality and data management are discussed in chapter 3, sections 3.2 to 3.5.

4.3 Nonmaleficence

The principle of nonmaleficence is often expressed by the well-known, Latin phrase *primum non nocere* which means 'first, do no harm' (Beauchamp and Childress, 2013). This prominent statement, while not derived directly from Hippocrates' writings, is closely aligned with obligations of nonmaleficence and beneficence set out in the Hippocratic Oath (ibid.). While the four bioethical principles have only prima facie standing, the principle of nonmaleficence may be considered to be the more stringent principle in many circumstances (ibid.).

The obligation to avoid harming others may override other principles, including those of beneficence and utility. For example, while it may save the lives of two innocent patients who require kidney transplants, it is morally unacceptable for a surgeon to kill a prisoner to provide the kidneys for transplantation (ibid.). This complies with the deontological theories of right action versus the consequential theory of utilitarianism, which values only the net outcomes. In other circumstances, the obligation of beneficence takes priority over nonmaleficence, for example when taking blood from

a child for important diagnostic tests. While the child is indeed hurt by the needle, the beneficence of accurate diagnosis and treatment override the maleficence of the painful blood draw.

The principles of beneficence and non-maleficence are closely related, but there are important differences. Beneficence requires moral agents to act to prevent or remove harm and to act to do good (ibid.). Non-maleficence requires moral agents to refrain from actions that are harmful to others. Refraining from causing harm may be considered more obligatory than performing helpful actions, but this distinction is not always appropriate (ibid.). Particular circumstances require specification of the principle to ensure ethical action.

When considering smart pills, the principle of nonmaleficence means that these devices should not cause harm, or the harm should be minimal and justified in terms of the benefits. As described in chapter 2, the smart pill devices and adhesive patches have been proven to be well tolerated and safe, from a pharmacological and clinical perspective (Plowman et al., 2018). Numerous controlled clinical trials and real-world usage show very low rates of adverse effects and no serious adverse medical effects have been reported with smart pills (ibid).

While the safety of these devices from a pharmacological and clinical perspective is assured, the potential harms of smart pill systems, described in chapter 3, include data mismanagement, confidentiality breaches, privacy concerns, damage to trust-based relationships, discrimination and inequitable access (Campbell et al., 2016; Klugman et al., 2018; Mittelstadt et al., 2014; Montgomery, 2016). To justify the use of smart pills, these harms must be prevented or minimized. Appropriate data practices must be adopted which protect the data of patients, especially in vulnerable populations (Tiffin et al., 2019). Data access protection infrastructure, policy and governance must be in place, to prevent unauthorized access and use of data. Patients must be protected from inappropriate discrimination by healthcare payers, insurers and providers (Klugman et al., 2018; Tiffin et al., 2019). The trust relationships between clinicians, scientists and patients will need to evolve to include objective measures of medication adherence. Appropriate information on smart pill functions, limitations and data management must be availed to patients and suitably

informed consents and user agreements should be attested to and understood by all parties.

The potential benefits of smart pills, especially improved medication adherence which leads to enhanced health outcomes for patients, reduced transmission of serious infectious diseases, better healthcare resource utilization and reduced medicine wastage, are very important and desirable outcomes. While the smart pills are pharmacologically safe, the risks of data mismanagement and privacy intrusions must be minimized to ensure patients are protected from potential harms. Patients must be well informed and able to consent and withdraw consent at any time, without suffering any prejudice.

4.4 Beneficence

The principle of beneficence imposes positive obligations on moral persons to provide benefits to others (Beauchamp and Childress, 2013). Whereas the principle of nonmaleficence compels moral agents to refrain from harming others, the principle of beneficence compels us “to take positive steps to help others, not merely refrain from harmful acts” (ibid. p.202). This principle is an ancient and core feature of the practice of medicine and the provision of healthcare. Helping individual patients by relieving their pain and suffering, and curing or managing their illnesses is beneficent to the individual patients, and public health programs which reduce the incidence, prevalence and severity of communicable and non-communicable diseases is beneficent to the public (Beauchamp and Childress, 2013). In addition to positive beneficence, the principle of utility is part of the overarching principle of beneficence (ibid.). The principle of utility compels us to “balance benefits, risks, and costs to produce the best overall results” (ibid. p.202).

Beneficence is a central principle in various ethical theories, including the ethical theory of utilitarianism (ibid.). Historically, philosophers have often prioritized beneficence as a central theme of morality. However, while utilitarians view the principle of utility as the only principle of ethics, Beauchamp and Childress view the principle as merely one of the prima facie bioethical principles, along with autonomy, nonmaleficence and justice (ibid.). They view the relative weight of the principles in terms of the specific situation. Whereas utilitarians value the interests of society as a

whole more than the interests of individual persons, the principle-based approach allows certain individual interests to override those of the public at large, depending on the situation (ibid.).

Some prima facie rules which are derived from the principle of beneficence include the obligations to protect others, to prevent harm to others, to help patients with disease and disabilities and to rescue people in danger (ibid.). While these positive obligations are morally desirable, they cannot be expected to be fulfilled in all circumstances (ibid.). Altruism and self-sacrifice are moral ideals, but not moral requirements (ibid.). It is not expected for clinicians to put themselves in grave danger to assist patients. For example, a paramedic must first ensure the scene made safe before providing emergency care at the scene of an accident on a busy freeway.

In the case of smart pills, the benefits for individual patients include increased adherence to treatment regimens, leading to improved clinical outcomes including disease control and cure. Benefits to individuals and society include the reduced risk of spread of serious infectious diseases like HIV and TB, which are better controlled by high levels of treatment adherence. Huge potential cost savings, due to reduced medicine wastage and better healthcare resource utilization, are important benefits to consider for individuals and for society as a whole. Avoidable healthcare costs, directly associated with poor adherence, are frequently quoted as being up to $300 billion per year (Frias et al., 2017; Iuga and McGuire, 2014; Viswanathan et al., 2012). Improving adherence may increase the spend on pharmaceuticals, but should result in an overall reduction in healthcare spend from savings on hospital admissions and readmissions, diagnostics and healthcare provider visits for disease progression due to poor compliance (Iuga and McGuire, 2014).

Benefits for the healthcare providers include an enhanced ability to address patients' side effects and lack of efficacy by obtaining objective measures of medication adherence, dosage consumed, timing of ingestion and other consumption related behavior. Better advice can be given to patients, based on objective adherence metrics and less time will be wasted trying to determine the veracity of self-reported adherence (Klugman et al., 2018). Additionally, the data gathered can be combined

with other data in predictive analytical models which will assist with accurate determination of future health needs, costs and outcomes (Cohen et al., 2014).

Various methods are used to balance the benefits, costs and risks of new technologies like smart pills. Cost-effectiveness and cost-benefit analyses can be performed which provide measurable indicators of beneficence and reduce purely intuitive and subjective decision making (Beauchamp and Childress, 2013). Cost benefit analysis (CBA) measures both the costs and benefits of a program or technology in monetary terms only, which allows direct comparison of various technologies; cost-effectiveness analysis (CEA) measures cost in monetary terms, but benefit is measured in non-monetary terms e.g. life years gained or quality adjusted life years (QALYs) gained (ibid.).

Other techniques employed to evaluate new technologies are risk assessment and risk-benefit analysis (RBA) (ibid.). A risk assessment involves the consideration of both risk probability and risk magnitude (ibid.):

		Magnitude of Harm	
		Major	Minor
Probability of Harm	High	1	2
	Low	3	4

Figure 4.1 Risk Assessment Tool (Beauchamp and Childress, 2013, p.233)

Risks in category 4 are likely to be regarded as inconsequential or de minimus, risks in category 2 and 3 require balancing with the potential benefits of the technology and risks in category 1 may be unacceptable unless substantial benefits accrue in specific situations (ibid.). Due to the proven physical safety, tolerability and acceptability of smart pills and adhesive patches (Plowman et al., 2018), the risks of physical harm from smart pill systems can be included in category 4. The potential harms of smart pills, such as overbearing surveillance, privacy concerns, data mismanagement and damage to trust relationships could be reasonably considered

to fall into categories 2 and/or 3. These risks should therefore be balanced against the expected benefits for individuals and for society, in a risk-benefit analysis (RBA) (ibid.).

The FDA reviewed and approved the Proteus™ ingestible sensor or IEM in 2012 (Plowman et al., 2018), and in 2017 the FDA approved the first smart pill, called Abilify MyCite™, which combines the Proteus sensor with the pharmacological ingredient aripiprazole (Klugman et al., 2018). The FDA applies various techniques of risk assessment and RBA, when assessing new medicines and technologies for market registration and when applying regulation (Beauchamp and Childress, 2013). For new drug applications, the FDA require three phases of increasingly large and complex clinical trials, which include RBA at each stage (ibid.), and therefore the beneficence and nonmaleficence of smart pills have been scrutinized to a major extent. The FDA and other regulators also perform ongoing monitoring of the safety of medicines, including smart pills, by collecting spontaneous and solicited safety reports and by performing post-registration safety studies in high risk medicines.

When performing CBAs, we assign a value to human life (ibid.). This is done to assist public and private health services to decide where to spend and apply limited resources. Different health programs will have different costs and returns of value (benefits) and standardized methods of measuring these costs and benefits are useful (ibid.). Two commonly used methods are discounted future earnings (DFE) and willingness to pay (WTP) (ibid.). Critics point out that these methods assign a purely monetary value to human life, which does not include other measures of the value of human life to society (ibid.).

DFE measures the monetary value of human lives by calculating what persons at risk of a certain illness of injury would earn in the future if they survived (ibid.). This unfairly prioritizes persons with higher earning potential (ibid.). WTP is a measure of "how much individuals would be willing to pay to reduce the risks of death, either through their revealed…or expressed preferences" (ibid. p.238). Weaknesses of WTP method include inaccurate understanding of the risks involved by affected persons, and misinterpretation of persons' expressed preferences (ibid.).

A method which is surpassing the use of DFE and WTP, is the measurement of quality adjusted life years (QALYs), which does not reduce the assessment of value to purely monetary terms (ibid.). The National Institute for Health and Clinical Excellence (NICE) performs evaluations of new medicines and technologies in the United Kingdom's healthcare sector using QALYs, which it defines as a measure of both the length of life and the quality of life (ibid.). The life years gained due to a medical technology are estimated and the years gained are then weighted for quality of life (ibid.). QALYs are based on utilitarian ethical theory, which is an important approach when measuring public health programs, as utilitarians insist on the best balance of healthcare outcomes amongst the entire population. However, QALYs may discriminate against the elderly, and the method fails to prioritize the value of each individual life saved, versus saving fewer lives with higher life expectancy (ibid.). CEA and QALY methods may clash with the duty to rescue, although they are all based on the principle of beneficence (ibid.).

In order to determine how their impact compares with other healthcare interventions competing for the same resources, smart pill programs will need to be rolled out in South Africa and be subjected to local CBA, CEA and risk analyses, especially the assessment of local data privacy protection infrastructure and regulation. South Africa has large HIV and TB treatment programs and it can be expected that smart pills will improve adherence to treatment, which will result in numerous benefits, including reduced medicine wastage, reduced infectious disease spread, better healthcare resource utilization, and improved health outcomes for patients and the population. The costs of smart pills versus regular pills will need to be assessed relative to the costs saved, to determine the cost effectiveness of smart pill programs. The principle of justice applies to this consideration and is discussed next.

4.5 Justice

Beauchamp and Childress (2013) describe the concept of justice as the fair treatment of persons according to what is due to them. They define the term distributive justice as the "fair, equitable and appropriate distribution of benefits and burdens determined by norms…of social cooperation" (ibid. p.250). There are numerous theories of justice, but all rest on the principle of formal justice, attributed to Aristotle: treat equals equally, and treat unequals unequally (ibid.). This principle is

formal, because it does not provide specific criteria to determine who are equals and who are not (ibid.). Material principles of justice are necessary to determine the relevant properties and criteria for the just allocation of benefits and burdens (ibid.). The principle of need is an example of a material principle of justice, which helps to shape public policy for access to healthcare (ibid.). For example, the provision of free healthcare to the poor and indigent is an example of distributive justice based on the principle of need.

There are six theories of justice that help us to identify the relevant material principles of justice to apply in various areas of welfare provision, public health, healthcare and policy development (ibid.). Four theories are regarded as traditional, including utilitarian, libertarian, communitarian and egalitarian theories; capabilities and well-being theories are modern theories (ibid.). Utilitarian theories stress the importance of criteria which maximize social utility or welfare. Libertarian theories maximize social and economic liberty by highlighting rights and fair procedures. Communitarian theories emphasize fair distribution based on the needs of moral communities. Egalitarian theories promote equal liberty and equal access to the goods that all rational persons value. Capabilities theories establish which capabilities and freedoms are required and how to protect them. Well-being theories focus on the essential elements of well-being, like health, and how to promote them (ibid.).

Utilitarian theories, developed in the nineteenth century by philosophers John Stuart Mill and Jeremy Bentham, promote societal welfare based on the best balance of value over disvalue (ibid.). The principle of distributive justice is an important principle in the maximization of utility. For utilitarians, a just healthcare intervention is one that promotes a good overall outcome for society. In the assessment of new technologies, utilitarians measure the costs, benefits and risks, using CBAs and RBAs, and compare different health programs to determine their relative cost effectiveness. For utilitarians, smart pills are just if they provide a net balance of benefit to society and are cost effective.

Libertarian theories are based on the importance of persons' rights to liberty and property, through application of just procedures (ibid.). The prominent libertarian philosopher, Robert Nozick, promotes a theory of justice in which the only time a government acts justly is when it acts to protect the rights to liberty and property of its

citizens (ibid). Whereas utilitarians focus on outcomes, libertarians focus on the lawful and just application of fair processes (ibid.). For libertarians, smart pills are just if they are available to those patients who freely wish to make use of them. From a libertarian view of justice, smart pills should not be allowed to infringe on the liberties of persons: privacy rights must be protected, and governments and funders may not coerce patients to make use of smart pills against their wishes.

Egalitarian theories emphasize that "all humans must be treated as equals because they are created as equals and have equal moral status" (ibid. p.256). However, seventeenth-century egalitarian philosophers such as John Locke and modern-day philosophers such as John Rawls and Norman Daniels, recognize that all persons cannot be treated as equals. They argue for qualified egalitarian theories based on distributive principles that insist on certain basic equalities, while allowing for certain inequalities (ibid.). John Rawls' Theory of Justice, published in 1971, recognizes two key principles: equal respect for persons and fairness. The first principle implies that persons should enjoy the maximum basic liberty that does not conflict with another persons' liberty. Fairness implies that society should reduce barriers to equality of opportunity (ibid.).

Rawls' and Daniel's theories form the basis of many national and international health policies. Illness and disability are regarded as "undeserved" (ibid. p.257) barriers to fair and equal opportunity, therefore society is obliged to provide access to healthcare and to heal illness and to correct disability. All people should be able to access to basic and adequate healthcare; more sophisticated and costly levels of healthcare will depend on available resources (ibid.). Egalitarians may argue that smart pills are too expensive to be justified as a basic healthcare initiative. If smart pills' higher acquisition costs are offset by savings from reduced medicine wastage and better health outcomes, then this argument is weakened.

Communitarian theories prioritize the common good over individuals' rights (ibid.). Communitarian philosophers like Charles Taylor and Daniel Callahan emphasize the importance of the communal and social aspects of life. Society should determine what goods are relevant for the community as a whole and reduce the focus on individual autonomy. Individual rights are secondary to common and communal goals such as welfare, common purpose and social constructs such as citizenship,

religious and cultural traditions (ibid.). Communitarian policy may support smart pills due to positive societal impact such as cost savings, control of TB and HIV and better health outcomes, and would allow for some risks to personal privacy.

Capabilities theory describes an approach to justice which emphasizes core capabilities which are essential for a person to achieve a state of functional well-being (ibid.). The theory was initially proposed by Amartya Sen and further developed by Martha Nussbaum. It is now applied in the fields of bioethics and also addresses issues of justice for the poor and disabled (ibid.). The theory emphasizes ten core capabilities (ibid.):

1) Life – to live a life of good quality and duration.
2) Bodily health – good health, food and shelter.
3) Bodily integrity – to move freely, protection from violence, freedom of choice about our bodies.
4) Senses, imagination and thought – freedom of thought, expression, education, full use of senses.
5) Emotions – to develop and experience the full range of human emotions.
6) Practical reason – to develop one's own conception of good and to plan one's life.
7) Affiliation – to live socially in the respectful company others.
8) Other species – to have concerns for animals, plants and nature.
9) Play – to play and enjoy fun activities.
10) Control over one's environment – to be a participatory citizen and make political choices which affect one's life and property.

Martha Nussbaum writes that these capabilities are essential for human dignity and flourishing. They should be protected and provided for, at least to a certain threshold (ibid.). Society should provide the circumstances and resources for these capabilities to be developed and protect them from violence and obstruction. The theory is global, and Nussbaum emphasizes the equality of political opportunity for all citizens in the world (ibid.). With reference to the capabilities listed above, smart pills can be considered just, as long as they are not used to infringe on peoples' freedom of choice and do not infringe on bodily integrity. Smart pills can improve health outcomes, and this affirms the capabilities of bodily health and life.

Whereas capability theory focuses on the capabilities and opportunities required for well-being, well-being theories focus on well-being itself (ibid.). Powers and Faden argue for six key measures of well-being (ibid.):

1) Health
2) Personal security
3) Reasoning
4) Respect
5) Attachment
6) Self-determination

While similar to the capabilities listed in capability theory, these six dimensions of well-being are not merely capabilities to pursue, but are fundamental states of being, in a just society. It is not sufficient for a just society to aim to achieve the capability to be healthy, but it is required to actually achieve the state of being healthy (ibid.). Powers and Faden argue that just policies must reduce inequality in the world, especially addressing the inequalities that poverty brings (ibid.). It is clear that the dimension of health is critical when developing health policy, but the other five dimensions are also equally important and must be considered together with heath when developing just healthcare policies (ibid.). Smart pills may assist to improve the health of populations, especially poor persons who suffer from high rates of infectious disease like HIV and TB, provided they are accessible to those who need them and provided they do not harm personal security, and self-determination. This can be ensured by creating suitable informed consent processes and robust data privacy controls.

All these theories provide information which is useful when allocating resources for healthcare and when developing healthcare policies. Cost effectiveness and cost-benefit analyses are based on the utilitarian goal of providing the greatest health benefits to society in a cost-effective way. This utility driven approach must be balanced with important considerations such as respect for the elderly, children and the disabled. While utilitarian outcomes remain a critical driver of healthcare policy, the egalitarian theories support fairness and the preservation of individual's rights

and due process. The modern theories emphasize the importance of the innate capabilities and dimensions of well-being.

Smart pills are likely to be more expensive that the non-smart versions of the medicines. In the USA, the Abilify MyCite™ smart pills are double the price of the regular Abilify™ pills (Klugman et al., 2018). While the acquisition costs may be increased, the potential for financial savings is impressive. Improved medication adherence should result in reduced wastage of medicines and more prudent use of other healthcare resources, which would have been taken up by the management of the consequences of poor adherence (Iuga and McGuire, 2014). The potential exists for smart pill programs to become sustainable and self-funding. The savings delivered by enhanced adherence may offset the higher acquisition costs of smart pills to a significant degree. This could result in smart pill programs that are affordable in poorer communities, appropriately funded without impinging on resource allocation for other important healthcare programs.

4.6 Conclusion

In conclusion, the bioethical principles of Beauchamp and Childress provide an approach for the assessment of the ethical issues of smart pill technology. The principle of respect for autonomy compels smart pill providers to ensure patients are well informed of the risks and benefits and are given opportunities to consent and to withdraw their consent, at any time. The rights to privacy and confidentiality must be protected by well-designed data management systems and ethical oversight. The principle of beneficence has been proven to a large extent in the clinical trials of smart pills. The trials conducted to date provide good, initial evidence of improvements in adherence and health outcomes, but larger, long-term studies and local cost effectiveness and cost benefit analyses should be performed to confirm the precise benefits for patients and society in the local environment.

Nonmaleficence is assured from a pharmacological safety perspective. The ingestible event marker (IEM) digital microchip device has been proven to be safe for ingestion and there have been no serious adverse events reported (Plowman et al., 2018). The adhesive personal monitor (APM) patch can cause mild skin irritation in up to 12% of patients (ibid.), but future enhancements will enable the use of smart

watches and wrist-worn trackers to perform the functions of the APM and preclude the use of the APM adhesive patches. Potential harms such as invasions of privacy, data mismanagement and discrimination should be minimized with ethical data management and oversight. Aligned with the principle of justice, cost savings due to improved adherence and reduced medicine wastage could enable the cost-effective rollout of smart pills in South Africa's large HIV and TB treatment programs.

CHAPTER 5: A UTILITARIAN PERSPECTIVE

5.1 Introduction

In this chapter I will introduce the consequential ethical theory of utilitarianism and review smart pills from a utilitarian perspective. Much of the information in this research report has a utilitarian feel, as smart pills are designed to yield improved medication adherence, reduced medicine wastage, better health outcomes for patients and better control of infectious diseases such as HIV and TB and non-infectious diseases such as diabetes, hypertension and mental disorders. These are utilitarian goals to a large extent.

5.2 The Principle of Utility

> "'The greatest happiness of the greatest number is the foundation of morals and legislation.' Jeremy Bentham, Collected Works (1843)" (Rachels and Rachels, 2015 p.99)

The father of utilitarian ethics was English philosopher Jeremy Bentham (1748-1832), who reasoned that moral acts are not those acts commanded by God, but that morally right acts are those that create the most happiness in the world (ibid.). Bentham and his followers, James Mill and John Stuart Mill, argued that the Principle of Utility was the supreme moral principle. This principle states that morally right acts are those that create the most happiness and the least unhappiness possible (ibid.). This principle seems intuitive to us in the modern world, but it is important to note that this was revolutionary thinking in its time, because the European population of the day was profoundly religious, and most moral thinking and legislation stemmed from adherence to God's commands and observance of the Judeo-Christian biblical canon (ibid.). The shift from puritanical obeyance to a pursuit of pleasure and happiness, a hedonistic utilitarian principle, revolutionized moral philosophy (Beauchamp and Childress, 2013; Rachels and Rachels, 2015).

5.3 Utilitarianism is Consequentialist

Utilitarian theory regards the principle of utility as the ultimate moral principle. Morally right acts are those that produce the most pleasure or happiness. Because utility is a measure of the amount of happiness or pleasure produced, utility is a measure of outcomes or consequences. These types of theories are called consequentialist moral theories. All consequentialist theories align on the norm that the moral rightness or wrongness of an act depends on the "non-moral goodness of relevant consequences" (Darwall, 2008, p.27).

Where these theories differ, is on which outcomes and consequences are valuable. (Beauchamp and Childress, 2013; Darwall, 2008; Hare, 2009). Hedonistic utilitarians, like Bentham and Mill, believe that utility consists of pleasure and happiness, which are human desires. R.M. Hare proposes that classical utilitarian theory contains three main components: consequentialism, welfarism and aggregationism (Hare, 2009). Beauchamp and Childress add two more characteristics: utilitarianism is maximizing and impartial (Beauchamp and Childress, 2013).

Utilitarianism is consequentialist, because the moral rightness of an act is based only on the results or consequences of the act (ibid.). Indeed, nothing other than consequences matter (Rachels and Rachels, 2015). The theory is welfarist, because the intention is to create good outcomes for humans (and animals), and it is impartial, because the value of outcomes is measured by the sum of benefits and costs to all affected parties (ibid.). Utilitarianism is maximizing, because moral actions should achieve the greatest overall value achievable in the circumstances (Beauchamp and Childress, 2013; Darwall, 2008; Hare, 2009). When summing the consequences, each individual's happiness counts equally and all persons are morally equivalent (Rachels and Rachels, 2015).

5.4 Challenges to Utilitarianism

Despite the prima facie appeal of determining morality based only on consequences, most contemporary philosophers reject the classical, hedonistic form of utilitarian theory (Rachels and Rachels, 2015).

The first argument against classical utilitarianism examines whether happiness is the only thing that matters (ibid.). The hedonistic insistence on pleasure as the only goal of right action implies that morality is about how acts make us feel (ibid.). However, bad actions can occur without making someone feel bad. For example, if someone tells lies about you but you never find out and your feelings are not hurt – a hedonistic utilitarian will argue that the act of lying in this situation has not been wrong, because the lying did not hurt your feelings. However, most of us would agree that the act of lying about you in this case is still wrong, regardless of whether your feelings were hurt or not. Examples like these expose the classical, hedonistic utilitarian theory as being incomplete or incorrect, as things other than happiness or pleasure are valuable to us, such as friendship and loyalty (ibid.). Contemporary utilitarians propose additional valuable consequences, such as health, wisdom, love, beauty and art (Beauchamp and Childress, 2013; Darwall, 2008).

The second argument against utilitarianism questions whether consequences are indeed the only things that matter (Rachels and Rachels, 2015). Utilitarians contend that consequences are the only things that matter, and that nothing else is relevant when determining the rightness of an act. However, there are numerous examples where good consequences may be achieved by acts that are damaging to individuals and their rights. If a peeping tom spies on someone undressing, but the victim is unaware, the utilitarian account is that the act of spying is not immoral, because the peeping tom increased his happiness and the victim was unaware and therefore her happiness was not diminished (ibid.). Similarly, to falsely accuse and convict someone of a crime to appease an angry mob who are seeking revenge, while delivering a good outcome on balance, clashes with the rights of the individual being falsely accused (ibid.). These examples demonstrate that utilitarianism may clash with our ideas of justice and individual persons' rights (ibid.). The woman who was spied on, had her right to privacy infringed by the peeping tom, and the falsely accused was denied his rights to a fair trial. Utilitarianism seems to support the "tyranny of the majority" (ibid. p.116) and promotes the concept that individuals' rights are unimportant, if most people benefit from an action.

The third argument against utilitarianism is that the theory does not accommodate retrospective reasons, for example promises and commitments (ibid.). If only consequences matter, then promises can be easily broken and we will not act to

preserve our commitments to others that we made in the past. With its focus on future outcomes, utilitarianism seems to devalue the past (ibid.).

The fourth argument is that utilitarianism is too demanding of us (ibid.). If we are to be strictly impartial and regard each person's happiness as equal, we will be compelled to uplift everyone less fortunate than us and we would eventually give all our own money away to charity. We would no longer pursue our own interests, hobbies and passions. While this is a noble and desirable goal, it cannot be expected from everyone. Philosophers call this type of act supererogatory, which means that it is beyond reasonable expectations (ibid). Additionally, we would destroy our personal and family relationships, as we would treat everyone impartially, including our loved ones (ibid.). We would treat a stranger's children the same as our own and care for family and strangers in the same way. This conflicts with our natural human emotions, our common sense, and our need for love, affection and family bonds (ibid).

5.5 Support of Utilitarianism

There are numerous arguments which may be provided to defend utilitarianism. Firstly, it can be contested what an act's eventual outcomes will be (ibid.). For example, the repeated act of bearing false witness against innocent persons will eventually lead to the failure of the criminal justice system and a revolt against the courts, despite it having a positive effect in the short term. Complete assessment of all possible outcomes over time can lead to a different measure of consequences and thus not support acta which may at first seem moral.

Another key defense of the theory is the adoption of an updated form of utilitarianism called rule-utilitarianism (Darwall, 2008; Hare, 2009; Rachels and Rachels, 2015). Classical utilitarianism, now called act-utilitarianism, depends on the outcomes of each particular act. By this account, it may be right to bear false witness against an innocent man, if an angry mob is thereby appeased. However, if we modify the theory to consider the consequences of rules, rather than of individual acts, we can mitigate against good consequences being used to justify bad acts (ibid.). This modified utilitarian theory seeks to understand what rules, rather than acts, will deliver the most happiness. A rule utilitarian will argue that a rule against bearing

false witness will lead to more happiness in most cases. The shift from justifying individual acts to justifying rules of conduct, that provide the most happiness in most circumstances, helps to bring the utilitarian theory in line with our common sense judgements (Rachels and Rachels, 2015).

5.6 Utilitarian Assessment of Smart Pills

Poor adherence to treatment is extremely costly to society and harms the health of patients. Annual losses in the USA attributed to poor treatment are estimated at 300 billion dollars (Iuga and McGuire, 2014). Studies have shown sub-optimal levels of adherence in South Africa's large HIV and TB treatment programs, which leads to poor clinical outcomes for patients and increased spread of these diseases (Georgette et al., 2016; B. Nachega et al., 2011; Omonaiye et al., 2018).

Smart pills are expected to deliver important benefits to society. Smart pills have the potential to enhance patients' adherence to medical treatment in chronic diseases. This can improve clinical outcomes, reduce disease complications, improve the overall health, quality of life and productivity of patients, and reduce the spread of serious infections. Smart pills have the potential to improve the effectiveness of large treatment programs, reduce wastage of medication and facilitate cost-effective WOT, instead of costly DOT, in TB programs (Au-Yeung and DiCarlo, 2012). Improved medication adherence should lead to more appropriate use of other healthcare resources. Physicians can verify if a patient's lack of response to treatment is due to an adherence problem, or something else. Data gathered by smart pill systems will be added to big data systems, together with other forms of healthcare data such as EHRs (electronic health records) and can contribute to predictive analytical models for healthcare improvements on individual patient and policy levels.

From a utilitarian perspective, these benefits outweigh the risks of data mismanagement, privacy concerns and damage to trust relationships between physicians and patients. Smart pills will be merely one type of device amongst a large number of connected medical and non-medical devices, that require ethical data governance. Robust privacy regulations are coming into effect all over the world, including South Africa. Relationships between healthcare providers and patients are constantly evolving, as the science and art of medical practice evolves. The

increased acquisition costs of smart pills can be offset against the significant savings expected from reduced wastage and improved healthcare outcomes.

The potential for smart pills to improve the cost effectiveness of the large HIV and TB treatment programs, and improve clinical outcomes in these diseases as well as common, non-infectious diseases such as hypertension, diabetes and mental disorders, are particularly appealing in South Africa from a utilitarian point of view. This utilitarian approach to smart pills aligns with the principles of utility and beneficence, however the protection of individual persons' autonomy, rights to privacy and confidentiality, may require additional theoretical ethical input from theories of right action, such as Kantian deontology.

CHAPTER 6: SMART PILLS AND UBUNTU

6.1 Introducing Ubuntu

Ubuntu is an African moral philosophy and tradition that has developed over thousands of years and is culturally embedded in Sub-Saharan African communities (Metz, 2007; Nussbaum, 2003; Tangwa, 1996). Ubuntu is a communitarian ethic, which places great value on the wellbeing of the community, and which values the community more than the individuals who make up that community (Chuwa, 2014; Tangwa, 1996). While the individual's rights are recognized within ubuntu, it is the community's rights which take precedence (ibid.). A person's value or personhood is measured with reference to the social and communal context (Nussbaum, 2003). Rather than personal autonomy, which is a prevalent consideration in Western ethical theories such as Kantianism, in ubuntu ethics it is a person's connectedness which is the key consideration (ibid.).

This philosophy is well articulated in the Nguni proverb: *Umuntu ngumuntu ngabantu*, which means *A person is a person through other persons*.

Despite Godfrey Tangwa's caution that ubuntu cannot be reduced to a singular ethical principle, a technique favoured by western philosophers (Tangwa, 1996), Thaddeus Metz (2007) developed a general principle which encapsulates the ubuntu ethic regarding right action:

> "An action is right just insofar as it produces harmony and reduces discord; an act is wrong to the extent that it fails to develop community" (p.334).

Ubuntu prioritizes the value of communal harmony and bases human rights on people's capacity for social relations, not on people's capacity for autonomy (Metz, 2011). Additionally, ubuntu recognizes the value of the Earth - nature, plants, animals and the environment (Tangwa, 1996). Ubuntu's ideal of harmony extends beyond people's relationships with other people, to people's relationships with the elements of nature and even God, in an ethic of "eco-bio-communitarianism" (ibid. p.192).

6.2 Ubuntu and Technology

Compared to traditional Western ethical theories such as deontology, consequentialism and Aristotelian virtue ethics, there is a relative lack of English language publications on ubuntu in the bioethical literature (Metz, 2007). There is little written in the literature about ubuntu and technology. An article on the CNN website describes how African entrepreneurs are embracing the communal and collaborative spirit of ubuntu to help drive the development of technology based companies across Africa (Uanikhehi, 2018). Due to the lack of infrastructure, unreliable electricity supply and connectivity challenges, tech startups are embracing the communal and collaborative spirit of ubuntu, to support each other to overcome these challenges (ibid.). They share training spaces, collaborate to overcome power supply constraints and use digital technologies to establish online groups for training and sharing ideas (ibid.).

6.3 Ubuntu and Smart Pills

Ubuntu may be considered to support technology such as smart pills. The ability for patients to share information about their treatment adherence is supported by ubuntu, which places less emphasis on individual rights to privacy and more emphasis on communal decision making. Enhanced collaboration between healthcare providers and patients fits well within the framework of ubuntu communitarianism. Since smart pills may improve healthcare outcomes and limit the spread of serious infectious diseases, smart pills are helpful to the community. Reduced wastage of medicines and more cost-effective TB programs, with WOT replacing DOT, are also community focused benefits. These benefits of smart pills are aligned with ubuntu as an eco-bio-communitarian philosophy.

CHAPTER 7: CONCLUSIONS

7.1 Medication Adherence is Suboptimal

In both the clinical trial and community settings, patients' adherence to medical treatment is suboptimal. This leads to poor health outcomes, especially in diseases such as HIV and TB which require extremely high levels of treatment adherence to ensure optimal disease control. Medicine wastage and increased healthcare resource utilization due to poor compliance are extremely costly. South Africa has large, national HIV and TB treatment programs and would benefit from more cost-effective compliance monitoring. The WHO recognizes the need to improve patients' compliance to treatment.

7.2 Objective Adherence Data

Smart pills are a new pharmaceutical-device combination technology. They combine a microchip sensor with active pharmaceuticals and are able to send a signal, after being swallowed, to a receiving patch device worn on the patient's body. Smart pill systems record information such as medication name, type, dosage and formulation. They provide objective medication adherence data by directly detecting medication ingestion events. The adherence data gathered by smart pills can help patients to improve their adherence to treatment and improve clinical outcomes and reduce the wastage of medicines. These adherence data can be combined with other physiological data collected from wearable and implanted devices, data from EHRs, claims databases and other data sources. These big data collections contribute to the formulation of predictive analytical models based on clinical and digital data points.

7.3 Accuracy and Effectiveness

Smart pills have been tested in numerous clinical trials. They demonstrate high levels of accuracy and precision and are able to detect numerous different smart pills ingested at once. Patients with non-communicable diseases such as hypertension, diabetes and hypercholesterolaemia have shown improvements in adherence, clinical parameters and disease control. More trials are needed to determine smart

pills' magnitude of impact on adherence levels, especially over the long term, although the initial signals are promising. The cost-effectiveness of smart pills has been proven in studies of diabetics, hypertensives and TB patients, where WOT may be a cheaper and more effective form of adherence monitoring than DOT.

7.4 Safety and Convenience

Smart pills are pharmacologically safe and well tolerated. They hold no additional pharmacological safety concerns over the regular version of the medicines and no serious adverse events have been reported. The most common side effect is skin sensitivity to the APM, which is not related to the actual smart pill IEM itself. It is expected for the APM to be replaced in the near future by the use of smart watches and exercise trackers to detect IEM ingestion, which will alleviate the need to wear an adhesive APM. In the clinical trials, the majority of patients and providers found the smart pill systems to be convenient and easy to use, including patients with chronic mental disorders.

7.5 Ethical Concerns

Ethical concerns generated by smart pills primarily relate to threats to personal autonomy due to digital surveillance and the resultant risks to privacy and the confidentiality of data. The specter of a digital panopticon looms, with the increasing number of connected devices surveilling our every move. Appropriate patient consenting procedures with clear information about the smart pills' functions, data usage and management must be provided to patients.

Device reliability and accuracy are vitally important to maintain patients' trust in smart pills. Smart pills can be expected to affect the trust relationships between clinicians and patients, as the veracity of self-reported adherence can be objectively verified. HCPs may feel that they are losing some of their professional autonomy, if smart pills' data are used to monitor clinicians' prescribing and monitoring habits. It is a concern that healthcare funders and payors may discriminate against patients that are poorly adherent. Smart pills are likely to be more expensive than the regular versions, but they can deliver cost savings by reducing wastage and improving

healthcare resource utilization. Access and availability of smart pills to poorer patients and communities are important considerations.

7.6 The Principle-Based Approach

Smart pills can be assessed using Beauchamp and Childress's principle-based approach to bioethics. The safety of smart pills aligns with the principle of non-maleficence. The excellent tolerability profile and minimal adverse event rate make smart pills themselves very safe. Smart pills have the potential to affect patients' personal autonomy due to data mismanagement, therefore ethical oversight of data collection is required, with particular consideration of local concerns about health and personal data management in LMICs. Database infrastructure and processes should be designed to enable oversight by digitally fluent bodies such as ethics committees data management committees. Personal autonomy and privacy rights must be protected by suitable consenting processes, clear user agreements, generous opt-in and opt-out opportunities and ethical data infrastructure and oversight. Smart pills' benefits, such as improvements in adherence, better clinical outcomes and disease control are aligned with the principle of beneficence. Aligned with the principle of justice, cost savings due to reduced medicine wastage and more prudent utilization of healthcare resources, could enable the cost-effective rollout of smart pills in South Africa's large HIV and TB treatment programs

7.7 A Utilitarian Perspective

Smart pills are justified in South Africa from a utilitarian point of view. As a consequentialist ethical theory, utilitarianism considers the rightness of an act based only on the outcomes. Smart pills have the ability to improve adherence, which is necessary for effective disease management of HIV and TB and to prevent the emergence of highly resistant strains. The potential for more cost-effective digital patient monitoring in South Africa's large HIV and TB treatment programs, using WOT compared with traditional DOT, is an important consideration for local healthcare providers. Additional outcomes include reduced medicine wastage and improved clinical outcomes in diseases such as diabetes and hypertension. The potential cost savings from reduced medicine wastage, reduced disease complications and reduced hospital admissions, can offset the increased acquisition

costs of smart pills. From a utilitarian point of view, these important healthcare gains justify minor losses in privacy and confidentiality, but ethical data management and prevention of unwanted surveillance remain important considerations.

7.8 Ubuntu

The local ethical philosophy and culture of ubuntu can also be considered to support smart pills in South Africa. Ubuntu is a communitarian approach to ethical conduct and prioritizes the well-being of the community. Individual autonomy and rights are respected but are viewed in the frame of communal and social life. Shared decision making and collaboration between all members of the community are encouraged. Ethical conduct is measured by the impact on the community. Digital technologies and mHealth programs are being employed in African communities to help solve a variety of healthcare problems. Many of the benefits of smart pills are communal: better control of HIV and TB can prevent resistance and spread, which assist with the health of the entire community. WOT can be used as a cost-effective replacement for DOT, which can deliver cost and efficiency savings to the community. In ubuntu culture, communities may be less concerned about personal autonomy and privacy rights than Western communities.

7.9 Limitations of this research

This research is purely normative and lacks an empirical component. Empirical research is required to validate the argument proposed in this research report. To validate the results seen in American and European studies, local evidence of smart pills effects on treatment adherence, clinical outcomes and cost implications should be generated in the South African healthcare environment. Qualitative research may provide more information on how smart pills are viewed in the ubuntu tradition. This research report is purely an ethical argument; further research of the legal issues affecting smart pills is required.

7.10 Recommendations

Smart pills have the potential to improve treatment adherence in South Africa's large HIV and TB treatment programs. Studies of smart pills should be conducted in South Africa, to determine the levels of patient and healthcare provider acceptability and the impact of smart pills on clinical and economic parameters. To prevent smart pills from infringing on patient autonomy, the data generated by these devices must be protected. Digital governance at all levels of the healthcare system is required and regulators, researchers, clinicians and ethics committees should ensure that their understanding of digital technologies and data management in healthcare is adequate to provide the necessary ethical oversight of smart pills and other data generating devices. A review of the legal framework is required to understand if any legal gaps exist and what updates are required to support the ethical oversight of smart pills and electronic adherence data.

7.11 Summary

In summary, smart pills are an important new medical device technology. The key benefit of smart pills is to monitor and improve patients' adherence to their medical treatment. This can lead to improvements in clinical parameters, disease control and health outcomes. Numerous clinical trials have been conducted in diseases such as TB, HIV, diabetes and hypertension which demonstrate high levels of detection accuracy, safety and convenience. The ethical concerns of smart pills relate to personal autonomy, privacy rights, confidentiality, data management and trust relationships between clinicians, patients and other stakeholders. Ethical data management and robust consenting processes are important considerations. Smart pills are ethically justified in the South African setting from a bioethical principle-based approach. The numerous benefits of smart pills are particularly appealing from a utilitarian perspective and the local ethical practice of ubuntu communitarianism may also support smart pills' potential to enhance communal healthcare.

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APPENDICES

Appendix A: Table of Published Clinical Trials of Smart Pills

Indication		n	Smart Pill type	Design	Objectives / Results	Comment	Citation
Healthy Volunteers		20	ID-Cap™ (eTectRx)	Open-label, single-arm exploratory study 4 weeks	Positive detection accuracy (PDA, accuracy of detected ingestions vs directly observed ingestions) = 100% Accurately measured adherence No adverse events	Exploratory study	Flores GP, Peace B, Carnes TC, et al. 2016
		10	Proteus™	Feasibility study Single-arm, open-label 8 days To measure PDA (positive detection accuracy) = detected ingestion / observed ingestions	PDA = 99% No adverse events	Feasibility study	Di Carlo L, Moon G, Intondi A, et al. 2012
Bioequivalence studies		24	Proteus™	1:1 randomized, single-dose, crossover, pharmacokinetic study, combining IEM with ARVs 72h	Confirmed bioequivalence of Tenofovir and Emtricitabine co-encapsulated with Proteus™ IEM	Healthy volunteers (HIV negative)	Ibrahim ME, Brooks KM, Castillo-Mancilla JR et al. 2018
		10	ID Cap™ (eTectRx)	Longitudinal, single-dose, crossover, pharmacokinetic study, combining IEMs with ARVs	Confirmed bioequivalence of Tenofovir over-encapsulated with ID Cap™	Healthy volunteers (HIV Negative)	Chai PR, Pereira LM, Guruprasad DJ et al. 2019
Mixed 111	Healthy	30	Proteus™	Four separate prospective, observational studies	High adherence rates (>95%) Reliability (=PDA) = 97.1% compared with direct observation Well tolerated	Pilot studies Short duration Funded by Proteus Biomedical Inc.	Au-Yeung KY, Moon GD, Robertson TL, DiCarlo LA et al. 2011
	Tuberculosis	30* *same patient cohort as Belknap et al.					
	Heart failure	8					
	Hypertension	43					
Cardiovascular		21	Proteus™	Prospective, single-	System-Determined	Demonstrate	Thompson

Disease			arm trial 12 weeks	Adherence (≥80%) = 57% vs. Self-reported adherence of 90% at baseline Safe. One AE: contact dermatitis with sensor patch High levels of acceptability	d the gap between patient self-reporting and digitally measured adherence Older population but high level of device acceptance (due to permeation of mobile phone technology into society, incl. mHealth) Device measures adherence and may increase adherence	D, Mackay T, Matthews M et al. 2017
Hypertension and Type 2 diabetes	109	Proteus	Three-arm, cluster randomized study of smart pill system (4 or 12 weeks) (n=80) versus usual care (n=29) Pilot study Primary endpoint to determine effect on SBP No comparison of adherence between the groups (but in the literature the average adherence rate is 50%)	Improvements in BP, HBA1C, LDL-C for smart pill groups vs. usual care Adherence ≥ 80% while using smart pill system Well tolerated with 12% of patients experiencing self-limited rash at site of adhesive sensor patch No SAEs >90% of patients reported 1) The system was: -easy to learn -easy to incorporate into their daily routines 2) The data was useful to manage and improved their health 3) Sharing their data with their HCP helped them	Smart pill system can help lower BP, HBA1C (non-significant change) and LDL-C Promotes patient self-care and HCP engagement Assists HCP decision making	Frias J, Naunihal V, Raja P, et al. 2017

				understand their treatment plan Most patients (81%) did not mind wearing the adhesive sensor patch		
Schizophrenia	49	Proteus™	Prospective, open-label trial 8 weeks	82% of patients able to complete the tasks with no or minimal help APM worn 70% of the time Adherence = 59% (detected / expected ingestions) Patient (78%) and Healthcare Professional (HCP) satisfaction (72%)	Assessed the tasks of application of wearable sensor (APM) and pairing with smartphone	Peters-Strickland T, Pestreich L, Hatch A, et al. 2016
Schizophrenia and bipolar mood disorder	28	Proteus™	Observational, 2-site Pilot study 28 days	Positive Detection Accuracy (PDA, accuracy vs directly observed ingestions) = 95% Mean adherence rate = 74% Safe and generally well tolerated 18% non-serious, device-related, skin irritation at site of APM 70% of patients found the concept easy to understand	Pilot study 28 days	Kane JM, Perlis RH, DiCarlo LA, et al. 2013
Tuberculosis	14	Proteus™	Randomized, bioequivalence study Compared wirelessly observed therapy (WOT) to directly observed therapy (DOT)	Accurate adherence measurement (PDA = 98%) WOT leads to more daily doses ingested overall than DOT Safe and bioequivalent to standard drug	Authors conclude that WOT is a new “paradigm” in TB therapy (USA)	Browne S, Haubrich R, Moser K, et al. 2015
Tuberculosis	30* *Same patient cohort as Au-Yeung 2011	Proteus™	Prospective, non-randomized, descriptive study	PDA of WOT compared with DOT = 95% No difference in accuracy for different BMIs	WOT could be a replacement for DOT in monitoring	Belknap R, Weis S, Brookens A, et al. 2013

				Specificity = 97% (3 false signals) Identification Accuracy (of multiple sensors with unique signatures ingested simultaneously) = 100% Well tolerated with minimal adverse events: 4 device-related AEs: 1 nausea and 3 mild skin rashes	TB treatment USA	
Hypertension	167	Proteus™	Registry / RWE 2 weeks	Successfully identified 1/3 of patients who could achieve BP control without therapy escalation Improved BP control: SBP and DBP decreased overall Well tolerated: minor skin irritation in 8%, GI symptoms in 3% Usable: 92% of patients did not mind wearing the sensor patch 87% reported a good experience with the ingestible	UK, NHS 75% of practices found the system improved their interactions with patients	Naik R, Macey N, West RJ et al. 2017
Hypertension	39	Proteus™	Non-randomized, open-label, community-based, real-world study 2 weeks 15 commercial pharmacies	BP decreased overall Inadequate use of prescribed therapy = 32% (i.e. 32% of patients had less than 80% adherence) Collaborative disease management with patients and pharmacists Patient usability of devices and apps was good	Root cause of uncontrolled BP identified in all patients: almost 1/3 had poor adherence and 2/3 had pharmaceutical resistance	Noble K, Brown, K, Medina M, et al. 2016
Type II Diabetes	5	Proteus™	Prospective, single-arm, observational, cohort study 37-42 days	Adherence and sleep patterns integrated into data-rich visualizations in natural setting	Small patient number	Browne SH, Behzadi Y &

						Littlewort G. 2015
Opioid ingestion patterns for acute fracture pain	16	ID Cap™ (eTectRx)	Descriptive, pilot study Open-label, single-arm, 1 week Opioid naïve	Direct monitoring of opioid ingestion Accuracy = Detected ingestions / pill counts = 84% (missed ingestions due to not wearing the APM)	Digital monitoring may provide information on opioid use and patient behavior in pain management	Chai PR, Carreiro S, Innes BJ et al. 2017
Kidney transplant	20	Proteus™	Pilot study Prospective, single-arm open-label 12-week	Detection accuracy = 100% Two IEM Detection rate = 99.3% Taking adherence = 99.4% Safety: no SAEs 7 patients had skin reactions to APM		Eisenberger U, Wüthrich RP, Bock A, et al. 2013
Economic Model in comorbid hypertension, diabetes and hypercholesterolemia	Not reported (NA)	Proteus™	Economic impact model	Reduced disease complications Cost savings due to reduced outpatient and inpatient services	US payer perspective	Kim YA, DiCarlo RP, Virdi N & Park H. 2015
Tuberculosis (active TB)	NA		Cost model comparing cost of WOT vs. DOT 4 months Retrospective review	WOT cost-to-treat is 36% of 7-day DOT WOT cost-to-treat is 71% of 3-day DOT	Cost of WOT TB treatment appears substantially cheaper than DOT	Au-Yeung KY, DiCarlo L. 2012

Appendix B: Ethics Clearance

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG | HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL

Human Research Ethics Committee (Medical)

Research Office Secretariat:
Faculty of Health Sciences, Phillip Tobias Building, 3rd Floor, Office 301/2/4, 29 Princess of Wales Terrace, Parktown, 2193
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Office email: HREC-Medical.ResearchOffice@wits.ac.za
Website: www.wits.ac.za/research/about-our-research/ethics-and-research-integrity/

Ref: W-CBP-191104-2 04/11/2019

TO WHOM IT MAY CONCERN:

Waiver: This certifies that the following research does not require clearance from the Human Research Ethics Committee (Medical)

Investigator: Dr Gary Sopher (Student number: 9400819V)

Supervisor: Dr Jillian Gardner

Department: Steve Biko Centre for Bioethics

Project title: The ethics of smart pills in South Africa

Reason: Information used will be in the public domain. No human participation/or human data will be used.

Doctor CB Penny

Chairperson: Human Research Ethics Committee (Medical)

Copy – HREC (Medical) Secretariat: Rhulani Mkansi and Zanele Ndlovu.

Appendix C: Turnitin Report

Submission date: 18-Dec-2019 08:15AM (UTC+0200)
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Word count: 24941
Character count: 147565

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