“Evidence, truth, reality and power: A Foucauldian analysis of the ethics of testing and using novel medical devices”

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Signed: Zeelha Abdool **Date: December 2018**

Abstract:

From the onset of time, human beings have used substances in all forms and shapes to promote health. Prior to the nineteenth century, traditional folk medicine, religious ceremonies, magical practices, herbs and the balancing of the 'humors' were popular methods of healing amongst others practiced by the Greeks. The various earlier Egyptian papyri detail the ancient Egyptian concepts of disease and cures, various ailments and anatomical observations. Informed consent was simplistically manifested by patient trust and cooperation. The nineteenth and twentieth centuries witnessed significant medical advancement is all spheres of medicine i.e. opening of hospitals, training of doctors, era of antibiotics, development of universities and research centres. Since the quest for science and health was a priority, doctors earned a high social standing and began to enjoy the privileged status in society.

This resulted in the birth of a heavily professionalized discipline. Developing Michel Foucault's ideas, we may regard that discipline is a specific technique of power, which aims to objectify human beings using three main practices i.e. dividing practices (e.g. birth of hospitals and asylums), scientific classification (medicine regarded as a discipline) and subjectification of human beings (humans considered as subjects). Using Foucauldian ethics, this thesis aims to deconstruct the power versus knowledge relationship between physicians and the healthcare industry in context of adopting novel medical devices.

The last century has been challenged by the invention of medical devices by the healthcare industry. Some of these medical devices have raised both scientific and ethical issues because patients suffered harm. The use of transvaginal mesh for pelvic organ prolapse is currently a global topic questioning how harm came to women. The rationale for mesh development, regulatory clearance and dissemination to society, and conflict with the four ethical principles is discussed. Three other gynaecological devices will also be the focus of this thesis.

The power of regulatory authorities to clear medical devices using a substandard clearance mechanism, and the power of the healthcare industry to employ vicious marketing strategies to physicians is critically analysed. Physicians as bodies of knowledge adopt these procedures with noble intentions. The implications of using novel medical devices are significant as physicians represent the final point of care for patients during which informed consent is finalized. The interplay between physicians and the healthcare industry illustrates the clash between the urge to 'develop' and market new technology (medical devices in this case) and the ethics of responsibility espoused by physicians to protect against harm, notwithstanding the role of regulatory authorities. Medical device innovation will continue to expand. Physicians aided by sound science and ethical principles have the responsibility to implement safe and efficacious treatment. As this may be not sufficient to prevent harm, the addition of virtue ethics and shifting of the power balance toward physicians is proposed.

Abstrak:

Vanaf die vroegste tye het die mens van geneesmiddels in alle vorme gebruik gemaak om sy gesondheid te bevorder. Reeds van die antieke Griekse tye en tot die 19e eeu was tradisionele geneesmiddels, godsdienstige seremonies, beroepe op die bonatuurlike, kruie en pogings om die ‘vier humorale stowwe’ in die liggaam te balanseer gangbare metodes. Nog voor die antieke Grieke is in ‘n groot verskeidenheid Egyptiese papyri besonderhede van die antieke Egyptiese konsepte van siekte en genesing, en anatomiese waarnemings opgeteken. Ingeligte toestemming is simplisties as vertroue in die geneser en samewerking deur die pasiënt beskou. Gedurende die 19e en 20e eeue was daar merkwaardige vooruitgang in alle sfere van geneeskunde: hospitale is geopen, dokters na behore opgelei, antibiotika ontdek en ontwikkel, en nuwe universiteite en navorsingsentra het tot stand gekom. Omdat die soeke na wetenskaplike ontwikkelings en gesondheid sosiale prioriteite was, verkry dokters buitengewone en bevoorregte sosiale status.

So ontstaan ‘n hoogs-professionele dissipline. In navolging van Michel Foucault se idees kan ons dissipline as as ‘n besondere vorm van magsaanwending beskou. Die doel is om persone te objektiviseer deur middel van drie meganismes: verdelende praktyke (soos die totstandkoming van hospitale en inrigtings), wetenskaplike klassifikasie (om geneeskunde as dissipline te klassifiseer) en die subjektivisering van persone (mense as ondergeskiktes te beskou). Deur aanwending van Foucault se etiese beskouing beoog hierdie tesis om die kennis-mag verhouding tussen geneeshere en die gesondheidsorg bedryf te dekonstrueer met verwysing na die aanvaarding van nuwe implanteerbare geneeskundige toestelle en apparate

Die ontwikkeling van sodanige innovasies oor die afgelope eeu het groot uitdagings meegebring, beide wat betref hul onderliggende wetenskap sowel as etiese kwessies omdat baie pasiënte by wie dit aangewend is benadeel is.

Die gebruik van transvaginale maas om pelviese orgaan prolaps te behandel het baie vroue benadeel, en die praktyk word tans wêreldwyd ondersoek. Die rasionaal vir die ontwikkeling van die maas, regulatoriese goedkeuring, die verspreiding na die samelewing , en die inherente konflikte met die vier bekende etiese beginsels word bespreek. Soortgelyke gebruik van drie ander ginekologiese innovasies word ook ondersoek.

Die tesis ondersoek ook die mag van die regulatoriese owerhede om sulke toestelle goed te keur, ‘n ontoereikende goedkeuringsmeganisme ten spyt, en die aggressiewe bemarkingsmag van die industrie teenoor geneeshere. Geneeskundiges as kundiges aanvaar hierdie innovasies met edele doelstellings. Die gebruik van hierdie geneeskundige innovasies hou betekenisvolle implikasies in omdat geneeskundiges die finale besluitnemers oor hul aanwending is, en ingeligte toestemming vir hul gebruik verkry.

CONTENTS:

DEDICATION

I dedicate this work to all my patients who have taught me the value of care.

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I would like to express my gratitude to Professor Barend Gerhardus Lindeque for inspiring and introducing me to the world of ethics, and to Professor Anton van Niekerk for his ‘state of the art’ philosophy curriculum ensuring quality ethical training.

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LIST OF ABBREVIATIONS:

AMA	American Medical Association
CDC	Centre for Disease Control
CE	Conformité Européenne
CME	Continuing medical education
DOH	Department of Health
DOJ	Department of Justice
DTI	Department of Trade and Industry
EBM	Evidence-based medicine
HPCSA	Health Professional Council of South Africa
HSG	Hysterosalpingogram
MAUDE	Manufacturer and User Facility Device Experience
MCC	Medicines Control Council
MDMSA	Medical Device Manufacturers of South Africa
MISA	Medical Imaging Systems Association
NMR	Nuclear magnetic resonance
OB-GYN	Obstetrics and Gynaecology
PBC	Permanent birth control
PET	Positron emission tomography
PM	Power morcellators
PMA	Premarket approval
POP	Pelvic organ prolapse
RCTs	Randomized controlled trials
SA	South Africa
SAHPRA	South African Health Products Regulatory Authority
SALDA	South African Laboratory and Diagnostic Association
SAMED	South African Medical Technology Industry Association
SUI	Stress urinary incontinence
TVM	Transvaginal mesh
US	United States

US FDA	United States Food and Drug Administration
WMA	World Medical Association

LIST OF FIGURES:

Chapter 1: Introduction:

Medicine: reality of an evolving discipline:

The word ‘medicine’ is derived from Latin *medicus*, meaning ‘a physician’. A physician is regarded as a professional who has ‘professed a commitment to a particular way of life via applying a set of principles applicable to humanity’. The practice of medicine requires the acquisition of discipline-specific clinical expertise, maintenance of knowledge and skills, and adherence to practice and ethical guidelines (White, 2004:186-190 ; McKenna, 2012: 889-908). In essence, physicians accept the fiduciary responsibility for a ‘duty of care’ by primarily focussing on the patient’s interest. It is this notion of responsibility reflected in our behaviour that develops us into moral agents to practice responsibly and professionally (Bauman, 1993).

The discourse on medical professionalism is vast and indeed complex as evidenced by several attempts to accurately define, assess and teach professionalism (De Roubaix, 2017: 79-83; Birden, 2012). The American Board of Medical Specialties defines medical professionalism as ‘a belief system in which group members (“professionals”) declare (“profess”) to each other and the public the shared competency standards and ethical values they promise to uphold in their work, and what the public and individual patients can and should expect from medical professionals’ (Wynia et al, 2014: 712-714). Most definitions include adherence to core principles, professional responsibilities and commitments. While the inclusion of moral content is regarded as ambiguous by some scholars, others consider it as a characteristic of professionalism. According to Rowley et al, ‘the term “professionalism” is a construct of attribution, meaning it consists of traits, characteristics, behaviours and qualities that are attributed to those that others hold in high esteem, especially colleagues in the same profession’ (Rowley et al, 2000: 110-114). The moral nature of professional competence is elegantly echoed in this statement by Epstein and Hundert (Epstein and Hundert 2002: 226-235):

'Professional competence is the habitual and judicious use of communication, knowledge, technical skills, clinical reasoning, emotions, values, and reflection in daily practice for the benefit of the individual and community being served'.

The Canadian Medical Education Directives for Specialists referred to as CanMEDS identified 'professionalism' as a core competency in addition to six other roles to successfully meet the healthcare needs of society. This framework describes professionalism to be composed of three core proficiencies to i.e. (1) deliver the highest quality care with integrity, honesty and compassion, (2) exhibit appropriate personal and interpersonal professional behaviours, and (3) practise medicine ethically consistent with the obligations of a physician (Frank, 2003: 972-978). Overall, the foundation of professionalism can be regarded as an interdependent two-tier system of clinical duty and moral precepts (De Roubaix, 2017: 79-83). This includes moral virtues such as compassion, trustworthiness, discernment, professional integrity and conscientiousness (Chervenak, 2001:875-880).

The above discussion is important as the medical discipline is continuously beset with new scientific discoveries and technologies. Historically, the practice of medicine was an art primarily focused on religious and philosophical beliefs and practices involving the use of herbs and prayers. Attempts to cure disease began with religious ceremonies in combination with medicinal herbs since most of early civilizations considered disease as a supernatural phenomenon (Ackerknecht, 2016). Greek medicine is regarded to have had a more rational approach in the evolution of medicine as endeavours to cure disease included more practical efforts, such as examination as opposed to observation or 'wishful thinking'. The inclusion of Greek philosophy also played a major role in the progression of medicine.

Most of their knowledge and clinical acumen is thought to have originated from ancient Egyptian medicine. Analysis of the Edwin Smith, Ebers and Kahun Papyri discovered during archaeological expeditions, revealed information on medical procedures and practices. The Edwin Smith Papyrus is an ancient medical text detailing surgical trauma (also referred to as Edwin Smith's Surgical Papyrus), and is believed to be named after the American dealer who had purchased it (Hughes, 1988: 71-82). The

Ebers Papyrus, (measuring 20.23 meters in length and 30 centimetres in height) is thought to be more complete and voluminous than any other papyrus from ancient Egypt addressing magical spells, supernatural intervention and medical formulas (Ebbell, 1937:123). The Kahun Gynaecological Papyrus however (believed to be the most ancient gynaecological document) details conception, contraception, pelvic organ prolapse and even toothaches during pregnancy (Stevens, 1975: 949-952).

Medicine in the land of the Pharaohs was regarded as highly advanced for that time, and through communication to other cultures paved the way for the development of modern/scientific medicine (Aboelsoud, 2010: 082-086). The 'scientification' of medicine started with physicians who were also philosophers, such as John Locke (1632-1704), an influential English political philosopher well-known for the social contract theory; Thomas Sydenham (1624-1689), commonly referred to as the 'English Hippocrates' (regarded as the founder of clinical medicine and epidemiology) who emphasized the significance of bedside observation and reasoning; and finally, Rene-Theophile Laennec (1781-1826), the inventor of the stethoscope in 1809, representing one of the symbolic powers of medicine (Dewhurst, 1963; Bates, 1977: 324; Bynum, 1994). It is fascinating that the stethoscope maintained its 'visible' permanence throughout time and undoubtedly has played a role in the personification of the competent medical doctor (Campbell, 2001: 748).

The formation of monastic hospitals and medical schools in Europe in the middle ages, coupled with advancement in human anatomy and training of physicians between the Renaissance and early modern period (16-18th century), paved the way for a more rigorous emphasis on the scientific approach of symptoms and diagnoses. Introduction of anaesthesia, prescription drugs, aseptic operating theatres, and statistical analysis and mapping in the 19th century revolutionized modern medicine. Drugs such as cannabis, 'magic' mushrooms, alcohol and opium that were used for thousands of years for meditative, euphoric and analgesic properties adopted a more widespread use. Interestingly, once cocaine was isolated in its pure form (in 1844), a steady supply from Merck Pharmaceutical was secured for use in Bavarian soldiers to increase resistance to fatigue! Similarly during World War II, amphetamines (colloquially referred to as 'speed') were used by soldiers for their performance-enhancing effects (Defalque, 2011: 21-32).

With reference to medical education, the ridding of superstition, expanding rationality and expelling the older apprenticeship system lay the foundations for more formalized teaching (medical schools), the introduction of technology and incorporation of medical research (Fulton, 1953: 457- 461). Research, albeit recent, has been used as a surrogate indicator of scientific progress in medicine and forms the basis of providing evidence in guiding clinical decisions (Norman, 2002: 1560-1562).In addition to the above discussion, the introduction of certifiable medical boards and various medicines and devices (including food and cosmetics) Acts illustrates the philosophical Foucauldian discourse of power and knowledge in the evolution of medical practice, and how human beings are transformed into subjects.

Foucault's intellectual legacy is based on his remarkable ability to illustrate that 'institutions' such as Medicine/Science/Regulatory authorities etc., through the use of discourse, have shaped peoples' thoughts, values, beliefs and behaviour i.e. had a great societal impact.

To understand power and control, Foucault draws a distinction between events at a specific historical moment and the broad concept of human nature, which he believed did not impact on the intricacies of scientific disciplines. He suggested that instead of searching for general principles to evaluate certain conditions, it is much more valuable to ask instead how power operates in societies/institutions, and how to alter power relationships. He believed that knowledge and power are closely related, and it is more meaningful to analyse the different modes by which human beings are made subjects through objectification i.e. the objectification of the subject.

These include 3 core strategies; dividing practices (isolation of lepers, prisoners and creation of psychiatric hospitals etc.), the creation of scientific classification (medicine regarded as a discipline and the body is treated as a 'thing' in the 19th century), and the process of subjectification (human beings become subjects) (Foucault ,1982: 777-795).

1. Power: Introduction of Regulatory agencies:

The landscape of medicine has evolved from an era of widely available unregulated use of drugs and devices to the current powerful country specific regulatory agencies. Prior to 1906, these agents were likely unregulated until Theodore Roosevelt prompted the United States (US) Congress to pass and enact the first American Pure Food and Drug Act, the first in the era of progressive legislation and consumer protection. Note that between 1879 and 1906 there had been unsuccessful proposals and lobbying for legislation regulating the food, beverage and drug industry to US Congress as a result of product adulteration and industrial fraud (Barkan, 1985: 18-26).

These regulatory agencies serve as guardians to society at large. Examples include the US Food and Drug Administration (FDA); United Kingdom (Medicines and Healthcare Products Regulatory Agency (MHRA)); Australia (Therapeutic Goods Administration (TGA)); Europe (European Medicines Agency (EMEA)); Ireland (Irish Medicines Board); Germany (Federal Institute for Drugs and Medical Devices) and South Africa (Medicines Control Council), but more recently to be replaced by the formation of SAHPRA (South African Health Products Regulatory Authority). These regulatory agencies are required to ensure the safety, quality and efficacy of medicines and devices, as well as coordinate legal procedures relating to drug and device development, distribution, monitoring and compliance (Vorster, 2016: 18-19).

2. Knowledge: Innovation by industry, risky business?

New procedures, drugs and technology that are introduced virtually daily, bear testimony to the rapid and exponential growth within the discipline of medicine. These ‘advancements’ have had a significant impact on how we live, eat, communicate and resolve conflict posing new ethical and regulatory challenges.

Examples include genetic engineering or modification of the organisms’ DNA; neuromorphic technology i.e. the creation of computer chips that mimic the human brain; and medical three-dimensional printing (creating viable tissue that is likely to be used in drug and device safety screening, facilitating rapid tissue healing and regeneration). These innovations are not without risk and ethical controversy due to the significant impact on the global balance of power, human dignity (relationship between man and machine) and social inequality.

The modern pharmaceutical industry owes its reputation to humble beginnings of local apothecaries to wholesale manufacturing and distributing in the mid 1800's.
Significant innovations by pharmaceutical industries have resulted in major improvements in disease control and a positive impact on human health. Intensive research and energy are generated to produce newer and better drugs alongside new technologies.

For the purpose of this thesis, I have chosen to use the term Health Care Industry (HCI) for its all-inclusive nature, i.e. it is an aggregation and integration of sectors within the economic system that provide goods and services to treat patients with curative, preventative, rehabilitative, and palliative care It comprises of providers of diagnostic, preventive, remedial, and therapeutic services such as doctors, nurses, allied health staff, hospitals and other private, public, and voluntary organizations. It also includes medical equipment and pharmaceutical manufacturers, as well as health insurance firms.

As health care professionals, we are ultimately tasked as gatekeepers of this knowledge and have a moral responsibility and obligation to protect the welfare and health of patients insofar as prescription of drugs and devices are concerned.
To summarise, generally prescription of drugs, devices and other interventions should firstly demonstrate proven safety and efficacy.
How is this taught or facilitated? As a form of guidance, many medical schools advocate evidence-based medicine (EBM) for both undergraduate and postgraduate students in making the best decisions about patient care. This philosophical concept has prompted the development of systematic reviews and meta-analyses, which allows for a more concise summary on the outcome of the evidence in question after pooling relevant data followed by critical analyses thereof (Masic, 2008: 219-225).
Although revised, EBM was originally defined as 'the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patient's' (Sackett et al, 1996: 71-72). As demonstrated in figure 1, the EBM triad includes consideration of patient values and expectations.

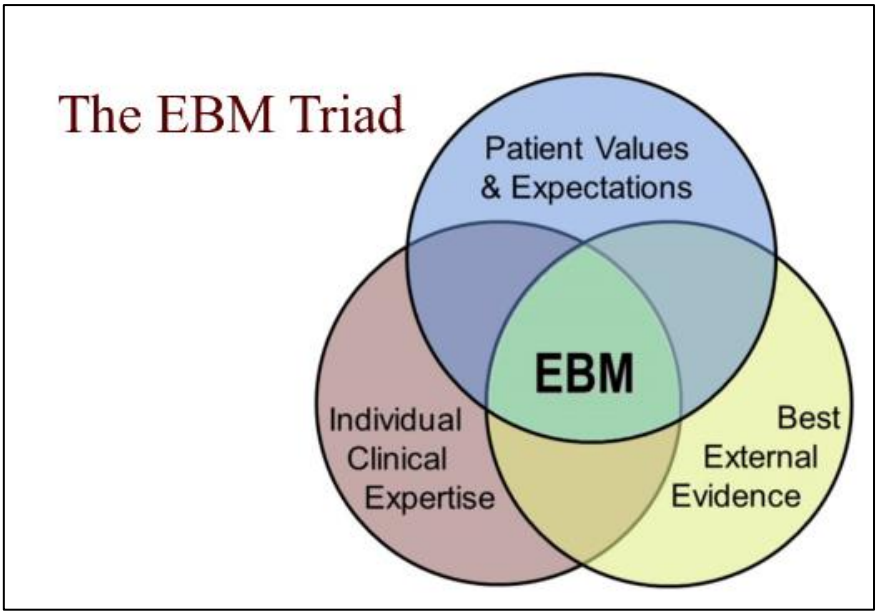

Figure 1: The evidenced-based triad.(Armstrong 2003: 351-356)

Secondly, the prescription of drugs and devices must meet the regulatory standards of the local authorities. Both consider the totality of research evidence in making any final decisions. This process seems simplistic and logical, which then begs the following questions:

1. Why the need for large settlements between Justice departments and HCIs around drugs and devices?
2. Why are there individual and class action lawsuits against industry?

The litigious discourse represents an unpleasant interface between technological advancements on the one hand and the adoption and use thereof by physicians.

Basic knowledge of the drug and device development and approval process is pertinent in order to critically evaluate this topic. This is briefly outlined below.

3. Deconstructing Innovation:

3.1. Drug development and approval process:

The use of drugs is advocated for their beneficial effects in curing and improving disease. The development and regulatory processes are important since there may be unintended effects (side effects), and even potentially lethal consequences such as the infamous Thalidomide and Avandia (or Rosiglitazone) drug scandals. Thalidomide, a sedative drug manufactured in 1953, was marketed off-label for treating morning sickness in pregnancy and resulted in significant and lethal fetal malformations during 1961-62 (Dally, 1998: 1197-1199). Avandia, a popular anti-diabetic drug resulted in cardiovascular deaths, bone fractures and liver toxicity (Lehman, 2010: c4805). Avandia was withdrawn from the South African market in 2011. Common violations resulting in massive settlements by the relevant companies included failure to disclose safety data, off-label promotion, 'kickbacks' (negotiated bribery) and fraud i.e. claiming illegitimate reimbursement. Thus, scientific research demonstrating appropriate and robust safety and efficacy data is necessary to avoid similar tragedies.

The science of drug development is usually a lengthy and expensive enterprise that can span up to a decade from initial conception to marketing. This timeline can vary i.e. from 5.2 years for Acquired Immune Deficiency Syndrome antiviral agents to 7.9 years for antineoplastic agents.

I will briefly describe the relevant stages of the drug development process followed by the medical device approval process, since this knowledge is important in understanding the impact of controversial and ethical dilemmas arising thereof.

- **Stage 1- Drug discovery**- following identification of new drug-target combinations, testing in cultured cell/animals is initiated to determine potential effects and toxicity.
-
- **Stage 2- Pre-clinical development**- aims to further develop the drug for its intended use. Studies on absorption, breakdown and clearance, and the finalization of drug medium i.e. pill, spray, cream, injectable are performed. Further clinical development continues following regulatory approval.

- **Stage 3- Clinical development**- referred to as clinical trials with testing on human volunteers to substantiate safety and efficacy. These clinical trials are divided into 5 phases as illustrated in figures 2 and 3. Note that small numbers are needed for phase 1 testing as shown in figure 3.

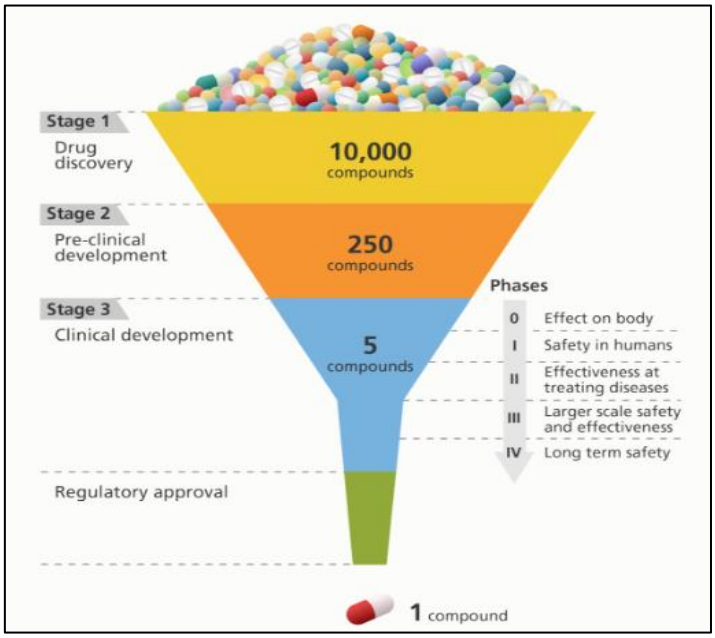

Figure 2: An illustration of the various stages involved in drug development Image credit: Genome Research Limited.

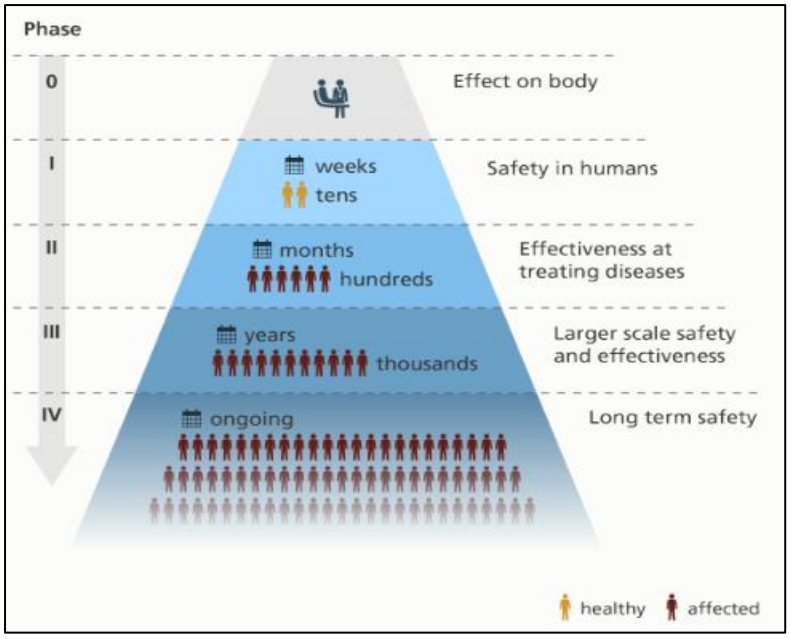

Figure 3: A flow diagram to illustrate the different phases in a clinical trial. Image credit: Genome Research Limited.

Finally, only one or two drugs will ultimately be submitted as new drug applications, referred to as market authorization application.

3.2. The current South African context: Medicines

SAHPRA (the former MCC) is the regulatory agency that applies standards stipulated in the Medicines and Related Substances Act, (Act 101 of 1965). All medicines to be sold in South Africa (SA) must be registered with the SAHPRA, who then provide guidance on registration and licencing for the sale and manufacture of medicines (www.mccza.com). The registration approval is based on:

- inclusion of a package insert,
- evaluation of scientific data to support the claim,
- patient information leaflet,
- description and consideration of manufacturing and quality control measures,
- details of the factory where the medicine is manufactured, tested and packaged (which is subject to MCC inspection).

All advertising must be based on the approved claim of the medicine and is regulated by the South African Code of Marketing Practice. According to this, a medicine may not be advertised or promoted prior to the registration with the medicines regulatory

authority or unless an application has been submitted in terms of Section 14(3) of the Medicines Act (www.marketingcode.co.za).

After approval, pharmaceutical companies are then granted a limited time to retain exclusive rights to market the drug before other companies follow suit. Some of the challenges that drug companies face include:

- Patent expirations/loss of patent protection resulting in the loss of sustainability. To overcome this threat, planning of mergers and acquisitions between companies begin.
- Funders requesting demonstration of therapeutic and economic value over other competitor products and non-pharmaceutical options.
- More stringent regulatory processes (mandated by local regulatory authorities to clear new drugs i.e. preapproval of safety evaluations and post-market clinical studies)

Currently delays in obtaining approval, spiralling costs, and complex protocols associated with the discovery and development of new drugs in the era of ground-breaking technology such as, pharmacogenomics[1] and proteomics[2] is a challenge facing all research-based industries.

Pharmaceutical industries are thus aiming to decrease development times, control costs, optimize protocols and patient recruitment, and develop core focus points demanding therapeutic intervention (www.yourgenome.org/facts).

Compared to the regulation of medicines, the medical device approval and regulatory framework for South Africa is not as clear and concise.

Footnote:

[1]***Pharmacogenomics*** *is a relatively new field that combines pharmacology (study of drugs) and genomics (study of genes and their function) to develop safe and effective medications tailored to one's genetic makeup* (Evans, 2003:538-549).

[2]***Proteomics****- the term was first coined in 1995 and involves detailed analyses of protein function, modification and interaction. This together with complementary technology such as molecular biology provides significant biological information to scientists.*

It seems that once the device has had FDA or the Conformité Européenne (CE) approval stamp, clinicians as well as ethics approval bodies felt more reassured for its use! Whether MCC approval was mandated is unclear.

As it stands, there is no regulation on medical devices subject to the formation of the South African Health Products Regulatory Authority (SAHPRA) as of mid-2017. I will thus briefly outline the American version (i.e. FDA) for the approval of medical devices. This discussion is important as the approval process was flawed and resulted in lawsuits against industries/manufacturers because of harm suffered by women globally.

3.3. Medical device approval process:

In 1938, the United States (US) Congress mandated that medical products (mainly drugs) demonstrate efficacy and safety. In the early 1970's, following alleged deaths, pelvic infections and infertility complications as a result of an intrauterine contraceptive device
(IUCD) called Dalkon Shield, the authority to regulate medical devices was handed over to the FDA. At the time Dalkon Shield IUCD was marketed as an alternative to contraceptive pills (which were the subject of safety concerns at that time), however following deaths and injury led to numerous lawsuits with the marketing company ultimately filing for bankruptcy. The relevance of the Dalkon Shield IUCD saga is elaborated upon in chapter four.

What does FDA approval mean? The function of the US Food and Drug Administration (FDA) is to protect public health by ensuring safety and efficacy of medical drugs, devices and biological products (https://www.fda.gov/aboutfda/whatwedo). In the simplest terms, 'FDA approval' means that the FDA has decided 'the benefits of the approved item outweigh the potential risks for the item's planned use'. This body essentially needs to provide reassurance of safety and efficacy of devices to the public, while avoiding overregulation of the medical industry.

The process for devices to enter the market includes preclinical testing, followed by device classification by the FDA into Class one (low risk), Class two (moderate risk) and Class three (considered high risk) which determines the need for clinical trials.

Both Class one and two are usually subjected to less rigorous criteria as opposed to Class three devices which requires a premarket approval process (PMA). This means the need for scientific testing to provide reasonable assurance that the device intended for use is safe and effective. An excellent article by Diana Zuckerman details the 'Medical Device Recalls and the FDA Approval Process' which clearly allows one to further understand the approval pathway (Zuckerman, 2011: 1006-1011).

In 1976, many medical devices were already on the market therefore the U.S. Congress introduced the 510(k) provision to allow newer versions of already existing devices to enter the market. The 510(k) provisions did not require scientific trials or manufacturing inspections to demonstrate safety and efficacy**,** but simply that the device is equivalent in mechanism of action, purpose and materials to the already marketed device i.e. the predicate device. This allowed manufacturers to improve on devices and facilitate competition between companies through bypassing the PMA process. Hence the conclusion: if the FDA deemed a product safe and effective according to the 510(k) provisions, the device was cleared for market rather than approved.

The continuing technological innovation by manufactures with a large influx of new and complicated devices used the 510(k) provisions as a dominant process for new device clearance as opposed to the stricter criteria for PMA approval. Mass marketing began with large revenues generated for shareholders/owners. Cost implications together with delaying the release of new products were reasons provided for the lack of clinical studies. For Urogynaecologists, this information is shocking.

The ProteGen sling for stress urinary incontinence (Boston Scientific Corporation, Natick, MA) was cleared via the 510(k) mechanism, and served as the progenitor device for the development of future sling and mesh kits for stress urinary incontinence (SUI) and Pelvic organ prolapse (POP). Already in 1998 slings were being recalled because of complications, however in the same year the tension-free vaginal tape and mesh kit called I.V.S Tunneller (U.S. Surgical, Norwalk, CT) (Nygaard et al, 2008: 1311-1316) was cleared under the 510(k) using ProteGen sling as the predicate device. This vicious cycle perpetuated against the background of limited resources by FDA to conduct appropriate surveillance.

Furthermore, it is important to note that the 510(k) provisions were intended for medical devices such as hearing aids and surgical gloves, and in 1976 only a few devices were intended for permanent implantation. The Medical Device Reporting program allows clinicians/surgeons to report adverse events to the distributor/company representative who then transfers this information to the FDA. The FDA then makes information about marketed devices available to the public via the Manufacturer and User Facility Device Experience (MAUDE).

In summary, although the FDA determines whether the benefit of drugs and devices outweigh the risks by reviewing evidence determined by clinical trials, expanded access via off-label use and 510(k) provisions have been met with controversy. The very existence of a regulatory framework such as the FDA is only significant in its protection of the end users.

3.4. The current South African context: Medical devices

Currently, the South African Medical Device Industry Association (SAMED) is a non-profit voluntary organization representing the interests of many companies operating in the medical device, medical equipment and *in vitro* diagnostics sector in South Africa. Associated members include:

The South African Laboratory and Diagnostic Association (SALDA), The Medical Imaging Systems Association (MISA) and MDMSA (Medical Device Manufacturers of South Africa). MDMSA is another non-profit voluntary organization consisting of companies in South Africa that manufacture medical devices. MDMSA brings together manufacturers and others involved in the South African medical device sector to discuss issues of industry-wide importance.

The medical devices manufacturing sector is made up of a wide range of basic products including instruments (disposable syringes and scalpel blades); wheelchairs; specialized furniture (hospital beds, dentists' chairs, operating tables etc.) and surgical implants and stents. At the more sophisticated end of the spectrum lies electronic monitoring and diagnostics equipment, including complex and expensive items such as NMR (nuclear magnetic resonance) and PET (positron emission tomography) scanners. Medical devices also include *in vitro* laboratory diagnostics used to detect

infection (sero-conversion) and monitor progress in the treatment of patients suffering from infectious and non-communicable diseases (www.mdmsa.co.za).

The association claims to be actively involved in commentary to the Department of Health (DOH) and the MCC on pending medical device legislation, as well as securing local manufacturing incentives through the DTI (Department of Trade & Industry).

However, as recent as the 1st of June 2017, the South African Government reassigned the regulating authority from the Medicines Control Council (MCC) to the South African Health Products Regulatory Authority (SAHPRA) regarding the oversight of medicines, medical devices, complementary medicines and *in vitro* diagnostic medical devices. The origin of SAHPRA stems from the MCC and is an independent state-owned entity formed to essentially oversee the country's drug and medical device market.

According to the preceding regulation, a licence from the Directorate of Radiation Control was needed in order to import electronic medical devices into South Africa, and surprisingly devices with a pharmaceutical substance were registered as a pharmaceutical with the MCC, and finally market authorization required European Union (EU) approval. There has been a shift in power to strategically regulate previously unregulated devices including homeopathic, Ayurvedic, Chinese and traditional African medicines that are sold to the South African public.

In 2017, all active companies were required to register and provide a list of all devices that are manufactured, imported and exported followed by the registration of devices in 2018. Trading will only be permissible upon submission of a manufacturer or distributor licence. For this purpose, in February 2018 the Minister of Health, Dr Aaron Motsoaledi, appointed a 15-member team for SAHPRA. This body will function as a separate entity to the National DOH and will be responsible for the monitoring,

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Footnote:

[3]*Stress urinary incontinence is defined as the involuntary loss of urine* (Haylen BT et al, 2010: 4-20).

evaluation, regulation, investigation, inspection, registration and control of medicines, scheduled substances, clinical trials, medical devices and related matters in the public interest. The outcome of this authority is yet to play out.

4. Ethical dilemma of novel medical devices applicable to gynaecology:

An excellent and relevant example of the clash between power (marketing, regulatory authorities), knowledge (industry and physicians) and society played out when millions of women around the world complained and litigated industry for adverse events after the implantation of transvaginal mesh (TVM) for pelvic organ prolapse (POP).

POP is a common gynaecological condition affecting both young and older women. The use of TVM in the form of 'mesh kits' was marketed directly by industry to physicians and indirectly to society via advertising, with the perception of providing long-term success for the surgical correction of POP.

Subsequently, millions of women worldwide suffered from complications and even permanent disability, resulting in anger and disappointment manifested by litigation (Mucowski, 2010: 103. e1- e4; Murphy et al, 2012: 5-9 ; Koski and Rovner, 2014: 380). This has thus raised various questions ranging from the manufacturing and approval process (as outlined above) to moral issues relating to prescription/recommendations by physicians.

Its ultimate use in women/society (subjects) in the absence of robust scientific data reflects the many layers of decision-making by regulatory bodies and physicians ('the powers'), and indeed the power of marketing. Society represents the interface between technological innovation and enhancement on the one hand and 'responsible practice' on the other, as the physician represents the final point of care. Patients expect and deserve responsible judgement based on clinical proficiency when planning management. This discussion must be balanced against a paternalistic attitude.

This thesis examines the ethical conundrum of using untested permanent medical devices, as well as three other gynaecological devices that cause harm to patients. In this respect, firstly, I will discuss the wide utilisation of TVM for the treatment of

symptomatic POP since this issue is topical and it presents an excellent example of dangers associated with the use of untested products.
This will be followed by a discussion of the clinical problem of POP and safety concerns and warnings arising from the use of TVM. The third chapter will focus on expansion to physicians in the form of marketing strategies and scientific publications, as well as conflict with the four basic ethical principles i.e. autonomy, beneficence, non-maleficence and justice will be examined.

The three other gynaecological medical devices, the Dalkon Shield IUCD, the Essure™ permanent birth control device and the use of power morcellators during laparoscopic surgery will be elaborated upon in chapter four. Regulatory Acts as a means to ensure patient safety will be briefly discussed in chapter five, followed by the conclusion in which I aim to develop an ethical template/flow diagram to be considered when evaluating the use of novel medical devices.

Chapter 2: Background

Innovation for pelvic organ prolapse: Role of regulatory authorities and ethical implications/dilemmas:

1. Pelvic organ prolapse: The clinical problem:

Prolapsus, a Latin term for *'slipping forth'* was described as early as 1555-1565. In the Hippocratic era, a woman with this condition would probably be shaken upside down, followed by the insertion of half of a pomegranate into the vagina coupled with a religious ceremony (Emge,1966: 997-1032) .

Figure 4: Demonstration of Hippocratic succussion as a remedy to allow the womb of a woman to slip back into place (From Appolonius of Kittium) (Emge, 1966: 997-1032).

Pelvic organ prolapse (POP) is the term used to describe the abnormal descent or herniation of the pelvic organs namely the bladder, uterus/vaginal vault, and/or rectum/bowel into the vagina. It is a common gynaecological problem affecting women of all ages. The exact prevalence is difficult to quote due to the use of different classification systems, heterogeneity of clinical studies and under-reporting due to social stigmatization.

Population based surveys have revealed that up to 8% of women report POP symptoms (Tegerstedt et al, 2005: 497-503 ; Rortveit G et al, 2007: 1396-1403). Currently there are no epidemiological studies evaluating the burden of pelvic floor dysfunction, specifically for POP in South African women.

Common symptoms include the feeling of a lump or bulge in the vagina and visualization of a bulge outside the vagina, incomplete bladder and bowel evacuation/voiding requiring the need to manually digitate (insert the finger into the vagina) to facilitate emptying. The negative impact on several quality of life domains including sexual and general health, results in women seeking treatment for this condition albeit underreported due to social stigmatization (Lowder et al, 2011: 441. e1-441. e5). Treatment of this condition has huge financial implications, as it requires significant healthcare resources, especially with the projected increase in prevalence within the geriatric population (Sung, 2010: 483. e1- e4; Wu J.M. et al. 2009: 1278-1283).

1.1. Risk factors for POP:

Several risk factors have been shown to be associated with the development of POP. These include:

- Disruption of the pelvic support mechanisms as a result of vaginal childbirth/s (which requires the pelvic floor muscle to stretch to almost three times its normal capacity during the second stage of labour, in order to allow the fetal head to pass),
- Chronically raised intra-abdominal pressure (e.g. constipation, asthma, chronic obstructive airway disease etc.),
- Parity (risk of POP increases with increasing parity),
- Congenitally weak connective tissue (e.g. Marfan syndrome),
- Obesity,
- Ageing,
- Menopause (Mant,1997: 579-585 ;Patel et al, 2006: 23-28; Tinelli et al, 2010: 204-212 ; Dietz, 2016: 441-448)

Commonly used terms to describe prolapse include:

- Anterior compartment prolapse - descent of the bladder into the anterior vaginal wall
- Posterior compartment prolapse - descent of the rectum into the posterior vaginal wall
- Apical compartment - descent of the apex of the vagina/vault/uterus

- Enterocoele - herniation of the intestines through the vaginal wall

A staging system called the pelvic organ prolapse quantification (POP-Q) system has been proposed by mainstream international bodies to allow clinical standardization of POP and assess outcomes (Haylen BT et al, 2010: 4-20). Figure 2 illustrates different types and stages of POP.

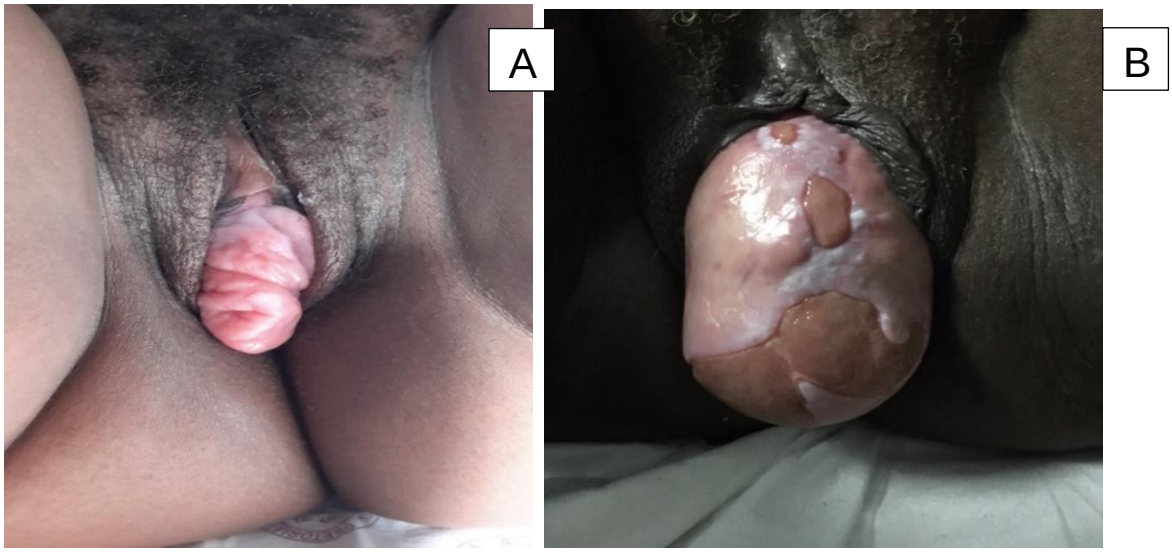

Figure 5: (A) POP-Q stage 3 vault prolapse and (B) POP-Q stage 4 uterine prolapse with ulceration. Pictures from Urogynaecology gallery database. Consent for use obtained from patients.

1.2. Treatment options:

Currently treatment options include the use of vaginal pessaries or surgical treatment. Previously surgery was regarded as the foundation of treatment and included either abdominal or vaginal repair procedures without the use of mesh implants. The use of mesh is a recent development. Surgery is not indicated if the patient prefers conservative management with vaginal pessaries. Traditionally, vaginal pessaries were considered in women who still desired fertility, had several concomitant medical co-morbidities and thus unfit for surgical intervention and who declined surgery for POP in pregnancy. In recent years, there have been several publications on the positive effects of vaginal pessaries that can be offered as a primary treatment option after further discussion with the patient (Fernando et al, 2006: 93-99; Abdool Z et al,

2011: 273-278 ;Lone et al, 2011: 56-59). In context of the mesh debacle this point is essential.

Vaginal pessaries are silicon devices manufactured in various shapes and sizes. The bioinert material makes them a favourable option for POP and urinary incontinence treatment. While this alternative is offered by a vast majority of American and British obstetrician and gynaecologists (OB-GYNs), only 23.6% of South African gynaecologists offer this option to women presenting with POP (Abdool 2011, 64-67). Lack of training was documented as the reason for the low uptake of pessary use.

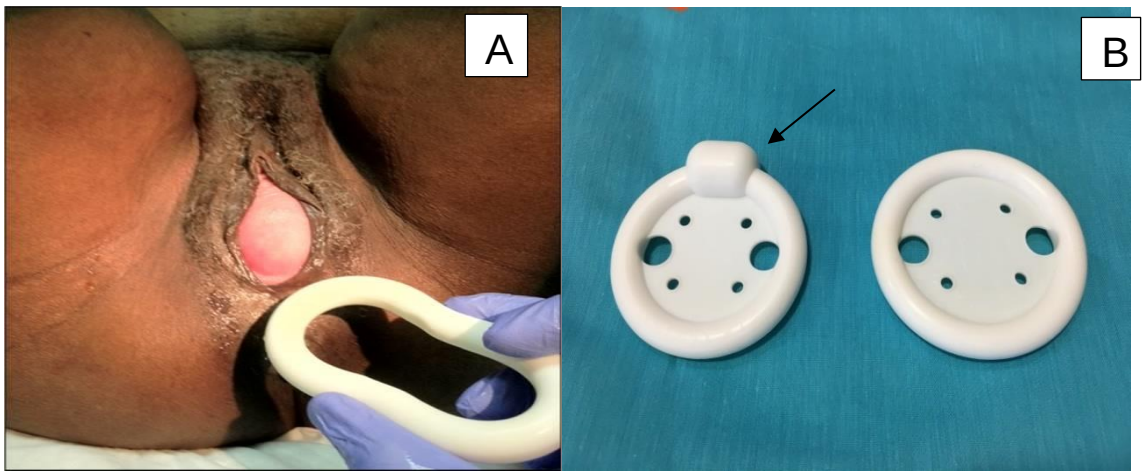

Figure 6: (A) Insertion of vagina ring pessary (without support) for bladder prolapse (B). Ring pessaries (with support) for pelvic organ prolapse and urinary incontinence (black arrow illustrating knob). Pictures from Urogynaecology gallery database. Consent for use obtained from patient.

1.3. The clinical dilemma and consequences of TVM for POP repair:

Traditional repair of POP includes surgical techniques to restore pelvic floor anatomy using the patient's own tissue (i.e. native tissue repair). A large proportion of women will require repeat operations (Olsen et al, 1997: 501-506). Recurrence of POP has been reported to be higher at tertiary academic centres. Thus, the recurrence of POP after the initial procedure has been regarded as an academic priority amongst pelvic floor surgeons, resulting in scientific discourse on how to prevent, optimise and treat recurrent POP. Surgical mesh was introduced with the aim to reinforce the structural integrity of the vagina and hence correct POP and UI.

Mesh is an interlaced structure of fibre made of either polypropylene, polyethylene, nylon and other materials, manufactured in different shapes and sizes and marketed as pelvic floor kits.

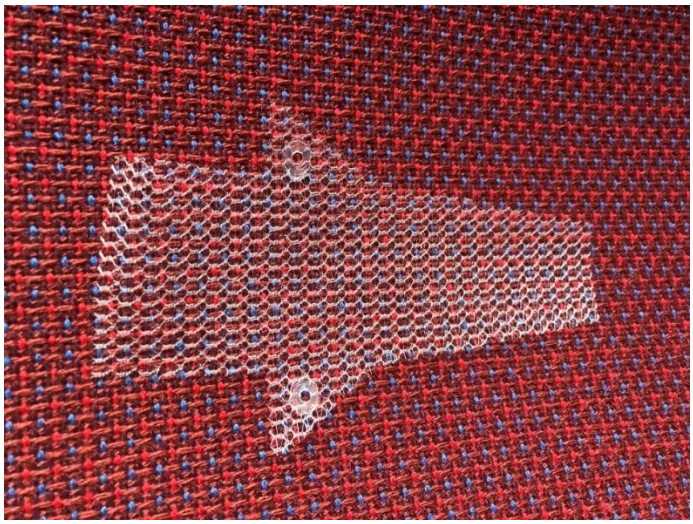

Figure 7: An example of a piece of polypropylene mesh used to correct pelvic organ prolapse.

Therefore, the concept of reinforcing the pelvic floor tissue with synthetic materials was introduced to deal primarily with the issue of POP recurrence after surgery. These materials labelled as biomaterials/biocompatible materials were designed to supplement, augment and reinforce native pelvic floor tissue. It was introduced based on the premise or understanding of inducing a favourable and sustainable host reaction with ultimate incorporation with the surrounding tissue, providing augmented support of the pelvic floor (Cervigni, 2001:429-435).

To ensure patient safety and optimise efficacy, biotechnological studies subsequently investigated and published properties of an ideal synthetic material/mesh, which included the following criteria:

- Materials should be non-carcinogenic
- Physically and chemically inert
- Durable
- Non-allergenic
- Non-modifiable by host tissues
- Readily available and affordable

Thereafter mesh classification was introduced based on pore size. The larger pore size (Type 1, greater than 75 microns) encouraged optimal formation of new blood

vessels and fibrous tissue, thus enhancing biocompatibility. Manufacturing companies adopted these guidelines which resulted in a myriad of mesh production, global marketing and distribution. As discussed earlier, the FDA granted permission via the 510k provisions therefore bypassing the need for robust safety and efficacy studies. Marketing this 'novel' surgical technique to enthusiastic pelvic floor physicians and innocent/naïve patients began with great enthusiasm and anticipation of a more permanent solution to repair POP.

As the use of pelvic mesh kits expanded, thousands of women reported complications (some even life altering/threatening) such as infection, erosions, bleeding, sinus tract formation, vaginal discharge, organ perforation, fistulas and seromas, pain during sex, urinary tract problems, vaginal scarring, nerve damage, POP recurrence and chronic pelvic pain. This culminated with the formation of several mesh blogs and support groups, such as the 'Australian Pelvic Mesh Support Group', 'Meshmenot' and 'meshangels.com'. These products have become the subject of class actions in the United States, Australia and the United Kingdom. Subsequently the Scottish government launched an Independent Review of the use, safety and efficacy of TVM implants, and soon thereafter the Australian Senate also conducted an inquiry. Currently three countries i.e. Australia, New Zealand and the United Kingdom have banned the use of mesh for POP repair on the basis that the risks outweigh the benefits, safety concerns and the lack of demonstrable long-term data (www.iuga.org/newsletter). It is likely that this ban will extend to other countries.

1.4. The voices of women who had mesh surgery:

Mesh testimonials:

"*I am a victim of a mesh implant that I was unaware I was having. I have not been able to return to my job since the day of implantation and I live in pain and agony every day. Mesh also eroded through my vaginal wall and has caused major nerve damage. Say NO to mesh because it is harming thousands of women worldwide".*

"I am one of thousands of women who has been permanently damaged by a pelvic mesh device that was meant to treat prolapse and stress incontinence, but instead made our lives living hell. The pain is excruciating, crippling-its stolen our ability to work, to be active mothers, and to function. Regulators failed us miserably. Pelvic

mesh implants were introduced over a decade ago in Australia without any clinical evidence of safety or efficacy.

Over 600 women have joined the Australian pelvic mesh support group, a community I started in 2014 after my botched surgery. This issue is global-in the UK and the US thousands of women have launched legal action against government and manufacturers that permit these devices." (www.change.org/stopmesh)

These testimonials and several others resonate with feelings of disappointment, pain, suffering and more importantly betrayal of trust by physicians. Complications especially chronic pelvic pain and resultant disability have impacted on the physical, emotional and financial wellbeing of these women and has therefore prompted global mass torts and litigation against both the manufacturer, distributors of the product and indeed the physician. This also resulted in simultaneous clinical warning alerts by regulatory authorities in the form of public health notifications to warn women against adverse events related to the use of TVM (US Food and Drug Administration and US Food and Drug Administration 2008).

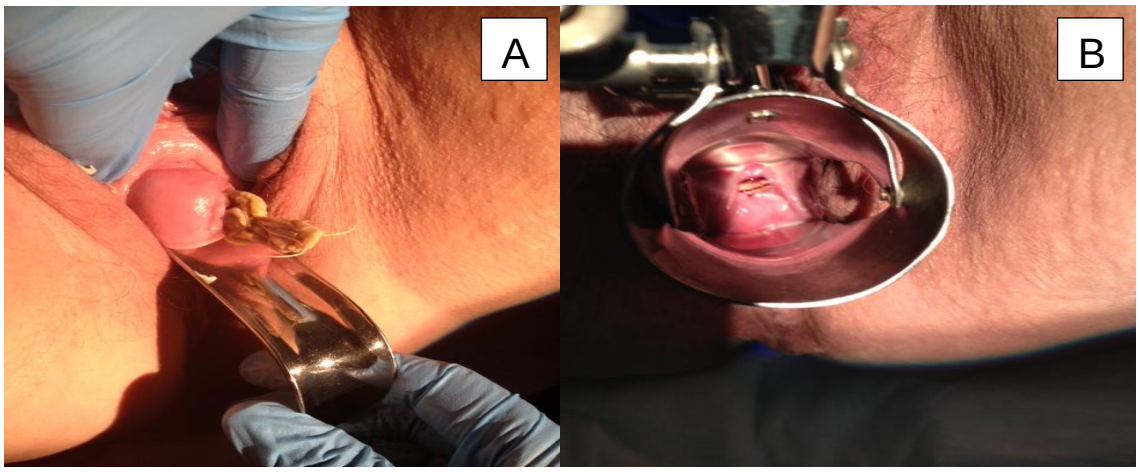

Figure 8: Transvaginal mesh extrusion and prolapse recurrence after transvaginal mesh placement (A) and mesh erosion at vaginal apex in a patient presenting with pelvic pain and chronic vaginal discharge (B). Pictures from Urogynaecology gallery database. Consent for use obtained from patients.

2. Lack of regulatory input and the Conundrum of using TVM: Evidence and reality, who's responsible?

2.1. United States Food and Drug Administration (FDA) warnings:

Pelvic floor surgeons began using mesh without official approval ('off label') to treat POP in the 1990's, with the first surgical mesh for POP only cleared by the FDA in 2002 (www.fda.gov). We refer to US data, as there is no South African information in regards to safety concerns/warnings. After receiving almost 4000 complaints related to vaginal mesh surgeries performed between 2005 and 2010, the FDA released a public health notification in 2008 and a safety communication in 2011 stating that: "serious complications associated with surgical mesh for transvaginal repair of pelvic organ prolapse are not rare," and that a review of scientific literature had shown "that transvaginal pelvic organ prolapse repair with mesh does not improve symptomatic results or quality of life over traditional non-mesh repair " (US Food and Drug Administration 2008, 2011).

The reality of the absence of scientific evidence and associated complications prompted the need for research studies on this subject. Subsequently, in 2012 the FDA noted that research is necessary in order to determine the safety of transvaginal mesh involving human subjects, and thus ordered manufacturers to conduct such studies. As a result, several popular companies initiated a recall of certain transvaginal mesh implants as of 2012 (Zuckerman, 2011:1006-1011). In 2014, the FDA published a proposed order requiring Premarket Approvals (PMAs) for the use of TVM in POP repair and initiated discussions on mesh device/instrumentation reclassification. Class I to III reflect the regulatory controls required to provide assurance of safety and efficacy.

The three categories of devices are class I (general controls), class II (special controls), and class III (those requiring premarket approval). Devices in Class III are considered those that 'support(s) or sustain(s) human life or is of substantial importance in preventing impairment of human health or presents a potential, unreasonable risk of illness or injury' (www.fda.gov/medicaldevices.com).

In the meantime, at least six medical device-manufacturing companies were targeted by litigation claiming that the mesh implants were dangerous, defective and unfit for use. Lawyers promptly advertised their services (no cost, no obligation) to recover compensation for injuries paralleled by patients seeking recourse through litigation.

2.2. Justice for patients: Mass torts/class action lawsuit against manufacturers and/or distributors:

A mass tort and class action share definite similarities in the sense that both include civil action from allegedly harmed plaintiffs against common defendants. The basis for the lawsuits involving TVM specifically claim that (www.classaction.org/transvaginal-mesh-lawsuit):

- Manufacturers failed to advise doctors on the risks associated with mesh implants
- The materials used to manufacture mesh implants can cause adverse immune and inflammatory reactions
- The permanent implantation of a defective sling or vaginal mesh can result in serious harm to patients, resulting in the need for repeat surgery
- Mesh implants do not work as intended and have caused severe irreversible damage

Currently thousands of women globally have filed lawsuits alleging that vaginal mesh placement induced serious harm especially pelvic pain, and thus claiming compensation should be forthcoming (Zoorob et al, 2016: 404-409).

Class action was first introduced in the United States to provide an avenue for the public to access justice and is usually conducted on a ‘no win no fee’ basis.
Conditions required for a class action include:

- Seven or more people to petition a claim
- The claim originates from a similar or the same circumstance
- Claim relates to at least one common issue of law/fact

The discussion of the mesh debacle portrays an excellent example of justice and restoration of dignity for society on one hand, and raises core ethical values and

standards of all the role players i.e. physicians, regulatory authorities, manufacturers and distributors.

The above discussion raises significant ethical questions such as:

- *Who is to blame?*
- *Is it the doctor/manufacturer/scientific community?*
- *Who is now responsible?*
- *Is it the doctor/manufacturer/scientific community?*
- *Was there data to support mesh use and if not why was it approved?*
- *What does the FDA approval process mean?*
- *Why was there a lack of governance and monitoring?*
- *Understanding the marketing strategy and process as this may have played a role;*
- *The natural history on the adoption of new technology by doctors;*
- *Is the ethical landscape of research studies appropriate?*

These questions form the basis of my concerns and the ethical principles upon which I argue, including the clash between the principles of virtue and applied ethics, as well as physicians' uptake of new technology in the absence of scientific data.
The ethical principles of respect for autonomy (including informed consent), beneficence, non-maleficence and justice and the implantation of untested devices with unknown consequences on patients represent a powerful juxtaposition. Thus a discussion of ethical guidelines for physicians is appropriate.

3. Ethical appraisal of doctor-patient conflict:

3.1. Ethical guidelines of professional medical practice:

While common morality is inclusive of shared norms, some disciplines require the application of specific moralities i.e. professional moralities in medicine. Professional moralities include the adherence to standards of conduct, which are usually codified e.g. the Hippocratic oath and the American Medical Association (AMA) code of medical ethics, amid many others (Riddick Jr 2003). All physicians must be familiar and knowledgeable with current ethical guidelines, and the regulation of medical research in their respective countries. A detailed knowledge of drugs and devices is

important before prescribing and/or usage/application on humans. Introduced in ancient Greece on the island of Cos as a guide to appropriate behaviour of physicians, the Hippocratic Oath is one of the oldest and most internationally applied codes of ethics. The oath represents the earliest expression of ethical standards in the Western world and has been adopted by several medical schools in many countries as a rite of passage for medical graduates. As it was not equipped to deal with issues such as informed consent and privacy, the oath has since been modified. In context of this thesis, this specific section of the Oath stands out, “I will use treatment to help the sick according to my ability and judgment, but never with a view to injury and wrong-doing. Neither will I administer a poison to anybody when asked to do so, nor will I suggest such a course. Similarly, I will not give to a woman a pessary to cause abortion. But I will keep pure and holy both my life and my art”.

The relevance of this particular excerpt is unique for its collective/ all-inclusive moral and ethical implications (such as discernment, trust, care, commitment) required for practicing modern medicine.

Locally, the HPCSA Guidelines for Good Practice in Healthcare Professions outlines the ethical and professional rules. In the introduction to each of its ethics guideline booklets, it states that ‘practicing as a healthcare professional is based on a relationship of mutual trust between patients and healthcare practitioners.’
To be a good healthcare practitioner, requires a life-long commitment to sound professional and ethical practices and an overriding dedication to the interests of one’s fellow human beings and society’. In essence, the practise of healthcare professions is a moral enterprise. In this spirit, the HPCSA presents the following ethical guidelines to guide and direct the practice of healthcare practitioners. These guidelines form an integral part of the standards of professional conduct against which a complaint of professional misconduct will be evaluated (www.hpcsa.co.za/Conduct/Ethics).

Both of the above statements make reference to several important ethical issues between patients and physicians and are constant reminders of the binding contract to always primarily consider the patients best interests. The implantation of TVM for POP repair in the absence of safety and efficacy data, and the subsequent issue of

FDA public health notifications, sets the scene for conflict between disregard of ethical principles and patient care.

In deontological ethics (the study of the nature of duty and obligation), morality of actions is subject to abiding by rules and core ethical values to promote a good standard of practice. But as moral beings, we should display focal virtues that play a significant role in the ethics of physicians (Beauchamp and Childress 2001).

There are many virtues applicable to medical practice, and here I will mention a few relevant to this thesis:

- Discernment – to make astute judgment devoid of personal attachments, commitments fears (should I use TVM, or offer other treatment options?),
- Trustworthiness (patients trust physicians judgements and decisions),
- Integrity (an honest and sincere decision is presented to patients), and
- Conscientiousness (am I exercising vigilance?)

Application of these and many other virtues together with the four-principle approach to biomedical ethics (i.e. respect for autonomy, beneficence, non-maleficence and distributive justice) provide a framework for formulating professional practice (Beauchamp, 2007: 3-10).

3.2. Conflict between use of new untested devices and respect for Autonomy:

It is generally accepted that a physician has a fiduciary responsibility of rendering the highest standard of care to the beneficiary i.e. the patient. Autonomy is the patient's ability to make his/her own decisions freely, without manipulation or external forces. To respect autonomy, physicians must obtain informed consent prior to an intervention and ensure its validity, threshold, informational and consent components must be considered. This process takes place over time and is the prime responsibility of the physician to ensure its completeness. This process begins verbally after an assessment and terminates with a written document detailing discussion and facts based on several elements of informed consent.

In the context of the mesh debacle, several questions were raised as to whether all these elements were discussed prior to use, especially informational elements i.e.

disclosure, recommendation/s and understanding of the procedure. It is commonly known that the core set of information should include: stipulation of relevant material when consenting for the proposed intervention, the purpose of seeking consent and the physicians' recommendations (if any).

This is paralleled with the understanding of information i.e. procedures, risks, benefits etc., which is reliant on patient factors (e.g. amount of information, attentiveness, level of education) and the physician factors such as time constraints and lack of remuneration in the case of institutional research (not a valid excuse but an important point).

In this case, adequate informed consent implies that the physician:

- Fully explained the benefits, risks and possible complications for the use of mesh to repair POP,
- Discussed the use of alternatives,
- Disclosed the lack/insufficient scientific data.

If these pertinent points were considered, is it possible that physicians would have altered their decision to use mesh in view of insufficient safety data? (thereby acting as the final purveyors of power to protect patients). Secondly, if complications were elaborated upon, the fact that most mesh is permanent, and that alternatives were available, it is likely that this would have resulted in less harm to patients.

3.3. Conflict between using a new untested devices and respect for Beneficence:

Applying the principle of beneficence demands that positive steps must be taken to assist or help others, and merely not refrain from harmful acts. This is accepted as an implicit assumption in medical institutions. Simplistically, beneficence refers to acts of mercy and kindness and the principle itself refers to the moral obligation to act to benefit others. Physicians adopted the innovation to increase the durability of the POP repair and indirectly improve patient care, without the intention of inflicting or causing harm.

There is much debate with regards to obligatory versus optional and ideal beneficence as illustrated in the New Testament parable of the Good Samaritan.

His action of care and mercy was benevolent and perhaps ideal, while the action of rendering assistance obligatory. This moral act reflects on the application of the principle when a physician plans to use an untested device. Relevant *prima facie* rules of obligation are important when considering any procedure or medical intervention. These are:

- Protect and defend the right of others
- Prevent harm from occurring to others
- Remove conditions that will cause harm to others

Consequently, one may argue that the insistence of clinical data (including long-term data) prior to TVM use may have avoided harm to patients and enabled physicians to honour the above *prima facie* rules of obligation.

By entering the healthcare profession and assuming a professional role, it is assumed that these obligations are met. In the case of the mesh fiasco, there were no clinical studies prior to marketing, communication of which to the patient may have steered outcomes in the positive/different direction. However, if the outcomes were superior using TVM for POP repair, with holding this option would have denied patients from its benefits.

Regarding the implanting of TVM, a physician has a *prima facie* obligation of beneficence to patient X if the following conditions are met:

- Patient X is at risk of damage to health with use of transvaginal mesh
- Physician's action is necessary to prevent damage - counsel for or against the use of transvaginal mesh
- Physician's action will probably prevent damage if an alternative such as vaginal pessaries or native tissue repair were offered
- Physician's action will not present significant risks, costs and/or burdens to the patient if offered the alternative as opposed to using an untested device
- The benefit that patient X can be expected to gain outweighs any harm, costs and/or burdens that the physician is likely to incur – thus obviating a case of medical negligence

3.4. Conflict between using a new untested devices and respect for Nonmaleficence:

This principle echoes the maxim *Primum non nocere*: “Above all (or first) do no harm”. This standard is essential when considering ordinary versus extraordinary treatments, and when one foresees harmful outcomes. I acknowledge retrospective bias in the following discussion points.

The concept of harm caused in this case resulted in patients suffering from an injury and a setback in the interest of patients. Simplistically, the physician had to inform the patient that the use of the new product is justified without creating undue harm. The FDA Safety communication of 2008 by this time alerted physicians of the potential damage of using the untested TVM kits. This is to say that the principle of non-maleficence also infers the obligation to not impose further risk of harm.

The adoption of these transvaginal mesh kits in the absence of safety and efficacy studies left physicians vulnerable to legal, financial and ethical issues. There was no data to compare outcomes. There was certainly no initial guidance on how to manage complications, and treat failures. So could physicians meet the ethical demands of beneficence and non-maleficence in the absence of this data?

3.5. Conflict between using a new untested devices and respect for justice:

The classic definition of justice includes the phrase ‘equitable and fair distribution of benefits and burdens’. Currently, four gynaecological devices used in women i.e. TVM for POP, the Dalkon Shield IUCD, the Essure^{TM} permanent birth control (PBC) system and laparoscopic power morcellators for the removal of large uterine fibroids have resulted in more harm than benefit. This ensued the ultimate banning of the Dalkon Shield IUCD, followed by a progressive ban on TVM commencing in Australia and expanding globally. The Essure^{TM} device will be taken off the market by 31st December 2018.The power morcellators discourse was ignited after its use resulted in Dr Amy Reed’s occult cancer spreading even further. The sales of these surgical devices have been suspended at the end of 2014.

It is likely that some women do benefit from innovative medical devices, and thus banning these products precludes transferring the benefits to these women. This raises issues related to justice and fairness; even more reason as to why both the

healthcare industry (HCI) and physicians need to improve scientific and ethical integrity to ensure delivery of safe and efficacious medical devices.

4. Recent recourse by Powers:

In January 2016, the FDA reclassified TVM for POP repair from Class II to III on the basis of insufficient safety and efficacy data. As mentioned earlier, a Class III device is one that 'presents a potential, unreasonable risk of illness or injury'. Due to the level of this risk, manufacturers of novel devices in this class, require approval of PMA application prior to marketing the device. PMA clinical studies require biocompatibility testing, preclinical animal studies and fulfilment of the criteria of a 'well-controlled clinical investigation' (www.fda.gov/MedicalDevices/DeviceRegulationandGuidance). This process aims to ensure that there is sufficient scientific evidence on the safety and efficacy of devices intended for use (www.fda.gov/medicaldevices.com).

Furthermore, the FDA states that manufactures must include both patient and professional labelling, and information with regards to risks versus benefits of the intended device as well as other available treatment options. The FDA believes that these regulatory actions will enable a better understanding of the use of surgical mesh for POP, therefore did not call for a ban or a total global recall yet. In 2012 the International Urogynaecology Association (IUGA) published a consensus document detailing the significance of the informed consent process specific to the use of vaginally placed mesh (Miller, Milani, and Sutherland).

As of 10th July 2018 the National Health Service in the United Kingdom (UK) and the Minister of Heath of the Republic of Ireland has issued a 'pause' phase for the use of mesh for both SUI and vaginal prolapse. They have introduced 'high vigilance restrictions on the use of vaginal mesh' until the following commitments are met (www.rcog.org.uk/en/guidelines-research-services/guidelines/mesh-safety-alert/)

Surgeons should only undertake operations for SUI if they are appropriately trained, and only if they undertake operations regularly

- Surgeons report every procedure to a national database
- A register of operations is maintained to ensure every procedure is notified and the woman identified who has undergone the surgery

- Reporting of complications via MHRA is linked to the register
- Identification and accreditation of specialist centres for SUI mesh procedures, for removal procedures and other aspects of care for those adversely affected by surgical mesh
- NICE (National institute for health and care excellence) guidelines on the use of mesh for SUI are published

In summary, the medical profession is entrusted to care for patients, and has a duty to ensure that safe and effective treatment is offered to patients with consideration of the principles of respect for autonomy, beneficence, non-maleficence and justice. Consent for surgery is essentially a process, during which the patient has the opportunity to gain further insight of the condition.

Launching/marketing devices devoid of robust safety and efficacy data questions the concept of morality i.e. guidance of one's conduct by moral reasoning. The above testimonials reflect great disappointment with physicians who are regarded as custodians to guide and fully inform patients before a surgical procedure, especially when using a new medical device with limited scientific data. It is not surprising that women began campaigning globally, resulting in class action lawsuits and litigation as a call to restore dignity. This illustrates the clash between an ethics of responsibility, and the urge to use new solutions or technologies on patients. Thus, chapter three focuses on the relationship between physicians and the HCI, and the marketing strategies employed in shaping both physician and patient opinions.

Chapter 3: Power versus knowledge

Successful use of medical devices (and other products) requires an interplay between the healthcare industry (HCI) and physicians. Manufacturers have substantial resources to design, produce, market and distribute their products. These abilities coupled with influencing techniques in marketing strategies indicate a unique position to disseminate their products, with the final aim to achieve 'provider of choice' status. For these reasons the HCI represent a 'power house'. Physicians have earned a high social standing probably attributable to knowledge gained by 'studying the human body in detail, ability to prescribe treatment, perform lifesaving surgical procedures, and possession of moral attributes such as honesty and trustworthiness', thus representing a 'knowledge' domain (Fones,1998). This relationship has been in the medical and public spotlight for a considerable time. (Wazana, 2000: 373-380; Woollard, 1993: 403-404; Guyatt,1994: 951-953).

This connection of power and knowledge is both a challenging and important topic to study debunk, as it significantly impacts on various moral and ethical principles of the medical profession. In addition, the consequences of this relationship affects delivery of patient care as illustrated by the use of TVM for pelvic organ prolapse in the previous chapter.

The thematic content of this chapter begins with understanding the aim and goals of the HCI. The mechanisms used to transfer their promotion and marketing strategies, and agendas to physicians thereby influencing prescribing behaviour, and the subsequent ethical implications, i.e. advancing the idea of physicians as ultimate purveyors of power, and their possible abuse thereof.

1. The Healthcare Industry: Position of power

The HCI (interchangeable with the pharmaceutical industry) is a multi-billion dollar business with a significant budget allocated to marketing, as well as physician payouts (Wazana, 2000: 373-380; Wolfe, 1996: 637-639; Woosley, 1994: 249-255). It represents one of the largest, rapidly expanding business sectors globally, with the aim to successfully disseminate products. Its return on investment (ROI) is dependent on developing, manufacturing, marketing and distributing drugs and devices via the

interaction with various stakeholders in the medical profession, i.e. physicians, allied healthcare workers, hospital groups, insurance companies and even lay persons. Thus engagement with the medical profession is largely inevitable and difficult to avoid. Ethical issues related to physicians' interactions are in the form of financial remuneration, research grants, acceptance of royalty contracts and gifts, involvement in CMEs, as well as promoting off-label use, although recent developments in the US view off-label promotion constitutionally protected by freedom of speech. It can thus be argued that the HCI is a powerful corporate conglomerate indirectly impacting on both the physicians' and patients' autonomy and authority in different guises. This relationship is analogous to Foucauldian discourse analysis of techniques of domination and power (represented by the HCI) via objectification of the subject (represented by physicians and patients). Foucault broadly described the process of objectification via three routes:

- Dividing practices,
- Introduction of scientific classification, and
- Subjectification of human beings into docile subjects (Foucault,1982:777-795)

With the aim to maximize impact, the HCI has implemented an array of techniques for subjectification of physicians and patients. These techniques are diverse and reflect elements of control. Examples include:

- Involvement in medical education programs, in the form of CMEs (which receive significant commercial support from HCI) (Brody, 2007)
- Sales representative visits to physicians
- Offering of gifts and/or company shares and royalty contracts
- Promoting off-label use of drugs and devices
- Direct-to-consumer marketing
- Out-sourcing clinical research to private practices/entities i.e. contract research organizations (CROs)
- Core marketing strategies (detailing, reminder effect and items, and social validation)

In 2005, the ethical implications of this association became public focus when the US Department of Justice (DOJ) investigated the financial relationship between five of the

largest orthopaedic hip and knee implant device companies and orthopedic surgeons (Healy, 2009: 1791-1805). The DOJ filed criminal complaints against these companies for violating federal anti-kickback statutes and the False Claims Act. An extensive number of surgeons were paid for using the implants, and in addition were offered royalty contracts, expensive meals, trips to luxury resorts and inappropriate gifts. The companies were accused of using consulting agreements as enticements to use the particular implant. This landmark investigation ended in settlement agreements with the DOJ, commitment to adhere to new corporate compliance procedures, an eighteenth month oversight by a DOJ appointed supervisor/inspector, and fulfilment of other key requirements.

This inquiry resulted in the examination and redefinition of policies that govern the relationship between physicians and implant manufacturers in the USA.

Connections between physicians and the HCI have been scrutinized by professional medical associations, colleagues, patients and the law with suggestions to regulate this relationship. The nature of this association between HCI and physicians is important so as to transfer medical benefits to patients. Conversely, it has also been controversial due to the implications of influencing physicians prescribing behaviour in favour of the HCI. This raises moral questions relating to 'trust' (a virtue of professional behaviour) between doctor and patient, as well as physicians' integrity.

The choice to prescribe a particular drug by physicians is assumed to be influenced by the results of robust scientific data, sound professional advice based on safety and efficacy that is essentially outcome-based medicine, and not by external inducements by the HCI. Thus, one of the pertinent questions to answer is whether the influence of the HCI prompts variation of physicians' prescribing behaviour and how doctors practice medicine? An analysis of the factors altering a physician's clinical judgment/prescribing behaviour follows.

2. Impact on physicians' prescribing behaviour: From 'discovery to delivery'

There is a paucity of objective data on the factors that influence physicians' prescribing behaviour, particularly in SA. Essentially alteration of prescribing behaviour include an increase in prescriptions of a preferred drug/device and motivations for additions to hospital formularies. Physicians are uniquely positioned for the HCI to launch its

marketing efforts. So, how does the HCI adjust prescription behaviour? Moreover, does the strategy work?

2.1. The effect of enticements: Trips, samples and gifts

Orlowski and Wateska examined whether an all-expenses paid trip to a luxurious resort would affect physicians' prescribing patterns of two new drugs to be used only in hospitalized patients in the USA (Orlowski, 1992: 270-273). Seventeen months after the trip, the mean usage of both promoted drugs significantly increased by 2-3-fold ($p<0.001$), which was analyzed via tracking of the hospital pharmacy inventory. More importantly, physicians who accepted the invitation believed that this elaborate inducement would not influence their prescribing behaviour (when questioned prior to the trip). While luxury getaways represent an elaborate enticement, smaller gestures such as free lunches and dinners are as equally effective in manipulating physicians' prescribing behaviour (Wall, 2007: 169-173). Gifts are a symbolic representation of power and relationships. Their moral implications lie in the innate power of the act, inevitably creating a sense of debt and pressure to appropriately reciprocate i.e. in relation to the size and cost of the gift.

Easy access to drug and device samples is another mechanism shown to influence prescribing behaviour (Adair, 2005: 881-884 ; Morelli,1992: 42-48; Chew et al, 2000: 478-483). A prospective randomized trial by Adair and Holmgren demonstrated that internal medicine residents with access to drug samples were more likely to write prescriptions of the sample drugs than those unadvertised, as opposed to peers without access to samples (Adair, 2005: 881-884). In addition, the study by Morelli and Koenigsberg confirmed that availability of drug samples was highly associated with drug sample dispensing and prescribing (Morelli,1992: 42-48).

To yield further insight as to why physicians dispense drug samples over their preferred drug choice, Chew et al performed a cross sectional survey of general medicine and family medicine physicians at nine US clinics. A response rate of 85% (n=131) found that avoiding costs to the patients was a motivator to use drug samples and furthermore 'perceived benefits of drug samples' was another reason why physicians prescribe and dispense sample drugs as opposed to their preferred drug

selection (Chew et al, 2000:478-483). Patients are completely unware of the hidden bias introduced by accepting samples.

In South Africa, according to Act 101, 'No person shall sample any medicine'. For the purpose of this section, a 'sample' means the free supply of medicines by a manufacturer or wholesaler or its agent to a pharmacist, medical practitioner, dentist, veterinarian, practitioner, nurse or other person registered under the Health Professions Act, 1974, but does not include the free supply of medicines for the purposes of clinical trials, donations of medicines to the State, tendering to the state and quality control by inspectors' (www.hpcsa.co.za).

In regards to gifts, past surveys reported that physicians perceived acceptance of inexpensive gifts ethically more acceptable than expansive gifts, and most believed that interaction with the HCI would not influence their prescribing pattern (Steinman, e 2001: 551-557; McInney,1990b: 1693-1697). A confidential survey completed by internal medicine residents to study their behaviour and attitudes toward industry gifts revealed that most who considered a gift as inappropriate, such as a conference lunch and pens had accepted those gifts highlighting malalignment of behaviour and attitude. This act demonstrates that something as simplistic as a pen has the power to alter integrity i.e. commitment to one's moral belief and uprightness. Many residents also believed that the prescribing practices of other physicians are swayed as opposed to their own (Steinman, 2001: 551-557).

In addition, the value of items has the power to influence clinical decision-making and/or behaviour. A review by Wazana et al summarizes that gifts in many forms has the potential to persuade the prescribing behaviour of physicians (Wazana, 2000: 373-380). When physicians are remunerated in any form and begin to preferentially promote the item (drug/device) of the relevant HCI, conflicts of interest and bias arise as ethical dilemmas. From a social science perspective, acceptance of gifts distorts judgments by unintentionally introducing self-serving bias (Dana, 2003:252-255). Can something as small as a pen have the power to distort judgement? The study by Steinman et al demonstrated inconsistent behaviour. Each resident who considered a lunch and pens inappropriate gifts had nevertheless accepted them, and expensive items were deemed more inappropriate than inexpensive offerings (Steinman, 2001: 551-557). According to the South African code of marketing practice (www.marketingcode.co.za) gifts are allowed as long as they are 'inexpensive and of

modest intrinsic value'. One may presume that the pressure to reciprocate is in direct relation to the nature and value of the gift.

Most physicians do not perceive themselves as biased, however admit that conflicts of interest may compromise other physicians' decisions (McInney, Schiedermeyer, and Lurie 1990a, 1693-1697). This finding is congruent with social science research that states that bias is most recognizable in others by others (Pronin, 2004: 781; Pronin,2002:369-381). While this remains a complex psychological and social science subject, examining the morality and mechanisms of marketing strategies to expand innovations to physicians is important to fully comprehend this topic. It is not surprising that gifts (emblazoned with the companies' logo or brand name such as pens, mugs notepads and cardholders) that are readily used by physicians are often handed to physicians and their secretaries, thereby reinforcing the 'reminder effect by reminder items' (Katz, 2003: 39-46).

The alteration of prescription behaviour is proof that physicians are subconsciously influenced by these strategies. Perhaps this is an unconscious attempt to reciprocate the HCIs' 'generous gestures'. On the other hand, do physicians who have designed and patented their own products, such as prostheses, escape the power of gifting? Simplistically it seems logical that they do not, and this is an interesting area that has to my knowledge not been accurately researched. There is certainly bias, with acute conflicts of interest, which have never been investigated.

2.2. Subjectification of the subject: Marketing strategies

Development of new drugs and devices requires dissemination to patients via physicians and allied healthcare providers. Therefore, a significant portion of the pharmaceutical sector's budget is allocated to promotion and marketing efforts with the aim to align physicians' behaviour with HCI objectives (Brody, 2007). I will discuss the marketing infrastructure as most suited to achieve the desired objectives.

2.2.1. Personal meetings with sale representatives:

Analysis of the literature identifies personal meetings with sales representatives (commonly referred to as 'reps'), as having a positive influence on prescription sales. This fact is evidenced by a significant financial allocation by the HCI to 'detailing' (Fugh-Berman, 2007: e150). This practice refers to one on one meetings with

physicians to ‘educate’ these professionals about the drug/devices’ indications, side effects, adverse effects, costing etc. Traditionally there are three types of detailing:

- Pharmaceutical detailing - trained representatives ‘educate’ the physicians
- Academic detailing - physicians with no financial links to the HCI educate other physicians
- E-detailing - build relationships with physicians via social networking platforms

Detailing requires skill: the sales representatives befriend and aim to develop a calculated relationship with physicians. Fugh-Berman and Ahari state that ‘drug reps are selected for their presentability and outgoing natures, and are trained to be observant, personable, and helpful. They are also trained to assess physicians’ personalities, practice styles, preferences, and relay this information back to the company’ (Fugh-Berman, 2007, e150).

Within this infrastructure physicians’ prescribing behaviour, i.e. the number of prescriptions per drug/device, is tracked via a pharmaceutical framework referred to as ‘behavioural prescriber segmentation’ (BPS), see figure 1. By identifying ‘high-volume prescribers versus low volume prescribers’, the HCI is able to measure its return on investment (ROI).

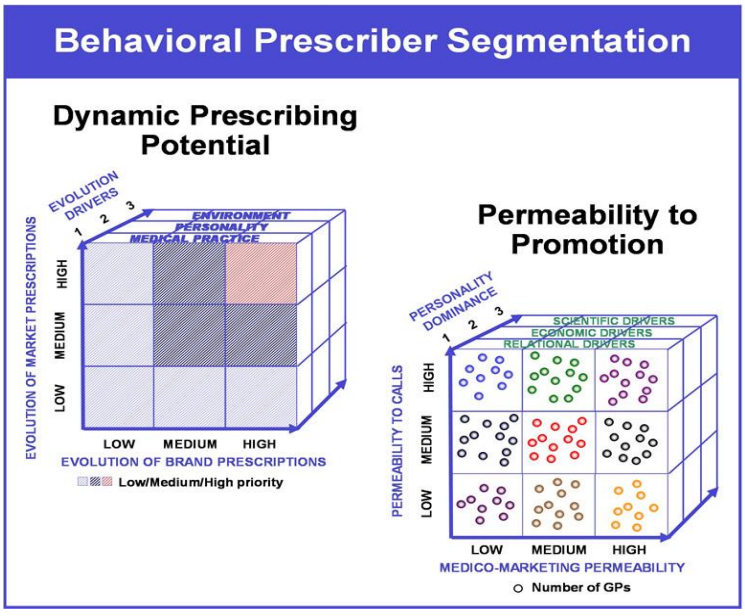

Figure 9: Illustration of the behavioural prescriber segmentation framework used by pharmaceutical companies with the aim to optimize the efficacy of promotional investments
(www.smart-pharma.com/business-tools/behavioural-prescriber-segmentation).

Use of this customized model allows the HCI to determine which promotional items or strategies (i.e. scientific, economic or relational drivers as depicted in fig. 1) are more likely to be successful for each prescriber. More effort, attention and rewarding with higher-end gifts, such as silk-ties and golf bags are awarded to the high-volume prescriber. Another proposed strategy is to detail to high-volume prescribers who have a considerable number of new patients since it is probable that a patient will rarely change the script even though they change the doctor!
To measure the success of the various marketing strategies, HCIs obtain prescription information from companies that track physicians' prescribing behaviour, such as IMS Health (in the USA) and other pharma-consulting companies. Critics have viewed this as a violation of medical professionalism and/or privacy, while proponents argue that the information may be used to monitor unnecessary prescriptions. To curb 'script tracking' in the USA, the AMA launched the Prescribing Data Restriction Program, which allows physicians to withhold prescribing information from HCI representatives.

2.2.2. Interaction via 'Continuing Medical Education' (CME) and industry sponsored research:

From humble beginnings, CME was initially an unfunded platform for physicians to interact and engage with each other in the form of grand ward rounds, case discussions and journal article reviews. As such, its responsibility belonged to the medical profession.

This changed however when the HCI began to fund CME events in the 1950's onwards. Currently, CME sponsored events are important components of physician interaction and information dispersion. Companies sponsoring CME events have been scrutinized for both intentional and unintentional information bias in the form of content specification, narrowing the focus of a product, as well as promoting off-label use thereof. In brief, CME sponsored events have also shown to influence prescribing behaviour (Bowman and Pearle, 1988: 13-20; Lexchin, 1993: 1401-1407). CME

guidelines have been introduced to regulate companies, although these may not be adequate to eliminate bias and address conflicts of interest. It is time that strategies are developed to separate pharmaceutical marketing from CME events (Relman 2001, 2009-2012). Early morning breakfast meetings, new product launches by experts and speaker honoraria are allowed in South Africa under the ambit of the code of marketing practice (https://www.marketingcode.co.za).

The HCI allocates a huge proportion of finances to research and development (R&D) that represents yet another mechanism through which physicians adopt new practices. The R&D process is vital to the HCI to ensure that the drug/devices pose no financial risk, thus ensuring a positive outcome. Strategies in study design to tailor confident results include (Lexchin et al, 2003: 1167-1170):

- Introduction of bias in study design
- Careful selection of inclusion/exclusion criteria, thus avoiding the uncertainty principle of clinical research
- Conducting poor quality trials
- Investing in trials that will probably yield positive results
- Bias in reporting of results
- Recruitment of physicians in private practice

Commercial funding of clinical research by the HCI is an inevitable reality. The HCI has also expanded its footprint by outsourcing to independent CROs that provide support to the pharmaceutical and device industry. These organizations have a more focused and precise role in the R&D of the HCI, and offer a range of services i.e. preclinical, clinical, regulatory, administrative and commercial. One of the CRO's main functions is to optimize the 'time to marketing' gap by speeding up the drug/device development process (Osakwe, 2016: 57). Having emerged in the late 1990's, this an established billion-dollar industry employed by numerous companies. The nature of their role is skewed towards companies having exclusive access to research data, with universities/academia and physicians having limited/no direct access. The data moves into a less regulated world of CROs. To this end, it serves its purpose in hastening the 'time to marketing' gap by avoiding all legal ramifications associated with R&D.

There is a scarcity of data on physicians' experiences with the HCI and CROs in terms of R&D. Henry et al examined the extent, nature and consequences of the close

collaboration among Australian medical specialists and the Australian pharmaceutical industry. Key findings of the questionnaire-based study revealed (Henry et al, 2005: 557-560):

- Greater initial contact from the pharmaceutical industry
- Negative experiences which included

  - premature termination of a study by the company (due to adverse drug events),
  - first draft report written by the pharmaceutical company or CRO
  - delay publication or failure to publish key findings
  - concealment of relevant findings that are potentially serious misdemeanors

These indiscretions have resulted in large settlements between the HCI and the US Department of Justice. Common violations by the HCI include off-label promotion or unapproved promotion of a medical product, violation of the False Claims Act, Medicare fraud and paying kickbacks to physicians. Between 2014 and 2015, there has been a notable reduction in fines and settlements in the pharmaceutical industry, which is viewed as a positive sign of the changing culture of compliance (Lerner and Nguyen). Indeed time will tell.

As gatekeepers of health, physicians must be knowledgeable about the implications of interaction with HCI sponsored research as the HCI is in the driving seat. A notable point is the fact that the dissimulation of research (involvement of CROs and private practices) implies that the company has full and complete access to all the data and control over its analysis. This is an excellent example whereby positions of power impact on knowledge gained, in fact, in a Foucauldian sense, on the creation of knowledge.

To the author's knowledge, there are no studies examining the extent and experience of HCI ties with South African physicians. In South Africa, the HCI is governed by both local and international legislation.

The SA code of marketing practice version 10 (https://www.marketingcode.co.za) is a comprehensive 53-page document that outlines regulations pertaining to the relationship between physicians and the HCI. Payment of reasonable honoraria to physicians, organizing continuing professional development meetings/events,

payment of travel and accommodation etc. is allowed provided it is aligned with the code.

2.2.3. Identification of key opinion leaders (KOLs) and ghostwriting: Shaping medical opinions

Key opinion leaders:

Identification and development of KOLs is vital to the continued survival of the HCI. According to the pharma-marketing glossary, a KOL is defined as a senior physician who assists in the marketing of the companies' drug/device (www.pharma-mkting.com/glossary/keyopinionleader). Physicians are mainly pursued from university/academic hospitals to advise the HCI on marketing optimization to increase sales. Included are practices such as presentations at conferences (seminars, breakfast symposiums), CME events and road shows hosted and organized by the HCI. KOLs are often remunerated for these services.

Essentially this process begins with the identification of physicians by the HCI who are prepared to endorse the product. Thereafter, a series of events ensue to develop these pinpointed physicians into KOLs. The power behind recruiting a KOL lies in the ability to directly and indirectly influence prescribing behaviour of other physicians through participation in professional societies and advisory boards (Moynihan, 2008:1402-1403).

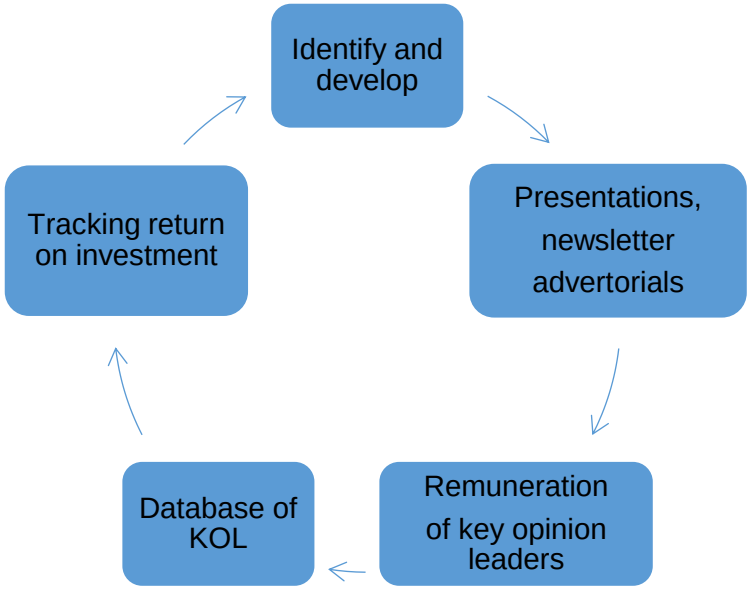

Figure 10. Schematic presentation of the lifecycle of key opinion leaders.

KOLs have been criticized as an Orwellian structure designed to be destructive to the welfare of a free society in the form of 'bribes to prescribe', which are not in the best interest of the public (Moynihan, 2008: 1402-1403; Blumenthal, 2005: 583). The effect of KOLs can result in biased opinions, and ultimately compromise patient care.

Ghostwriting:

It is common knowledge that HCIs often shape and control research outcomes (Fugh-Berman, 2005: 546-548; Elliott, 2008: 1-29; Blumsohn, 2006: 1-4). This includes involvement in all stages of study design, data analysis (use of in-house statisticians), manuscript writing by hiring professional writers and ensuring publication in high impact journals through commissioning of communication companies (Sismondo, 2007: e286). Academics are then invited to serve as authors on these publications essentially written by the HCI.

In some cases, the identified academic author is requested to edit the manuscript. This practice is referred to as 'ghostwriting' i.e. when a writing company is appointed to produce a manuscript on a piece of research to fit the drug company's needs, and subsequently a prominent 'authority' is identified as a 'guest author'. The inclusion of an academic author allows readers to subconsciously assume that the named author was involved in the study and endorses the findings, all of which indirectly

improves the credibility of the publication (PLoS Medicine Editors ,2009: e1000156). Guest authorship refers to the lack of mentioning an author who has made a substantial contribution to the writing of the manuscript.

Several lawsuits that have permitted access to the HCI's research information have exposed ghostwriting and ghost authorship. While this has become an accepted profitable norm for most HCIs and academic authors, the majority agree that ghostwriting is an abuse of scholarly publishing. This strategy is criticized for its power to control the eventual outcome and conclusion of a drug/device using research as a vehicle. As it currently stands, the HCI usually promotes and designs the publication of data in favour of the company, and is therefore biased. The addition of ghostwriting, ghost authorship and recruitment of CROs perpetuates this bias (Lexchin et al, 2003:1167-1170; Sismondo, 2008: 109-113). Generally, CROs have no claim to ownership and escape the publication process, and are consequently regarded as 'ghostly' (Mirowski,2005: 503-548). The aim is to ensure publication of selected findings in favour of the products of the HCI. These publications are written and edited by ghost personnel, wherein the process constitutes scientific misconduct. This is yet another strategy aimed to influence healthcare decisions of both physicians and patients, which has resulted in the US Senate appealing for tougher rules to prevent ghostwriting (Tanne, 2010).

2.2.4. Development and promotion of adherence programs: Shaping patient opinions

This new strategy represents an additional mechanism of Foucauldian discourse manipulation, as well as on the 'subjectification of the subject' (Foucault, 1982: 777-795). The primary aim of these newly introduced programs is to ensure patient adherence to taking medication or using devices. The fact is that non-adherence is a financial loss to the HCI (Forissier, 2012: 2013).

The term 'adherence' replaces 'non-compliance' as the latter term reinforces an authoritarian and paternalistic physician-patient relationship (Holm, 1993: 108-110). Patient adherence strategies have been launched in various forms, e.g. repeated and constant contact, as well as interaction with 'people of trust' such as nurses, pharmacists, physicians including fellow patients who are in fact HCI ambassadors. Patients' (including societal) beliefs and attitudes can be adjusted or changed

accordingly as this represents a powerful point of constant contact (Lamkin, 2014: 492-500). For the politicians and HCI stakeholders, adherence to safe and effective treatment for medical conditions (especially chronic) is a logical endpoint, as adherence improves health. The patients' health is maintained, the HCI profit margins continue to rise via prescriptions, and the healthcare system is spared from unnecessary cost i.e. it is 'a win-win situation'. Based on this premise, penalties for non-adherence have been introduced in the USA in the form of increased premiums. This form of expanding the HCIs' footprint by policing patients can be regarded as authoritarian and impacts on patient autonomy, and possibly a violation of privacy by the tracking of adherence.

To summarize, I have discussed several carefully calculated marketing strategies which result in formulating a medical opinion (evidenced by the alteration in prescription behaviour). By moral, ethical and medical standards, physicians are entrusted caregivers who are expected to make the best and unbiased decisions for ensuring optimum health for their patients. Physicians need to be familiar with the discussed HCI strategies as the resultant byproduct is conflict of interest and bias. This topic should be included in the ethics curriculum of medical students, as these young scholars will invariably engage with the HCI as qualified professionals.

3. Embracing new technology: Physicians as purveyors of power?

Physicians play a vital role in the dissemination of drugs and devices to patients. In fact, they can be regarded as gatekeepers of this process. From the previous discussions, it appears as if physicians endorse/support marketing strategies. If so, does the power relation not then shift further down the line between patient and physician? Physicians represent the purveyors of power for both the HCI and patients and are thus empowered to effectively manage this innovative relationship with the HCI. However, this relationship may well suit the physician for a variety of reasons, which are complex and almost impossible to unravel.

The HCI forms an integral part of the practice of medicine, and the development of new drugs and devices will indeed continue. The following chapter explores three 'innovative' gynaecological devices that resulted in harm, disability and death in women. How does the uptake of innovation reconcile with physicians' ethical duties towards patients? To buffer this relationship 'disclosure of conflict of interest' is offered

as an antidote. Do physicians expect the patients to understand the nature of this disclosure during consultation with an ‘expert/ knowledgeable person’ for treatment of a medical condition?

Is this a reasonable expectation when the treatment decision can have potentially long lasting effects such as the case of TVM for POP? Should the medical profession accept this standard?

Consideration of the Aristotelean notion of the practice of virtues could assist us in finding a route through this maze. The solutions are not simplistic, and for these reasons, in the final chapter I will incorporate such virtues in the development of an ethical template, which can considered when faced with adopting new technological innovations. But first, a discussion of gynaecological device innovations that *have* caused harm.

Chapter 4: Gynaecological medical devices that caused harm:

In this chapter, I intend to focus on three other gynaecological devices that sparked huge concern in the Gynaecology discipline, and to highlight the significance for more improved oversight by regulatory authorities.

There is a lack of accurate data on morbidity and death consequent to medical device use, failures and/or errors. The reality is that patient death, disability and injury are common consequences of medical device use errors (Zhang et al, 2003: 23-30). The field of gynaecology is no exception. Apart from the use of TVM for POP, two other contraceptive devices, and laparoscopic power morcellators (PMs) deserve discussion to illustrate the dangers that can be associated with untested and substandardly tested medical devices in women's health. PMs are surgical instruments used to cut large masses inside the abdominal cavity into smaller pieces in order to remove them through a smaller incision.

Female contraception in the form of sterilization or intrauterine devices remains a popular choice among women globally. A 'fast, cheap, easy procedure, less risky, need for the latest and greatest, and quick return to work' are some of the reasons women opt for these procedures (Barbieri, 2014:10-15) . Minimally invasive gynaecological surgery has become popular for its ability to lessen surgical morbidity. The addition of PMs allowed laparoscopic surgeons e.g. to remove large fibroid(s) via a much smaller incision as opposed to large abdominal incisions in standard operating techniques.

I shall start off by describing two intrauterine contraceptive devices, and the problems associated with each.

1. The Dalkon Shield: The Cadillac of contraception?

From discovery to delivery, intrauterine contraception has had a troubled history. When medical devices are poorly designed, improperly used, and unsafe, their use can result in death, injury and disability. The history of the ill-fated Dalkon Shield is a frightening example of what can go wrong in the absence of proper oversight and safety testing.

The Dalkon Shield saga deserves discussion for three reasons: it was responsible for the FDA ushering in a new law governing the introduction of new medical

technological innovations balanced against efficacy and patient safety; it caused gynaecological death and injury and lastly reminds physicians, politicians and regulatory powers of the need for demonstrable safety and efficacy.

A design flaw of the string of the Dalkon Shield intrauterine device (see fig. 1) tainted the IUCD safety reputation for decades. A gynecologist, Dr. Hugh J. Davis (on the faculty of John Hopkins Medical School) conceptualized and designed this device in 1968. This plastic device attached to a multifilament nylon string was marketed for its distinctive new design and also as a safer alternative to oral birth control pills, which were at the time controversial due to the high incidence of thrombotic incidents. Spearheaded by large marketing campaigns, already by 1970, just two years after its introduction, three million women in the US were using the device. The device was initially marketed by the Dalkon Corporation, (founded by the inventor) and subsequently acquired by A.H. Robbins Company in 1970 (Sobol 1991). This was permissible since there were no federal regulations on advertising, and the FDA did not require safety testing of intrauterine contraceptive devices IUCDs.

Figure 11: The Dalkon Shield intrauterine device (from http://www.professorwalter.com/2011/08/the-case-that-hung-by-a-thread.html)

Shortly after its debut, questions arose as regards its quoted pregnancy rate, and its safety profile. Numerous cases of pregnancy, septic miscarriages and severe gynaecological infections resulting in loss of fertility were reported prompting an inquiry by the Centre for Disease Control and Prevention (CDC) (Tatum et al, 1975: 711-717; Hurt, 1974: 491-495; Lee et al ,1983: 1-6). The manufacturer also claimed a false 1.1% failure rate instead of 5.5%, which is according to a study performed by

Dr. Davis (Davis, 1970: 455-456; Sobol, 1991). These events prompted the need to focus on regulatory oversight as a means of ensuring patient safety. Thus in 1976 the Medical Device Regulation Act was introduced by the US Congress resulting in amendments to the Food, Drug and Cosmetic Act of 1938 (Food 1938, 21). In the aftermath more than 300 000 lawsuits were filed against the company which ended in the company filing for bankruptcy protection in 1985 (Horwitz,2018).

IUCDs are generally designed as a 'T'-shaped structure that lodges inside the uterus attached to threads that are visible through the cervical opening. Visibility of the thread is essential during the removal process. Scientific scrutiny of the Dalkon Shield revealed that the tail was both structurally and functionally different form other IUCDs at the time.

It was suggested that being multifilament (composed of numerous filaments woven together) as opposed to the more usual in other devices, monofilament (composed of a single filament) , it was more prone to harbouring vaginal microorganisms contributing to the infectious morbidity and mortality. This was regarded as a design flaw. Furthermore, the company only tested its effectiveness (and found a 1.1% pregnancy rate), not its safety and the designer shared in the profits from sales of the Dalkon Shield, which may constitute a conflict of interests. Women were thus exposed to unnecessary and unacceptable harm.

2. Essure™ PBC device:

True to George Santayana's philosophy, history repeats itself. The Spanish philosopher, poet, and novelist is known for the popular aphorism, "Those who cannot remember the past are condemned to repeat it" (Santayana, 1905). Such is the case for the Essure™ PBC device (Figure 2) which was developed by Conceptus Inc. and approved by the US FDA in 2002. It is a permanent form of birth control designed as a metal coil which is inserted into the Fallopian tubes under hysteroscopic guidance. This induces tissue growth (fibrosis) into the coil over a three-month period, resulting in occlusion of the fallopian tubes. This is responsible for its contraceptive mechanism of action. To confirm correct placement and occlusion women have to undergo an additional procedure i.e. a hysterosalpingogram (HSG) three months later before discontinuing the current contraceptive method. An HSG is a radiological investigation to determine the patency of the Fallopian tubes. It was marketed as a 'minimally invasive procedure,

requiring no cutting, no visible scars and can be performed in your doctor's office', and more appealing due to the lack of the need for general anaesthesia (Kerin, 2001: 364-370).

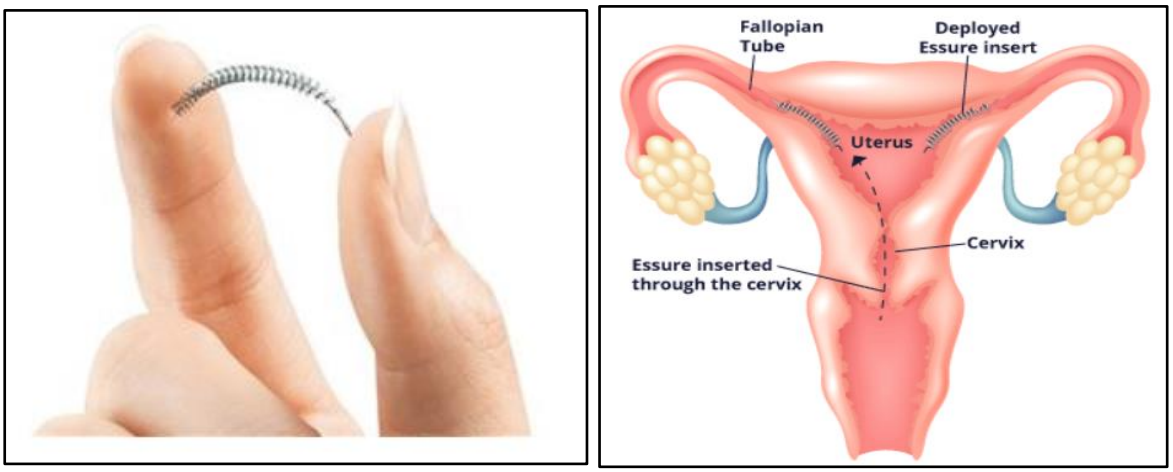

Figure 12: The Essure™ permanent birth control device (from https://www.nytimes.com/2018/07/20/health/bayer-essure-birth-control.html, and https://www.drugwatch.com/essure/)

It was approved as a Class III medical device, using the PMA process. This meant that the device fulfilled the FDA scientific requirements of ensuring device safety and efficacy for its intended use. As a condition, the FDA required the company to obtain five-year follow-up information on participants that were included in the PMA studies. Both the PMA and post market surveillance process by the US FDA had several flaws. PMA was based on two non-randomized prospective, single-arm clinical studies that lacked a comparator group. Only women on whom Fallopian occlusion was confirmed with HSG were included in the study, i.e. a skewed cohort (Dhruva, 2015: e17) . Yet the FDA deemed the device reliable.

There was a 14% failure rate at first attempt of placement i.e. user related. Safety and efficacy data were based on twelve and twenty-four month follow-up data respectively. According to US FDA standard this was acceptable. User device failures and the lack of a comparator group in the study were not identified as potential scientific flaws, and subsequently, by 2001, seven hundred and fifty thousand women had undergone this procedure.

The first post approval study was published 13 years after device approval and not at five-years as per the regulation. (Chudnoff, 2015: 951-960). It is unclear why there

was a delay, and why the regulators did not question the delay. Between 2011 and 2018 there were numerous changes as regards physician and patient labelling e.g. warnings against contraindication in nickel sensitivity, risk of pregnancy, chronic pelvic pain and device migration (www.fda.gov/medicaldevices/essurepermanentbirthcontrol). Women who had unsuccessful placement, who became pregnant before the three month HSG and who underwent hysterectomy were excluded from the analysis thus inflating the success rate. Four hundred and fifty seven adverse events were reported by Chudnoff et al, and 5093 by the US FDA since the 2002 approval (mostly relate to safety concerns of the device). While the complications associated with successfully placed devices is reported to be low the success of bilateral placement at first attempt is approximately 94.6% as per manufacturer data (Povedano, 2012). The unintended pregnancies as well as the fact that side effects had serious consequences, resulted in thousands of lawsuits have been filed against the company for adverse events and deaths related to this device.

In 2012 the company acknowledged the high rate of unintended pregnancies in the instructions for use, and recently informed the FDA of its decision to voluntarily discontinue US sales of Essure™ PBC after 31st December 2018 due to business reasons, and not for safety and litigation issues. In 2017, certain countries adopted a more stringent approach due to growing safety concerns of the device. The National Standards Authority of Ireland did not renew the product license and the company halted sales in Europe. The Therapeutic Goods Authority of Australia also recalled the device in 2017. As of August 2018 this safety warning appears on the Essure™ website. Physicians with access to the device need to be vigilant of this information as the device is still available within the supply chain.

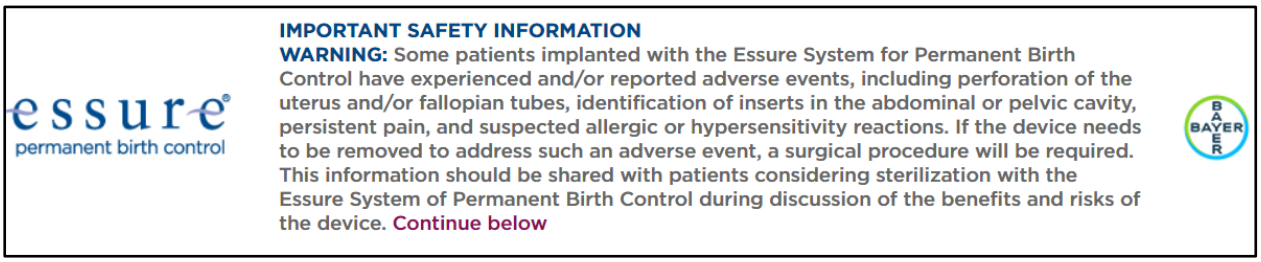

Figure 13: Safety warning on http://www.essure.com/permanent-birth-control/essure-procedure

Currently the FDA has restricted sales of the Essure™ PBC device only to physicians and healthcare facilities that review, sign and complete the "Patient-Doctor- Discussion Checklist-Acceptance of Risk and Informed Decision Acknowledgment." The company states, "it will continue to educate healthcare providers about the importance of appropriately counselling each patient on the benefits and risks of Essure" (April 2018, CNN Story highlight). This stance allows physicians more control in the decision-making process (i.e. informational elements are specifically relevant in this case). However, is this a strategy to shift responsibility and the associated legal ramifications in the interim onto physicians? Is it acceptable for a company to continue providing a device that is soon to be discontinued for safety reasons (apart from business reasons)? Usually a device recall is initiated by companies soon after it is considered harmful. Why was there not an immediate decision by the company and FDA to initiate a global recall of this device soon after reporting of adverse events?

So, in summary, the flaws, mistakes and questionable actions and policies were as follows:

With respect to the manufacturers:

- efficacy data reported by the manufacture have been criticized
- failure to report post surveillance data within five years

With respect to the FDA:

- The application of the device was fast-tracked
- Lack of explanation for the delay in receiving post approval surveillance data
- Pursue inquiry of this unusual behaviour

With respect to physicians:

- Adopted the use of the device based on success of skewed cohort
- Perhaps lack of request for better training for device placement
- Failure to carefully counsel women about possible risks and inquire about allergy to nickel or any other metal alloy (the device is composed of many metal ingredients)

Laparoscopic power morcellators (PMs): An FDA Class II device:

Uterine fibroids (leiomyomas) are the commonest benign pelvic tumour found in women. They are composed of muscular and fibrous tissue that originate from the muscle of the uterus. Options of treatment include oral medication, embolization of the uterine arteries and/or surgical removal either via open abdominal surgery or via minimally invasive laparoscopic surgery.

PMs are medical devices designed for surgical removal of leiomyomas or uteri during a laparoscopic procedure. This drill-like device cuts or shreds tissue into smaller fragments which are then removed in a protective bag typically via a two-centimetre incision or less. Using these devices large fibroids can be removed via a small laparoscopic incision. The associated benefits include: lower risk of surgical wound infection, less postoperative pain, shorter hospital stay and quicker return to activities (Barbieri, 2014:10-15) (Visit: the Morcellator: Youtube). The first PM was approved in 1991, and in1993 the first PM was introduced into the US market.

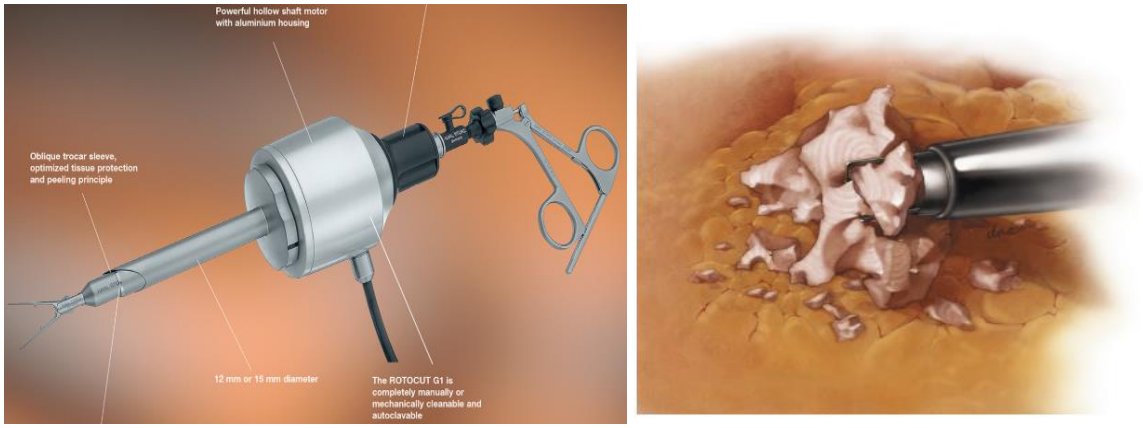

Figure 14: (A) A power mocellator used during laparoscopic removal of fibroids (www.baumhedlundlaw.com/defective-medical-device-injuries), (B), The device allows removal of large fibroids via a small abdominal incision (Illustration by Alex Baker, DNA Illustrations, Inc.).

The nature of the procedure carries the risk for dissemination of undiagnosed uterine cancer (such as leiomyosarcomas) resulting in further spread (upstaging) of the cancer because of the spillage of tissue into the surrounding abdominal and pelvic cavity. The approximate prevalence of this cancer is rare, 1 in 2000 patients with fibroids (Pritts, 2015). However, leiomyosarcomas of the uterus are aggressive and

have a poor survival rate of only 40% five year survival. Other concerns include injury to surrounding organs such as the bladder, bowel, major blood vessels and ureters as well as the risk of adhesion formation.

The death of an anaesthesiologist, Dr. Amy Reed, ignited the controversy over the safety of these devices. In October 2013 Dr. Reed underwent a laparoscopic hysterectomy for fibroid removal during which a PM was used. This resulted in the dispersion and upstaging of occult leiomyosarcomas to stage 4 disease. This serious adverse event was well-publicized and resulted in 284 more adverse event case reports to the US FDA. Together with her husband, Dr. H Noorchashm, they began a high profile campaign to ban the use this device in particular, and called for the need of improved oversight by the US FDA.

Ms Reed subsequently succumbed to the spread of the cancer in May 2017. Prior to this case the risk of spreading cancer via morcellation had been published, and thus the question is how could a device associated with spreading cancer be approved by regulatory authorities?

Secondly, how could responsible doctors use such a device? Dr Reed claims that she was not informed about the risks associated with the use of PMs, adding a third concern: absence of proper informed consent, in itself a violation opening the door to serious malpractice claims. Although the prevalence of leiomyosarcomas is rare, the fact that the associated consequence is likely to be lethal makes this a serious emotive issue for both patients and physicians.

The efforts of Dr Reed and Dr Noorchashm resulted in the FDA issuing a warning alert in April and November 2014 stating that the use of PMs during removal of fibroids can result in spread and upstaging of occult cancer. Subsequently manufacturers suspended sale of PMs, and the FDA required hospitals and manufacturers to report such cases directly to the FDA. This responsibility did not directly extend to physicians, although they were encouraged to do so by the FDA (www.medscape.com/viewarticle/875662). A significant number of physicians stopped using PMs because of hospital mandates and fear of litigation (Mandato et al, 2016: 206-214) ; Lum et al, 2016: 548-556). One can argue that this controversy gained significant momentum because of the publicity and real risk of further ‘spreading cancer’, but may be regarded as an over-reaction due to the rarity of leiomyosarcomas

So, in summary, the flaws, mistakes and questionable actions and policies were as follows:

With respect to the manufacturers:

- Was the need to counsel patients on the risk of further spreading of cancer stressed to physicians, albeit rare

With respect to the FDA:

- In view of this potentially lethal consequence, greater vigilance for following up on post use surveillance reports, perhaps even mandatory
- Therefore serious gaps in postmarket surveillance system

With respect to physicians:

- Failure to communicate the point of upstaging cancer in the consent process as illustrated by Dr Reed's case.

Need for oversight in women's health:

There clearly is an urgent need for improved oversight with respect to devices and technology which may have an impact on the lives of women. One route to attaining this is for physicians and in particular gynaecologists to get more involved in the lifecycle of the development of products meant to ensure and promote female health – in a sense, to take ownership of new advances. The way in which these products are currently used clearly illustrates the power of the HCI. In both instances, the employment of vigorous marketing strategies coupled with enthusiastic early adopters in the medical profession (e.g. physicians who are driven to be the first to use every new device and technique) and a malleable society resulted in unsafe device placements in millions of women by physicians.

One can argue that those in positions of power i.e. regulatory bodies and physicians could have avoided these adverse device events if there had been greater emphasis on scientific safety measures and ethical principles. In all instances, there was clearly limited and or obscured data on safety and efficacy, a lack of long-term outcome studies and a delay in recognizing safety issues. In addition, the delay in reporting of post-marketing studies within a specified timeline resulted in women continuing to undergo the procedure. This delay should have been timeously investigated as it represented non-alignment with science and ethics.

The prevalence of harm resulting from the use of untested devices is in all likelihood higher since the FDA only examines reports that are voluntarily submitted to the Manufacturer and User Facility Device Experience (MAUDE) database. This is a searchable online database developed by the FDA to capture medical device reports. Despite the best intentions of physicians to confer the benefits of devices to their patients, the potential for harm in the cases quoted outweighed the overall benefits. The ethical principles of *primum non nocere,* and non-maleficence are not simplistic principles to abide by especially if medical devices are to receive approval by regulatory authorities. The principle of non-maleficence obligates physicians to abstain from and prevent harm to their patients.

Why does harm come to patients if we as physicians are the final purveyors in the system? Possible reasons include:

- Physicians automatically assume a sense of assurance after device approval by regulatory authorities, i.e. accept marketing information instead of reading all the available literature and forming their own opinions.
- Regulatory authorities prioritize manufacturers' interests above patient safety interests
- Physicians obtain insufficient training in the use of the devices and to promote research integrity
- Physicians do not give detailed thought before offering these innovations to women and do not maintain an air of Socratic skepticism about their practice (i.e., constant rethinking, revisiting, questioning, revising what seems to be accepted knowledge)
- Essential elements of informed consent are not emphasized when consenting for these procedures: patients are not informed of potential morbidity and informed consent is therefore inauthentic.
- Physicians too quick to use these devices (early adopters). Acceptance of innovation runs along a bell shaped curve. About 25% of US are early adopters, and this is not always an advantage since not all side effects and complications are apparent then. Most of us (50%) fall into the body of the curve: we wait until we are satisfied regarding safety and efficacy. And 25% never change their practice.

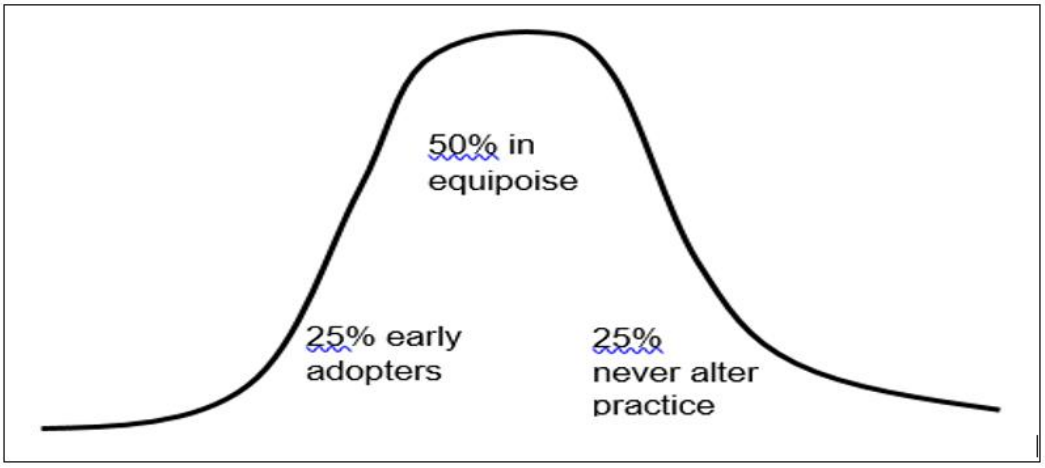

Figure 15: Graphic illustration of the natural history of adopting novel products

As regards physicians' uptake of innovation, Scott's parabola is an ideal example of describing the lifecycle of adopting innovation. The typical rise and fall of the utilization of for example drugs, devices and procedures should be altered to one of proven sustainability. Instead, following the uptake of these devices, harm ensued, regulatory warnings flowed from harm, and the devices were subsequently taken off the market. This raises the question: where do physicians position themselves with respect to the life cycle of the usage of novel devices? Furthermore, where should they be positioned?

Lifecycle of adopting innovation by physicians: Analysis of 'boom and bust' phenomenon

Following a launch of a new drug, device or surgical procedure, there is great excitement and enthusiasm amongst physicians and the HCI, albeit for different reasons. This represents the 'boom' phase of innovation: 'promise of cure', 'better drug', 'new device' etc. Using the war metaphor so popular in medicine, 'victory' can be proclaimed when the innovations ultimately become the standards of care.

To begin with, initial reports are promising, marketing is at its peak, and physicians are ready to listen and learn more about this encouraging innovation. British gynecologist, J.W. Scott in 2001 described the rise and fall or boom and bust phenomenon, in a landmark publication entitled "Scott's parabola: the rise and fall of a surgical technique (Scott, 2001: 1477) . Orthopedic devices such as the Artelon^{R} arthroplasty, metal-on-metal hip arthroplasty devices, Infuse^{R} bone grafting and

gynecological devices (Dalkon Shield IUCD, Essure™ PBC, and PMs) are some examples of rising to fame and then falling to ultimate disuse (Hamilton et al, 2012). The natural history from adopting innovation to ending with 'taken off the market' is illustrated by the parabola below. This parabola is powerful in its ability to graphically highlight the need for greater responsibility of all stakeholders involved in developing and disseminating innovation and 'new knowledge'.

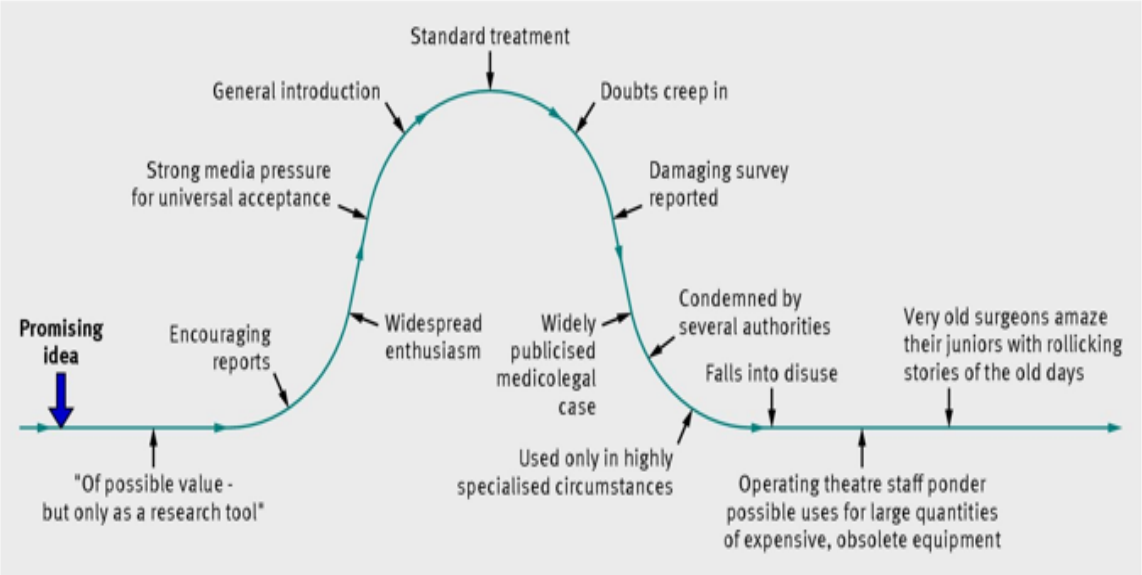

Fig 1 "Scott's parabola" (reproduced from Scott JW. Scott's parabola: the rise and fall of a surgical technique. *BMJ* 2001;323:1477)

Figure 16: Scott's parabola illustrating the natural history of innovation.

The parabola demonstrates the interplay of the relationship between the HCI, physicians and patients. I have explored this parabola in relation to the history of Dalkon Shield, Essure™ PBC, TVM for POP and PMs used during laparoscopic surgery.

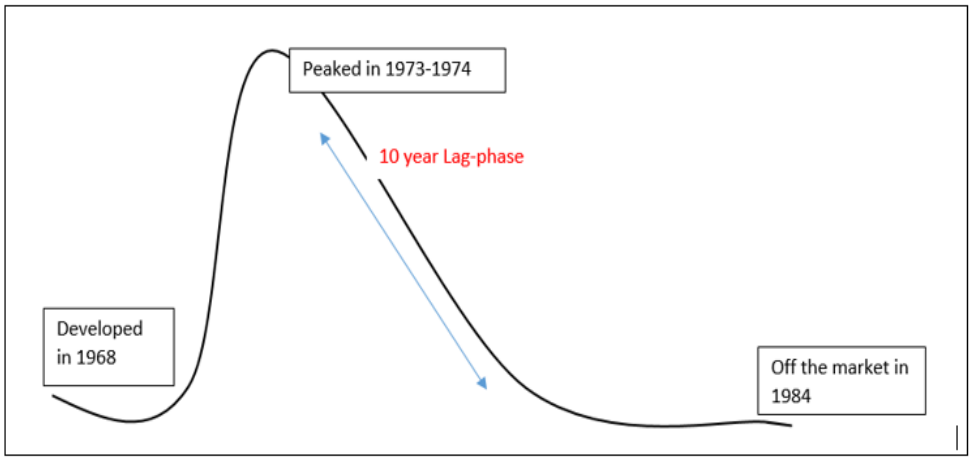

Figure 17: Graphic representation of natural history of timelines of Dalkon Shield intrauterine contraceptive device.

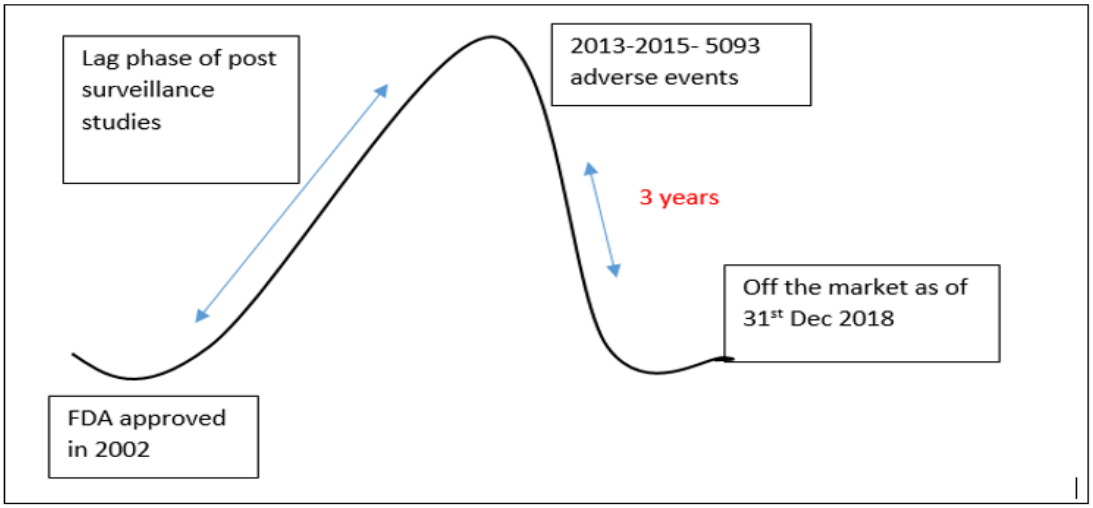

Figure 18: Graphic illustration of natural history of timelines of Essure™ PBC (permanent birth control); FDA, Food and Drug Administration

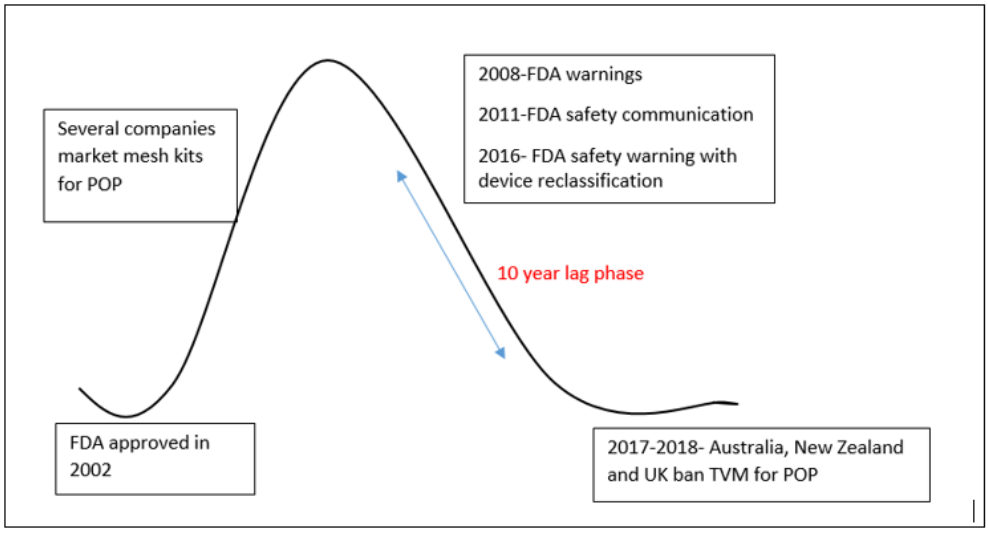

Figure 19: Graphic illustration of the natural history of timelines of transvaginal mesh for pelvic organ prolapse. POP, pelvic organ prolapse; TVM, transvaginal mesh; FDA, Food and Drug Administration

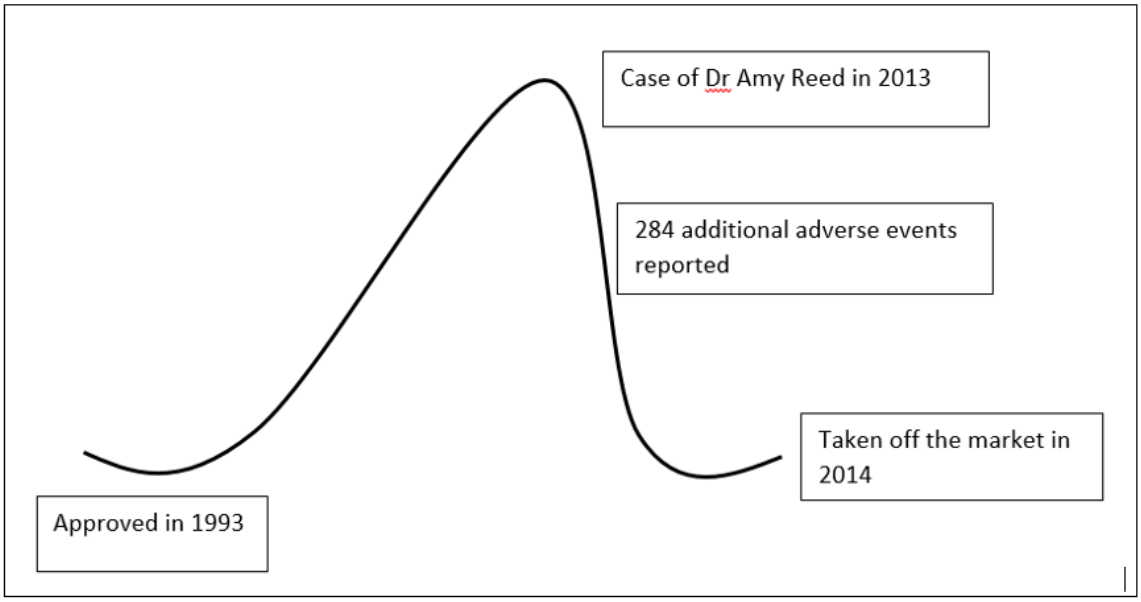

Figure 20: Graphic illustration of the natural history of timelines of laparoscopic power morcellators.

Figure 17-20 illustrate the following points: overall physicians generally are too quick in adopting products. As illustrated on the down-slopes, however, the delay in reporting adverse events and removal from the market is often unacceptably long, given the nature of the morbidity described. At least a decade lag phase ensued

before the Dalkon Shield IUCD and TVM kits for POP were taken off the market. In contrast, the lag in the case of the Essure™ PBC was three years, and one year with PMs. This reflects a deep sense of concern over inflicting further harm to female patients or perhaps for financial reasons in the case of the Essure™ PBC.

Physicians are the ultimate 'clients' to the HCI and also the final point of care for patients. Who is to blame for this phenomenon illustrated by Scott's parabola, and why do we allow ourselves to be easily controlled? Is it a lack of integrity in the profession as such, perhaps something amiss in our training? Integrity means following and practicing something you believe to be true. In the forgoing physicians very often knew right from wrong, at least one hopes they did, yet chose the wrong option.

South African physicians should also take note of the implications of consumer protection legislation. Extension of responsibility for the use of any item/ product/ device is outlined in the South African National Consumer Protection Act 68 of 2009, which came into effect in April 2011. This legal framework was designed to empower consumers (by having rights e.g. rights to choose a product, right to safe and good quality products, right to disclosure of information in understandable language etc.) and holds responsible all persons involved in the chain of the product (supplier responsibility) i.e. manufacturing, marketing, dissemination, and eventual utilization of the product. Thus physicians can potentially be held liable if medical devices have inherent problems, such as those that I have described.

The regulatory authorities and HCI have important responsibilities regarding patient safety. Nevertheless, physicians should also understand their responsibility and diligently pursue patient safety as a prime priority.

Failure on their part cannot be ascribed to the regulators or HCI. Physicians cannot claim ignorance as we understand the wrongs we are doing. Either we do not fully comprehend the ethical duty of the principle of non-maleficence, or the ethical principles are insufficient to deal with these issues. Innovation will continue and is necessary. New drugs undergo a rigorous research process before they are released and registered, followed by continued surveillance, and so should device innovations.

Each role player is guided by a unique set of Acts/ laws, rules and/or codes.This thesis would be incomplete without discussion the evolution of Acts in relation to the regulation of novel medical devices. The discussion that follows outlines a sequence of events that occurred in the US, and since SA draws on international guidance, this discussion is relevant.

Chapter 5: Development of safety codes, rules and regulation for ensuring safety:

Clinical research disasters have violated the ethical principle of ensuring patient safety. Laws, Acts, Amendments and Regulations were put in place by governments to prevent harm, and have evolved to incorporate both ethical principles and scientific validity/scrutiny. On a lighter note, 13th century medieval English bakers prompted King Henry III to pass the Assize of Bread and Ale law in response to lesser weight of bread and volume of ale sold to customers. Thus thirteen loaves instead of twelve were given to avoid penalization in the form of a beating or jail time as an act of kindness to preempt penalty (for a loaf of bread). An interesting point to note is that consequences of actions resulted in an altered behavioural pattern.

Physicians begin practicing medicine by professing an oath similar to the Hippocratic Oath. We promise to uphold just and ethical practice in order to protect patients from harm. In the last few decades, that responsibility has been carried over to include research by introducing various Acts and Amendments. In the ensuing section, I outline events that shaped the development of the applicable Acts below (www.cdn2.hubspot.net):

Regulatory events:

In 1906 the Pure Food and Drug Act was enacted by the US Congress because of unsafe and unsanitary meat packaging of slaughtered animals. The aim was to protect consumers and raise the standards in the food and drug industry.

Between 1932-1972, the Tuskegee Syphilis study was conducted to observe the progression of untreated syphilis in rural African-American men in Alabama under the pretense of receiving free health care from the US Government. Over the 40 year period penicillin was withheld from those who were infected, men were lied to and there was lack of communication as regards diagnosis and no ‘real’ informed consent.

Decades later (in 1997), surviving victims of the Tuskegee experiment were invited to the White House and received a formal apology and a monetary settlement from President Bill Clinton.

The Federal Food, Drug and Cosmetic Act of 1936 was promulgated in response to public outrage to more than 100 deaths after consuming the Elixir Sulfanilamide which had poisonous diethylene glycol (DEG) as a solvent. This Act required proof of safety prior to market approval and labelling ‘instructions for use’. At this time, animal testing was not a regulatory requirement. The manufacturing chemist, Harold Watkins committed suicide while awaiting trial (Mihm, 2007).

In 1947, as a consequence of the Nuremberg trials, a set of research ethics principles for governing human medical research was formulated. It was called the Nuremberg code and constituted ten points. These include: the requirement of voluntary, well-informed human subjects; the experiment should be set up in a way that avoids physical and mental suffering; the experiment must aim at positive results for society and be based on previous knowledge; the risks of the experiment should be in proportion to the expected humanitarian benefits; preparation and facilities must protect subjects from risks of the experiment; the experiment must be abandoned if there is a risk of death or disabling injury; the staff involved must be fully trained and scientifically qualified; participants must be able to freely quit, and finally the experiment must be stopped at any point when they observe that continuation would be dangerous (Annas, 2008:136-140).

The Kefauver-Harris Amendment is a 1962 amendment to the Federal Food, Drug and Cosmetic Act. It was initiated after lethal birth defects and other congenital deformities involving the limbs resulted from ingestion of Thalidomide by pregnant women. The drug was marketed off-label to alleviate morning sickness. This Act required proof of safety and efficacy studies and disclosure of side effects by manufacturers.

The World Medical Association (WMA) developed the 1964 Declaration of Helsinki for physicians. It expanded on the Nuremberg code to include respect for human subjects and informed decision-making. Although not directly legally binding unless incorporated into local guidelines (as is the case in SA), it is morally binding on physicians who are members of a Medical Association affiliated with WMA. The declaration is regarded as a cornerstone document in human research ethics.

Throughout this period, technological advancement in the medical device industry continued to boom and enjoy cover under the 1938 Federal Food, Drug and Cosmetic Act. To address the need to regulate devices the FDA created the Bureau of Medical Devices and Diagnostic products in 1974.
The Dalkon Shield saga as discussed earlier, prompted the 1976 Medical Device Amendment Act. This Act resulted in device classification and the requirement of proven safety and efficacy data prior to marketing.

In 1979, The Belmont Report which was written in response to the Tuskegee Syphilis Study, introduced three ethical principles in clinical research i.e. respect for persons, beneficence and justice (as a primary ethical framework).
In 1981, the FDA and the Department of Health and Human Services revised regulations pertaining to human subject protection by creating the Code of Federal Regulations (CFR) Title 21. This codified document contains general and permanent rules that are utilized by the US Government, and is updated annually. Title 21 has several parts ranging from the governing of food and drugs, medical devices, cosmetics, biologics etc. This is an important development as it deals with issues such as:

- Regulations for protection of human subjects (which include a thorough description of informed consent of human subjects, and safeguards for children in clinical investigations)
- The need for financial disclosure by investigators
- Description of the general provisions, functions and operations of Institutional Review Boards
- Investigational New Drug Applications and exemptions
- Regulation of electronic records and electronic signatures

In 1990, there was a move towards global harmonization of regulatory requirements for research resulting in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines. This project draws the regulatory and pharmaceutical experts together with the aim to harmonize scientific and technical aspects of pharmaceutical product registration. The ICH Good Clinical Practice (GCP) guidelines define a set of research standards and indirectly enforce ethical aspects of clinical research. Completion of the Good

Clinical Practice (GCP) course is mandatory for every clinicians involved in clinical research in the US and a similar up-to-date certification is required in SA. Simultaneously, the Safe Medical Device Act requires physicians and hospitals to report incidents to the FDA and manufacturers in the case of injury or death. The Act also includes the authority of the FDA to order a device or product recall.

These Acts/Regulations were drafted by a responsible group of regulators and ethicists. Yet we are still faced with defective devices resulting in harm, litigation, device recalls, and black-box warnings ending with the ultimate demise of the product. I believe the success of these Acts align with the concept of human integrity i.e. accurate data, timeous reporting and detailed information on deaths in early animal studies, meticulous adverse event reporting, omitting the use of fraudulent safety data and concealment of results. This implies strict and responsible abiding by the rules. It therefore seems opportune to relook at the device approval process and formulate a template to guide physicians when faced with innovative medical products.

This is the purpose and aim of the next section. However, before we get there, a short note development of the classification of medical devices seems appropriate. Regulatory Acts as outlines above are useful only insofar as they protect patients from harm, are accepted and honoured by all role players. The number of applications for medical device approval/clearance is escalating and it is opportune that loopholes and inadequacies are identified and dealt with timeously. In Chapter one 2, I have only briefly outlined the three classes of medical devices. While Class I has a history of safe use and includes low risk devices such as tongue depressors (thus exempt from premarket notification and postmarket studies),Class II devices (e.g. infusion pumps) requires premarket notification clearance (referred to as the 510k notification) and postmarket surveillance studies. Class III (i.e. life sustaining devices like defibrillators) requires evidence from prospective randomized controlled trials (RCTs).

Since 2000, more than 30 000 medical devices received clearance from the FDA under the 510k notification, the vast majority being Class I and II devices (www.nap.edu). Devices for approval have increased in number, and are more complex as illustrated by the gynaecological devices such as TVM mesh kits, Essure^{TM} PBC and PMs. Under this rule, patients who had TVM insertion for POP

sustained harm and thus the credibility of the 510k notification for TVM is under federal, political and public scrutiny. Yet the impression is that the rule is less of a problem than the integrity of those who apply it. A postmodern approach to ethics state that the morality of rules lie in the way they are applied i.e. with responsibility. What this implies that sets of rules should never be seen as maximal standards (as we invariably are wont to do) but as minimal standards.
Under the 510k rule, if a device demonstrates substantial equivalence to a legally marketed predicate device, then no clinical trials are required to demonstrate safety and efficacy. The 510k rule was intended to deal with the influx of new device applications and not designed to assess safety and efficacy of medical devices.

Yet a responsible approach would imply a skeptical view of new devices, irrespective of their 510k clearance.
Currently, in brief, the typical natural history of medical device development involves Research and Development, followed by an application to FDA in the US and SAHPRA in SA (as from February 2018). Based on the class of device, a decision is made for the submission of premarket approval studies and postmarket surveillance studies. This process is country dependent.
A potential flaw in the US process lies in the 510k rule and the lack of timeous report back of postmarket surveillance study requirements, which may result in ongoing harm to patients. This process is also passive in that the regulatory authority depends on data from the manufacturer and physician. It can also be an active process where the regulatory body actively seeks information on device related adverse events, injury, malfunctions and deaths.

It is time to relook the approval and dissemination process of novel medical devices. Thus in the concluding chapter I propose an ethical template to be considered by physicians prior to using novel medical devices and the consideration of the role of virtue ethics in guiding doctors

Chapter 6: Conclusion

An ethical template for adopting novel devices: From discovery to delivery

In 2018 we are still faced with medical device associated adverse events, disability and deaths of patients despite adoption of several codes by both physicians, the HCI and regulatory authorities. In this chapter, I develop and propose an ethical template to guide practitioners who contemplate using novel devices.

1. Innovation in healthcare, a means to an end?

Studies on the process of innovation are of recent interest. The theory of diffusion of innovation described by Rogers is a popular model in both the educational and technological innovation fields (Sahin, 2006: 14-23). This model provides valuable insight as to why certain practices are adopted and others rejected (Sanson-Fisher, 2004: S55). Rogers describes innovation as, “an idea, practice, or project that is perceived as new by an individual or other unit of adoption”, and its success lies in the innovation-decision process, which involves five chronological steps:

- Knowledge (individual seeks information about the innovation),
- Persuasion (individual develops an opinion on whether to adopt or reject innovation)
- Decision (individual chooses to adopt or reject innovation),
- Implementation (innovation is put into practice)
- Confirmation (individual seeks support of her/his decision) (Rogers, 2003).

Understanding the mechanism of dispersing innovation is relevant as it is generally thought that innovation is necessary and essential. The basis for this stance is that new medications, surgical procedures and diagnostic techniques in medicine have improved the quality and duration of life in millions of persons (Fuchs, 2001:30-42; Cutler et al, 2007: 97-110; Woolf et al, 2007: 679-683). Physicians thus find themselves engaging with innovators (i.e. the HCI) at various levels as discussed in chapter three.

While this relationship is important and will continue to evolve, the question arises whether the current status of healthcare has generally been improved given the significant medical and technological advancements in the last century?

Globally, healthcare remains expensive and inaccessible to most people (Paterson, 2002: 169). However, this disparity is greater for societies in low- and middle-income countries compared to high-income countries (Peters et al, 2008:161-171). Current healthcare debates involve discussion of the vast 'chasm' between the actual quality of care rendered to patients and the much higher quality that should be delivered considering significant innovations in all spheres of medicine (Wolfe, 2001: 233-235). It has also been shown that access to expensive healthcare in the US does not equate to better healthcare since up to one third of American patients receive contraindicated care and up to 98 000 of them die annually as a result of medical errors (Starfield, 2000: 483-485; Schuster,1998: 517-563). Reid et al suggest that lack of attention to safety regulation, quality control and optimization of healthcare systems may plausibly add to this unacceptable phenomenon (Reid et al, 2005).

Locally, there is a lack of data as regards deaths due to medical errors, and the current reality is the high rate of medical malpractice litigation (Pepper, 2011: 29-35). The current realities of healthcare include soaring costs, rising litigation, death due to medical errors, lack of health insurance for a significant majority of the population, and a globally fragmented healthcare delivery system (Kohn, 2000). Although innovation may, in addition to economic drivers, also have noble intentions, it can result in harm. It has also introduced new scientific, ethical and moral dilemmas such as warning alerts, recalling of medical devices, harm to patients and litigation(Zuckerman, 2011: 1006-1011; Reitsma, 2002: 792-801). The terms innovation, discovery and invention represent different states of knowledge and it would be interesting to study which of these knowledge states brings us closer to the ideals of ethical practice and sound science.

Analyzing healthcare is complex, multifactorial and controversial. It is not clear which indicators should be ideally used in the analysis. The regulatory and professional safeguards notwithstanding, innovative devices have caused death and disability and resulted in lawsuits costing both the government and HCI billions of dollars. The system is thus clearly not infallible.

The various role players i.e. governments, the private sector, regulatory and professional bodies have the responsibility to deliver safe innovations (technological, medicinal and medical devices) to society, and promote a high level of

professionalism. Abiding to sound scientific and ethical principles is one mechanism of ensuring patient safety. Thus below I outline the development of an ethical template to be considered before adopting the use of novel products.

2. An ethical template: A Passion for protecting patients

The pathways for medical device approval need to be re-adjusted towards incorporating a stronger ethical component of preventing harm to patients. The flow diagram below illustrates my view of the process of new medical device evaluation.

Step 1: Ethical norms and standards

- The process should commence with the development and promotion of research integrity by all stakeholders (combination of principle-based approach and virtue-based ethics)

Step 2: Sound science (promotion of scientific principles and ethical practice by adhering to the following):

- Physician (academic) and Manufacturer consultation for planning
- Rationale for device design and concept discussed and criticized
- Preclinical (in vitro and vivo studies) and animal study analysis
- Human testing: safety studies in a larger number of both healthy volunteers and pathological groups
- Documentation of safety and efficacy within a specified time period
- Meticulous attention to adverse events/ death/ injury/ disability/ device malfunction

Step 3: Premarket authorization (Undertaken by a PMA team equipped with scientific and ethical knowledge):

- Review by local regulatory authorities i.e. dedicated ethics committee , SAHPRA and SAMED
- Independent safety analyst

- If deemed safe and effective with minimal risk for harm, then development of safety nets such as:
    - Mandatory national registry setup
    - Setting up of user-friendly adverse event reporting mechanisms
    - Annual vigilance updates to ethics committee

Step 4: Responsible marketing to physicians and society

Step 5: Responsible postmarket surveillance:

- Ongoing evaluation by all stakeholders to ensure best practice
- Online accessibility to report events
- Tracking device and device identification
- Mandatory and timely review by physicians and regulatory authorities

Step 6: Endorsed by all stakeholders

- May evolve to become standard of care

Prior to 2017, there were no regulations pertaining to the use and sale of medical devices in South Africa. The Medicines Control Council (MCC) regulated medicines or products with medicinal components and electromedical devices were regulated by the Directorate of Radiation Control. The SA market has long recognized the need for medical device regulation and thus the South African Medical Technology Industry Association (SAMED) was formed. Together with the South African Health Products Regulatory Authority (SAHPRA) (discussed in chapter one), the aim of both bodies is to ensure access to safe, effective, good quality medicines and medical devices, and create and maintain an ethical ethos of protecting and promoting human and animal health, service excellence and integrity. While the steps proposed represent a guideline for adopting new innovation, I do acknowledge that use of new innovation by early adopters in step 2 allows the gathering of safety and efficacy data prior to dissemination to society.

Aristotle: where do virtue ethics fit into the equation?

In the previous chapters I have mentioned the notion of virtue ethics several times and in a sense created the expectation that I would eventually attempt to integrate that notion into a revision of our approach to solving the dilemmas created by medical innovation. That expectation has not been satisfied as yet, and I shall attempt to do that in the next section.

The algorithm above is no more than an outline – it would require much more, including the involvement of the regulatory bodies, to turn it into anything useful, though physicians would benefit even now in accepting those sections that do not require regulatory involvement. I. Have not written a separate section on the limitations of this study, but this is in a sense a limitation.

Note that the suggested algorithm commences with promoting research integrity; integrity is a prime virtue. The principle-based approach, developed by Tom Beauchamp and James Childress is based on four principles of biomedical ethics, respect for persons, non-maleficence, beneficence and justice. It focusses on the adherence to principles which are important components of ethical conduct (Beauchamp 2007, 3-10). In isolation, this approach has been criticized for its lack of exploring the relationship between motivation and ethical conduct and the inability to resolve ethical conflict (Resnik, 2012: 329-343). This gap can be plugged by recourse to virtue ethics.

Aristotle (384 BC – 322 BC), an ancient Greek philosopher, is considered as one of the most influential philosophers of all times. Aristotle believed that habit is more important in making moral decisions than theoretical knowledge and practical skill, as moral decisions require appropriate action, in the right amount and at the right time (referred to as *hermeneia*) (Gadamer, 1965/1975: 274-289) . He laid the foundations of western philosophy, and his best-known work on ethics is captured in *Nicomachean Ethics*, believed to be named after his son or father *Nicomachus.* The thematic content describes moral codes of conduct to achieve good living. He believed that we should all aim to achieve a state of eudemonia i.e. happiness, blessedness and human flourishing. While attempting to live a good life is the final goal, it is not a means to anything else. He suggested that this state ‘of true happiness’ can be achieved by a life devoted to virtuous actions. He also suggested

that human beings have the ability to make choices and judgments because of the unique ability to reason. A virtuous person will thus use practical wisdom to decide how and when to exercise a particular virtue. This principle needs to be applied in the present dilemma.

A *virtue* is a 'depositional trait of character that is socially valuable and reliably present in a person and a *moral virtue* is a dispositional trait of character that is morally valuable and reliably present' (Beauchamp, 2007:3-10). Virtue ethics focusses on the significance of moral attributes.

These largely positive attributes develop over time and become deeply rooted in our lives. Virtues and the application of practical wisdom are key concepts in Virtue ethics, as opposed to Deontology which emphasizes rules and duties, and the Utilitarian approach which emphasizes consequences of actions.

While Aristotle proposed four cardinal virtues i.e. prudence, temperance, courage and justice, the list of virtues is extensive and value-laden. Certain virtues warrant special significance in relation to the role and responsibilities that need to be fulfilled. Overall, the range includes:

- Practical virtues (e.g. courage, temperance, etc.),
- Intellectual virtues (e.g. knowledge, wisdom, etc.),
- Scientific virtues (e.g. respect, sincerity, etc.)
- Professional virtues (e.g. honesty, truthfulness, etc.)

Beauchamp and Childress suggest five focal virtues for healthcare professionals. These include compassion, discernment, trustworthiness, integrity and conscientiousness. While other virtues are no less important, these virtues are closely connected to one's personal and professional life and have the power to uncover goals and motivations (Resnik, 2012: 329-343). In the context of healthcare professionals, it is vital that moral attributes of professionalism are also considered. As discussed in chapter one, many philosophers have pondered over the most precise and complete definition of professionalism. The definition proposed by Ellison most accurately embodies the innate significance of moral virtues in professionalism in the following citation:

'Professionalism starts with a commitment to achieve something more satisfying than immediate and personal gain and requires a commitment and devotion to quality,

excellence and personal sacrifice that goes beyond an eight hour day. Professionalism must rest on a solid base of education, experience and skill and must encompass real respect for other professionals as well as patients' (Ellison, 2003: 9-10).

In essence being a healthcare professional involves acquiring a set of clinical skills and competencies in medical school and via professional bodies. However, the value of personal behaviour and attitude is not officially prioritized (De Roubaix, 2017: 79-83). The incorporation of virtue ethics has a distinct advantage to provide guidance in medical decision-making by introducing the human element, devoid in the principle based approach. Pertinent virtues applicable to gynaecology include sincerity, honesty, patience, kindness, compassion, commitment, beneficence, devotion, discretion.., in fact the list is ongoing…These virtues predisposes the moral agent always to act in a specific fashion, i.e. dictated by the virtues held dear.

What I suggest is that the decisional power balance be tipped toward the physician. By this, I mean physicians are in control of the various steps of the innovation and dissemination process but never in a paternalistic sense. Equipped with ethical integrity, moral attributes, scientific knowledge, clinical training and most importantly, as purveyors of patients' decision-making, physicians will have the unique power as professional agents to guide all role players involved in innovation, and patients who seek our guidance. Thus the ultimate *telos* or aim is to become a virtuous doctor. To relate this to the present discussion: While it is perhaps impossible to determine whether a medical device is completely safe, a virtuous physician will most likely seek to ask the right questions when faced with innovation. These questions are bound to be quite different from those asked from a deontological or utilitarian point of view. It is therefore also a question of attitude. Some questions that will generate solutions that are more creative include the following (note that these questions do not by themselves represent a virtue ethics approach; the appropriate virtue would rather be apparent in terms of the attitude and reason for asking the question, and the nature of the response):

- Analyze and question the rationale for device development. How does it compare to the current standard and what makes it 'novel'?

- Examine outcomes of animal studies as physicians commonly omit this step. This provides useful information to the further development of the product, or maybe a reason to abandon the project altogether
- Does the product have robust safety and efficacy data? Evaluate timelines since inception (i.e. 24- months, 36-month data). The inclusion and exclusion characteristics of the comparator group in any clinical trial must also be analyzed
- Examine the side effects, adverse events, injury, disability and device malfunction issues
- The associated learning curve in context of the device must be examined.
- Are there safer alternatives and how do they compare?
- Does it meet the local regulatory standards of the country?
- Does the use and outcome of the device align itself with the four ethical principles and virtue based ethical principles?
- Finally the physician will decide either to adopt, reject or remain in equipoise

These are questions each physician should ask when confronted by medical innovation.

Physicians are endowed with the immense responsibility of protecting patients, and represent the final point of care. While it is important to deliver the 'best and safest care possible', moral responsibility prompted and supported by virtue ethics should guide the practitioner in the final decision making process. Apart from the salient points in the above algorithm, ethical coaching including the significance of moral attributes, commencing in the undergraduate program will arm physicians more holistically. In addition, future studies must explore perceptions of adopting innovations, and determine whether there is a morally driven base.

Medical innovation is currently disparate, essentially driven by the HCI. It is time that physicians determine whether the HCI should gain access to the professional field of medicine. By guarding our profession and ensuring sound scientific and ethical excellence, we once again can be in the driver's seat.

I end with this,

"Life is short, art long, opportunity fleeting, experience deceptive, judgment difficult". ----***Hippocrates***

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