# PARALLEL REGULATORY–HTA REVIEWS: IMPLICATIONS FOR IMPROVING ACCESS TO MEDICAL DEVICES IN SOUTH AFRICA

**Urvishi Raghununan**

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***This research report has been approved for publishment by the University***

## DECLARATION

I declare that this research project is my own, unaided work. It is being submitted for the Degree of Master of Science at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

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**(Signature)**

__20th __day of ____June___2022___at_Benoni_____

## ABSTRACT

The South African Health Products Regulatory Agency (SAHPRA) although technically proficient, has challenges with timely reviews of medicines despite significant improvements. The recent regulation of medical devices may detract from SAHPRA's improved performance trajectory. The economic evaluation of medical devices, a form of health technology assessment (HTA) by a separate entity, is complex due to its attributes. HTA in South Africa is fragmented and lacks a national HTA body. Timely access will be dependent on efficient regulatory and HTA reviews, and harmonization synergies seen globally. HTA recommendations in terms of outcome and efficiency is the *de facto* barrier to access. No literature exists on SAHPRA adopting harmonization with HTA bodies. A literature search strategy was conducted using defined keywords on electronic databases, to find countries that currently undertake parallel regulatory-HTA reviews in some manner or form, within an established framework. As the grounded theory approach was used in research extraction, the initial findings highlighted an even more critical process impacting access to health technologies, termed the HTA outcome or recommendation procedure, resulting in an additional analysis of this principal function and impact thereof on the regulatory-HTA timeline. This study demonstrates that adoption of a parallel regulatory-HTA review framework with the soon to be established national HTA body in South Africa, can improve access to medical devices, and align with other strategic objectives such as universal healthcare coverage. In preparation for such an alliance, there needs to be consideration given to immediate dialogue and workshops between existing public and private sector HTA bodies and SAHPRA, for learnings and future collaboration with the national HTA entity. It would be ideal if appointments can immediately be made to the leadership structure, to ensure early and effective synergies are enhanced.

## DEDICATION

The past few years culminating to this point have been one of the most challenging times of my life. Navigating through the COVID pandemic whilst serving in a critical healthcare supply chain role, has been tumultuous, unprecedented, unnerving and at the same time, was the honour of my life. A pregnancy thrown into the mix was the proverbial cherry on the chaotic cake!

I thank my supervisors for their patience, guidance and understanding during this journey, without which I would have been adrift.

To my family - for their patience, love, and support – I am incredibly grateful. My children for their understanding, which overwhelms we with emotion thinking of their age and how precious time spent together is. My husband for the weekend cooking and my dad for chipping in with bread and milk runs! Finally, yet importantly, to my dear mum, who has stepped in to help during her golden years (and for many prior years too). Your sacrifice was immeasurable. I dedicate this work to you all.

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## ABBREVIATIONS

| | |
|---|---|
| **AHRQ:** | Agency for Healthcare Research and Quality |
| **AOTMiT:** | Agency for Health Technology Assessment and Tariff System (Poland) |
| **BfArm:** | The Federal Institute for Drugs and Medical Devices (Germany) |
| **CADTH:** | Canadian Agency for Drugs and Technologies in Health |
| **CDR:** | Common drug review |
| **CHEERS:** | The Consolidated Health Economic Evaluation Reporting Standards |
| **CIRS:** | The Centre for Innovation in Regulatory Science |
| **CMS:** | Centers for Medicare and Medicaid Services (USA) |
| **EMA:** | European Medicines Agency |
| **EXCITE:** | Excellence in Clinical Innovation and Technology Evaluation |
| **FDA:** | Food and Drug Administration (USA) |
| **G-BA:** | Federal Joint Committee (Germany) |
| **HSP:** | Healthcare service package |
| **HTA:** | Health Technology Assessment |
| **HTAi:** | Health Technology Assessment International |
| **ICER:** | Institute for Clinical and Economic Review |
| **IMB:** | Irish Medicine's Board |
| **INESSS:** | Institut National d'Excellence en Santé et en Services Sociaux (Canada) |
| **IVDs:** | In vitro diagnostics |
| **MaRS:** | Medical & Related Sciences |
| **MCC:** | Medicines Control Council of South Africa |
| **MEB:** | Medicine Evaluation Board (Netherlands) |
| **MHRA:** | Medicines & Healthcare Products Regulatory Agency (UK) |
| **MPA:** | Medical Products Agency (Sweden) |
| **MSAC:** | Medicines Advisory Services Committee (Australia) |
| **NASs:** | New active substances |

| | |
|---|---|
| **NCEs:** | New chemical entities |
| **NDoH:** | National Department of Health |
| **NHI:** | National Health Insurance |
| **NHS:** | National Health Services (UK) |
| **NICE:** | National Institute for Health & Care Excellence (UK) |
| **NLEM:** | National List of Essential Medicines |
| **NOC:** | Notice of Compliance |
| **NRA:** | National Regulatory Authority |
| **OECD:** | Organization for Economic Co-operation and Development |
| **OHTAC:** | Ontario Health Technology Advisory Committee |
| **PBAC:** | Pharmaceutical Benefits Advisory Committee (Australia) |
| **PBS:** | Pharmaceutical Benefits scheme (Australia) |
| **PDC:** | Prosthesis & Devices Committee (Australia) |
| **PMS:** | Post marketing surveillance |
| **PSA:** | Parallel regulatory–health technology assessment scientific advice |
| **RCTs:** | Randomized controlled trials |
| **RWE:** | Real world evidence |
| **SAHPRA:** | South African Health Products Regulatory Authority |
| **SAMED:** | The South African Medical Technology Industry Association |
| **SMC:** | Scottish Medicines Consortium |
| **TGA:** | Therapeutic Goods Administration of Australia |
| **TLV:** | Dental and Pharmaceutical Benefits Agency (Sweden) |
| **WHO:** | World Health Organization |
| **ZIN:** | The National Health Care Institute (Netherlands) |

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# CHAPTER ONE – INTRODUCTION

## 1.1 Introduction & literature review

### 1.1.1 Roles of the regulator, HTA body and payer/coverage entity

The WHO (2017) defines a health technology as “any intervention that may be used to promote health, to prevent, diagnose or treat disease or for rehabilitation or long-term care”. It further elaborates that a health technology includes medical devices ranging from simple wooden tongue depressors and assistive devices, to the most sophisticated implants, medical imaging systems; drugs (or medicines or pharmaceuticals); medical and surgical procedures; and the organizational and supportive systems within which such care is provided.

The transition of a product from bench side to clinical use involves several stages and engagements with different stakeholders (Ofori-Asenso *et al*., 2020).

The first stage, encompasses the regulatory review process, where requirements may differ between countries, and any health technology must have regulatory approval in order to progress further in the process. Most countries have a regulatory framework in place to ensure that there is proper control and management of health technologies, specifically with regard to medical devices and medicines (pharmaceuticals). This function falls under the mandate of National Regulatory Authorities (NRAs). The NRA will therefore assess the product’s risk–benefit profile (i.e. evaluation of safety, efficacy/performance, and quality) (Ofori-Asenso *et al*., 2020). Health technologies that meet these required standards, are approved for use and provided with a marketing authorization.

However, having a medical device or medicine approved for use by the regulator, does not automatically entail that the product will be available for patient access in a healthcare system. Regulatory approval is a necessary condition before reimbursement (Tsoi *et al*., 2013), but once a product has gained this marketing authorization, market access is further dictated by the particular healthcare system’s financing mechanisms (Ofori-Asenso *et al*., 2020). This separate process of reimbursement or coverage falls under an entity known as the payer.

Once the payer lists the product for use within their network, the listed product is assured of reimbursement or coverage/funding in a healthcare system, and patients may then gain access.

So where do health technology assessment (HTA) bodies fit into the above? HTA bodies and their role will be explained later in detail, however for the purpose of this introduction, a HTA body ensures that their assessment of a health technology, will guide payer or coverage entities, on whether listing a product will add value to their respective formularies. These value assessments usually focus on relative performance (such as relative safety, relative effectiveness, and cost effectiveness) of a technology against currently available clinical options (Ofori-Asenso *et al*., 2020). This is especially important as all healthcare systems have budgets, necessitating careful management to ensure provision of quality healthcare in a sustainable manner.

Patient access is accordingly determined by the willingness of payers or coverage entities to list the products in their networks, and therefore agree to reimburse or fund their use. Of significant importance, is the HTA body, from which payers or coverage entities take guidance, on what technologies should be listed.

The three categorizations of stakeholders in bringing a health technology to patients is summarized in Table 1.1 in terms of their roles and responsibilities (Henshall *et al*., 2011), depending on the specific jurisdiction they are found in.

**Table 1.1 Regulatory approval, HTA, and coverage processes *(Henshall et al., 2011)***

| | Regulatory approval | Health technology assessment (HTA) | Coverage |
|---|---|---|---|
| **Legal authority** | The statutory body operates within public health legislation, and has a reporting structure into the relevant country's government | HTA entities need not necessarily operate within a legislative framework, and may constitutes bodies within and reporting into a coverage body, hospital network, or government department | Operates within the rules and regulatory framework of a particular health system to which they are then accountable to make recommendations on whether to adopt technologies. There may be instances where coverage bodies are defined in legislation which will then enforce that they are under the control of government |
| **Role** | Assess technologies in terms of the safety, quality, efficacy, and benefit-risk profile, for market authorization. Responsible for the promotion and development of new treatments addressing important unmet health needs | The outcome of the HTA process is to provide scientific evidence, in order to make effective decisions on reimbursement or coverage in a system. This may also take the form of clinical practice guidelines to assist with effective implementation in practice | The determination of whether a technology should be paid for or reimbursed. This decision can only be made by assessing the relative effectiveness, value for money, current utilization patterns, available monetary resources, key focus areas in a system |
| **Decision** | Does the product do more good than harm for patients? | Will the technology be cost effective for patients i.e. is it advantageous and appropriate at a given cost? | Will the technology be cost effective for some or all eligible patients? i.e. is it advantageous and appropriate at a given cost? |
| **Evidence considered** | Pre-launch focus, notably efficacy demonstrated in randomized controlled trials (RCTs). Some focus post-launch on relative efficacy or effectiveness for ongoing benefit-risk profile assessment | Here evidence shifts post-launch to relative effectiveness/efficacy trials and where necessary other study designs e.g. modelling | Initially effectiveness gathered from trials and other study designs and/or analytic techniques. May also grant conditional coverage on the proviso of the collection of further evidence post-launch. |

Table 1.1 has served to provide a stakeholder overview for the various processes, Table 1.2 will further define the concepts of regulatory approval, aims of HTA and the coverage body.

**Table 1.2 Definitions of regulatory approval, HTA and coverage**

| Regulatory approval: | HTA: | Coverage: |
|---|---|---|
| The system and processes that follow in approving a health technology for use in a country (marketing authorization). | The systematic and robust methodology applied to the evaluation of health technologies, in determining their clinical and cost effectiveness. | The process of determining which health technologies are to be paid for or reimbursed, for a given network of patients |

To demonstrate the above concepts in the current regulatory–HTA frameworks both from South Africa and internationally, some examples of these entities per country are provided in Table 1.3.

South Africa has a complex healthcare system, as can be seen in the data presented in Table 1.3, which will be discussed in more detail in Chapter Four. The terminologies of ‘private’ and ‘public’ refers to the whether the entity or body in the HTA or payer/coverage scope, is government funded or owned (‘public’ entity), whilst ‘private’ refers to all other non-government funded bodies.

**Table 1.3 Stakeholders per country involved in bringing health technology to patients**

| Country | Regulator | HTA body | Coverage entity |
|---|---|---|---|
| **Australia** | TGA | PBAC<br>PDC | PBS |
| **Canada** | Health Canada | CADTH<br>INESS | *Public:* Canadian Medicare<br>*Private:* Direct payments via patients out of pocket (OOP) |
| **United Kingdom (UK)** | MHRA | NICE | NHS |
| **United States (US)** | FDA | *Public:* No national / governmental HTA body. Medicaid via an HTA arm within the organization.<br>*Private:* Limited HTA entities:<br>• ICER<br>• AHRQ<br>(Mulligan et al., 2020) | *Public:* CMS<br>*Private:* Health insurers |
| **South Africa** | SAHPRA | HTA in South Africa is not yet institutionalized or consistently applied (MacQuilkan et al., 2018). There are certain streams involved in HTA though:<br>*Public:* Some entities and hospitals<br>*Private:* Hospital Group networks, some medical schemes | *Public:* South African Government via tax revenue<br>*Private:* Medical schemes and small portion from direct patient payments, known as Out of Pocket (OOP) |

***AHRQ:****Agency for Healthcare Research and Quality;* ***CADTH:****Canadian Agency for Drugs and Technologies in Health;* ***CMS:****Centers for Medicare and Medicaid Services;* ***FDA:****Food and Drug Administration****; ICER:****Institute for Clinical and Economic Review;* ***INESS:*** *Institut National d'Excellence en Santé et en Services Sociaux;* ***MHRA:****Medicines & Healthcare Products Regulatory Agency;* ***NHS:****National Health Services;* ***NICE:****National Institute for Health & Care Excellence;* ***PBAC:****Pharmaceutical Benefits Advisory Committee;* ***PBS:****Pharmaceutical Benefits scheme;* ***PDC:****Prosthesis & Devices Committee;* ***SAHPRA:****South African Health Products Regulatory Agency;* ***TGA:*** *Therapeutic Goods Administration*

A focused assessment on the differences between regulatory and HTA entities and associated processes, as well as impact on timely patient access, will now follow.

### 1.1.2 The regulatory approval process in the context of ensuring timely patient access

The regulatory approval process in terms of impact on timely patient access cannot be reviewed in isolation, without assessing the global picture of the interdependence and impact of the NRA and HTA or coverage body.

The NRAs regulatory procedures, follows a specific set of guidelines and requirements within their mandate, to approve health technologies. Regulatory approval is a necessity before reimbursement via a payer/coverage entity.

Regulatory processes are developed to ensure that there are robust and stringent mechanisms to ensure that the quality, safety and efficacy/performance of health technologies can effectively be assessed, and if approved, result in marketing authorization of these technologies. This can be a complex process, depending on the NRA, and the regulatory approval process itself, will not form the basis of this discussion.

Following marketing authorization, the process of reimbursement for the technology via HTA assessment and subsequent guidance to the payer/coverage body, then occurs. The payer/coverage body will then list the health technology for their respective network. This event has a particular terminology attached, known as the ‘magic moment’, a phrase cited in a study by Duane *et al*. (2014). It is the point at which following marketing authorization granted by a regulator, the HTA entity or coverage body approves the technology for use via a positive recommendation, and the technology is available for patient use.

However, despite the regulatory approval being a mandatory process, their timeframes have long been criticized as being too lengthy, resulting in unacceptable delays in marketing authorization approvals, and consequently delaying patient access to health technologies.

Adding more complexity is the interdependence between the NRA and HTA body,

where in the current framework, there is a general lack of cooperation and sharing of information. Therefore improvements to the regulatory process, whilst ensuring quicker marketing authorization approvals are granted, may not necessarily equate to immediate patient access, due to a disjoint between the NRA and HTA body.

Therefore, there is the need and the opportunity for better linkage between current regulatory (licencing) and HTA processes (Ciani *et al*., 2017). Although the objectives of NRAs and HTA bodies are distinct, according to Tsoi *et al*. (2013), in most international jurisdictions it is HTA that drives healthcare system funding and therefore acts as the *de facto* barrier to medical device access (as cited in Ciani *et al*., 2017).

This type of synergy and linkage referred above, must be achieved in a manner that drives efficiency, but does not contravene the mandate and legal framework that each entity operates in.

### 1.1.3 HTA in context of timely patient access

Healthcare spending throughout the world continues to rise at alarming rates, and the requirement for HTA is needed now more than ever.

According to Banta (2009), HTA is a systematic process applied in health care, to generate data on a number of important elements including the clinical, economic, social and ethical value of health technologies; it is also applicable to an array of sectors such as pharmaceuticals, medical devices, clinical procedures and organizational systems, with the aim of informing the formulation of safe and effective health policies, particularly in relation to reimbursement or coverage decisions (as cited in Ciani *et al*., 2017).

To ensure this value assessment of health technologies, requires clinical data which is strong and relevant, providing evidence on not only the safety and efficacy of products, but ideally its effectiveness generated from use in the clinical setting (Tarricone *et al*., 2014). It is therefore evident, that the most important time to undertake HTAs, will be in the clinical setting, at the point when the technology is made available for use. It is at this stage that the evidence generated will offer

insight into the reimbursement and true cost proposal presented (Tarricone *et al*., 2014).

The concept of effectiveness which drives proper HTA assessment needs further consideration. Henshall *et al*. (2011) differentiates between efficacy, effectiveness, relative efficacy, and relative effectiveness of a health intervention in the context of the purpose and setting of use.

Efficacy evaluates whether a health intervention is achieving more good than harm when assessed in an ideal environment (e.g. a clinical trial), whilst relative efficacy assesses the same criteria in the same environment, but benchmarks the technology under review with alternative and similar clinical interventions.

Effectiveness seeks to review whether a health intervention is achieving more good than harm and is undertaken within a real world context or environment. Accordingly, when relative effectiveness occurs, it will follow the same principles as effectiveness, but incorporates benchmarking against alternative and similar clinical interventions.

The previous stakeholder comparison (Table1.1) will now be expanded to focus on the differences in the clinical requirements of the NRA and HTA body, as these fundamental elements clearly distinguish their respective roles, and may present conflicting priorities, resulting in delayed access to health technologies. The data presented in Table 1.4 has been extracted from Tsoi *et al*. (2013).

**Table 1.4 Differences in regulatory approval and reimbursement processes clinical evidence focus *(Tsoi et al., 2013)***

| | Regulatory approval | Reimbursement (based on HTA) |
|---|---|---|
| **Type of evidence** | Safety, efficacy and quality (here quality is assessed more on the production of the technology such as good manufacturing practices) | Safety, effectiveness and quality of life, economics and budgetary impact, social, ethical, legal, organizational impact |
| **Evidence considered** | Pre-launch: RCT Some focus post-launch on relative efficacy or effectiveness for ongoing benefit-risk profile assessment | Pragmatic RCT, observational studies, relative effectiveness and costs, as determined from trials and other study designs e.g. modelling |
| **Endpoint** | Lab findings; surrogate endpoints | Quality of life (QALY), 'hard' clinical outcomes (e.g. death, heart attack) |
| **Comparator** | Placebo | Active control, ideally standard of care |
| **Time horizon** | Trial duration | Total life cycle of assessment which can be any given time period, that is required to document all risks and benefits |

Table 1.4 highlights that the key clinical evidence requirements from the HTA entity, are centred on effectiveness and practical clinical environments (e.g. organizational impact), as opposed to efficacy and simulated environments.

Effectiveness is evidence generated from utilization in clinical practice with some comparator applied, also known as real world evidence (RWE). This is in contrast to regulatory evidence requirements, which are achieved under ideal or simulated conditions with no necessity to compare to standard of care/current competitors (especially pre-launch).

The above complexities are compounded when medical devices undergo HTA assessment. The current economic evaluation framework has been formulated for

pharmaceutical products and therefore the generic application of this framework to non-drug technologies, especially medical devices, is inappropriate, as they overlook important differences between drug and devices (Ciani *et al*., 2017).

The specific attributes of medical devices, primarily require a more RWE based HTA approach, as true benefits, can only be determined when used in clinical practice.

### 1.1.4 Characteristics of medical devices and medicines

According to the US, a prerequisite for a product to be classified as a medical device (as opposed to a medicine), is that it does not achieve its principal action in or on the human body by pharmacological, immunological or metabolic means, even though it may be assisted in its function by such means (Tarricone *et al*., 2014).

The portfolio of medical devices is far more expansive than medicines due to the broad definition and scope, spanning from wound dressings to blood composition analysers or pacemakers (Tarricone *et al*., 2014).

It should be noted that whilst it has been demonstrated that there is a clear differentiation in attributes and functionality of medicines and medical devices, for the purpose of this study, the findings of all problems, issues and consequently solutions, are applicable to both categories. This position, is also supported by some literature review findings, contained within this report, in terms of solutions applicable to both categories. In fact, in some instances the solutions proposed are even more suitable to medical devices, due to this very differentiation of medical devices as has been shown. Further, there is far more research that has been done on medicines vs medical devices, due to the former having an established and extensive regulatory framework. The terminology in the information that follows, may be referred to as a health technology or medicine (or pharmaceutical or drug) and consequently these terms when read, are applicable to medical devices as well.

### 1.1.5 Medical devices and the complexity in economic evaluation

Medical devices contribute significantly to healthcare expenditure due to both the volume of items used, expansive range, and high cost of certain specialised products (e.g. implantable medical devices).

Within the Middle East and Africa (MEA) regions, South Africa is one of the largest markets (SAMED, n.d.). This is due to its sizeable population of 58.8m (Stats SA, 2020), and further that it is Africa's most industrialized nation (SAMED, n.d.). In terms of monetary value and growth, the South African market continues to increase, having an estimated worth of $1.3 billion in 2019, and expected to expand to US$ 1.8 billion by 2023 (SAMED, n.d.).

Economic evaluation is broadly the method for the clinical and cost effectiveness assessment of health technologies. The current international guidelines or methods to assist with economic assessment, may appear to be applicable to all health technologies, however these have been largely formulated based on extensive experience with pharmaceuticals (Drummond *et al*., 2009). Therefore, although these methods of economic evaluation are equally applied to both pharmaceuticals and devices, the differences with devices and their attributes, present challenges in the methodology of evaluations. These challenges will require management and correction in order to ensure meaningful evaluations are conducted on devices, to generate robust evidence (Drummond *et al*., 2009).

These differentiations of medical devices therefore have a profound impact when it comes to the cost effectiveness assessments undertaken by HTA bodies – a form of economic evaluation. A summarized overview on some of the differentiating concepts of medical devices are shown in (Table 1.5).

**Table 1.5 Summary of the differentiating concepts of medical devices**

| Randomized controlled trials (RCTs) | Diagnostic devices | Dynamic pricing and cost analysis | Organizational context | Requirement for Real world effectiveness (RWE) / Post marketing surveillance (PMS) |
|---|---|---|---|---|
| • RCTs are currently the gold standard for HTA clinical preference (Griffiths *et al*., 2017).<br>• Devices have less stringent requirements, and thus not subject to the rigorous regulatory process that drugs undergo (Ciani *et al*., 2017).<br>• The requirement for RCTs, is dependent on a device's risk classification, which at present, lacks a global harmonized system in place. This leads to variability amongst NRA requirements.<br>• Device frequent incremental modifications (Drummond *et al*., 2009) impacts efficacy; and by the time a RCT is completed the original device is redundant with upgraded models in use (Tarricone *et al*., 2017b). | Diagnostic devices according to Drummond *et al*. (2009) pose the following challenges:<br>• When it comes to the economic evaluation of diagnostics, as diagnostics lead to an intervention or treatment, the improvement in patient outcome is impossible to determine for diagnostics only. Multiple applications (e.g. x-ray machine) ensure it cannot be divided for exact evaluation assessment. (like drugs) | • Device pricing is more dynamic than that of drugs (Tarricone *et al*., 2014) due to factors such as rapid market entry of new products due to the less stringent regulatory requirements (Drummond *et al*., 2009).<br>• Total device costs often comprise an array of variables such as disposables, equipment, maintenance etc. | • This refers to the setup and process flow of the facility including clinical processes, staffing, equipment etc.<br>• Devices can have wider economic implications (Drummond *et al*., 2009). For example, purchase of an expensive robotic system for joint arthroplasty should only be considered by a hospital able to ensure same day hospital discharge due to sound clinical processes etc. | • End user ability, training and experience will directly influence the clinical outcome of a device (Tarricone et al., 2014), e.g. surgical staplers<br>• Now see a shift from efficacy to effectiveness or RWE.<br>• Conversely with drugs the clinical outcome relates to its pharmaceutical structure, and not dependent on user ability, provided administered according to its dosing guideline (Drummond *et al*., 2009). |

### 1.1.6 Global solutions currently explored or implemented for improving patient access

#### 1.1.6.1 Harmonization of the regulatory–HTA process

Following marketing authorization of medical devices by a NRA, it often follows that there is inadequate clinical evidence presented to the HTA body. Consequently this can lead to either a delay in HTA review, or approval of the technology will be declined or receive a negative recommendation, resulting in delays in patient access.

Synergies must therefore be instituted between the NRA and HTA body, to bring about improved efficiencies in patient access to health technologies. This may be achieved through harmonization of the regulatory–HTA review process.

Broadly, harmonization refers to the pathways to achieve systematic alignment or streamlining of the regulatory and reimbursement processes, including the alignment of evidentiary requirements (Tsoi *et al*., 2015). Harmonization therefore is process oriented and centred on reducing the time between regulatory and reimbursement decisions and minimizing duplication of work (Ofori-Asenso *et al*., 2020).

Harmonization conducted in the correct manner, will ensure that each entity still conducts their reviews in accordance with their respective mandate, but certain processes or activities occur in collaboration or joint engagement.

The practical application of these pathways have been in the domain of drugs, however this is not indicative of equal application and benefits to non-drug healthcare technologies (Tsoi *et al*., 2013).

Regulatory–HTA harmonization (Figure 1.1), is categorized into five different approaches (Ofori-Asenso *et al*., 2020):

(1) Early tripartite dialogues.
(2) Alignment of evidentiary requirements.
(3) Parallel reviews.
(4) Adaptive licencing pathways.
(5) Post authorization data generation.

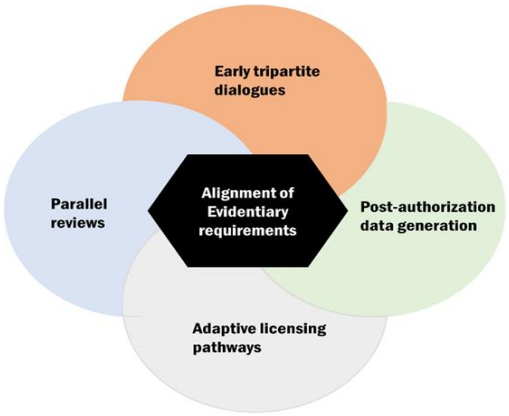


**Figure 1.1 Five approaches to harmonization of regulatory–HTA processes**
***(Ofori-Asenso et al., 2020)***

These approaches are not mutually exclusive and instances exist where elements from different approaches have been combined (Tsoi *et al*., 2013). There is no harmonization pathway that is more superior to the other. Rather, each strategy or pathway will need to be assessed in context of its benefits and disadvantages, relative to a particular setting. These disadvantages associated with the harmonization pathways will face several barriers that will need to be addressed to achieve greater alignment in the current regulatory and reimbursement landscape, including legal, organizational, and resource-related factors (Ofori-Asenso *et al*., 2020). These barriers though, have not been explored any further in this report, and will require additional research.

As parallel reviews are the basis of this research project, more detailed discussion will follow, however to completely understand all pathways to the harmonization concept, a depiction of the key features, benefits and pitfalls of the alternative pathways are presented in a summarized format (Table1.6).

**Table 1.6 Key features, benefits and pitfalls of alternative harmonization pathways *(continued on next page)***

| Harmonization pathway | Early tripartite dialogue | Alignment of evidentiary requirements | Adaptive licencing | Post authorization data generation |
|---|---|---|---|---|
| **Overview** | • Involves early collaboration between the manufacturer, NRA and HTA body(s).<br>• Also known as 'early scientific advice', it serves to discuss the clinical trials and desired outcomes from each entity. | • Evidence requirements of both the NRA and HTA body will be changed to a mutually agreed upon set of criteria. | • Does not approve or decline technologies in a once-off process, but allows for utilization in a defined population, and then starts the process of iterative and data generation from clinical application. This allows for a flexible process resulting in regulatory, licencing and coverage adaptation (Tsoi *et al*., 2013). | • Post authorization or Post market surveillance (PMS) is the generation of additional data after authorization (Ofori-Asenso *et al*., 2020). |
| **Benefits** | • Potential to improve the efficiency of the decision-making process (Ofori-Asenso *et al*,. 2020).<br>• An analysis by Hofer *et al*. revealed that from 2008 to 2012, 85% of applications that received and followed early scientific advice by the EMA were ultimately granted marketing authorization compared to only 41% that did not (as cited in Ofori-Asenso *et al*,. 2020). | • Reduces the conflict for manufacturers in terms of prioritizing stakeholder requirements.<br>• Allows for synergies in aligning certain evidence categories for efficiency, whilst at the same ensuring autonomy. | • Data is generated throughout life cycle (adverse events, indications etc.).<br>• Tsoi *et al*. (2013) opines that adaptive licensing would be particularly suitable for medical devices due to their specific attributes (learning curve, RWE, incremental innovation etc.) | • Ensures the continued safety and performance of devices in use (Tarricone *et al*., 2014).<br>• Assesses effectiveness in regular use (Tarricone *et al*., 2014). As an example, in 2011 the FDA expanded a once restricted technology (carotid stents) to the 'general' patient population. This was a remarkable PMS activity jointly undertaken by the FDA and CMS (payer) over the period 2004-2011, spanning multiple centres of excellence (Gray and Verta, 2014). |

**Table 1.6 Key features, benefits and pitfalls of alternative harmonization pathways *(continued)***

| Harmonization pathway | Early tripartite dialogue | Alignment of evidentiary requirements | Adaptive licencing | Post authorization data generation |
|---|---|---|---|---|
| **Pitfalls** | • If there is no evidentiary alignment, the manufacturer may prioritize the NRAs requirements (over the HTA body) and thus serve as a fruitless exercise. | • Some elements may be challenging in terms of alignment e.g. a study by Wang *et al*. (2017) showed that a key clinical element had the most disagreement in priority setting for alignment between stakeholders. For the inclusion of an active comparator arm in the trial, regulatory agencies were the most negative to alignment, as comparative efficacy is not a priority in their assessment, rather just the demonstration of efficacy. | • Requires a well-defined and structured process to monitor throughout the product life cycle, which will be resource intensive on all stakeholders.<br>• Requires accurate, real time and transparent information sharing (end users, manufacturers). | • Requires a well-defined and structured process to monitor throughout the product life cycle, which will be resource intensive on all stakeholders.<br>• Requires accurate, real time and transparent information sharing (end users, manufacturers). |

### 1.1.6.2 Parallel reviews

Parallel review or submission aims to reduce the time between regulatory and reimbursement decision-making primarily through a process efficiency approach, involving alignment of the regulatory and HTA review processes and may involve the participation of either one or both parties (Tsoi *et al*., 2013).

In a sequential review process, the decision-making processes of the regulator and HTA entity(s), occurs in sequence. A company may only submit to the HTA entity(s) for approval, once the regulator has completed their process, and the technology has received marketing authorization (approval).

Conversely, in a parallel review process, the decision-making processes of the regulatory and HTA entity occur just as defined, in a parallel mechanism. The manufacturer may make a submission to the HTA entity, whilst the technology is still under marketing authorization review at the regulator.

A visual depiction of the various regulatory–HTA processes (Figure 1.2) provides an outline of the different timelines or periods of review as illustrated by Liberti (2018).

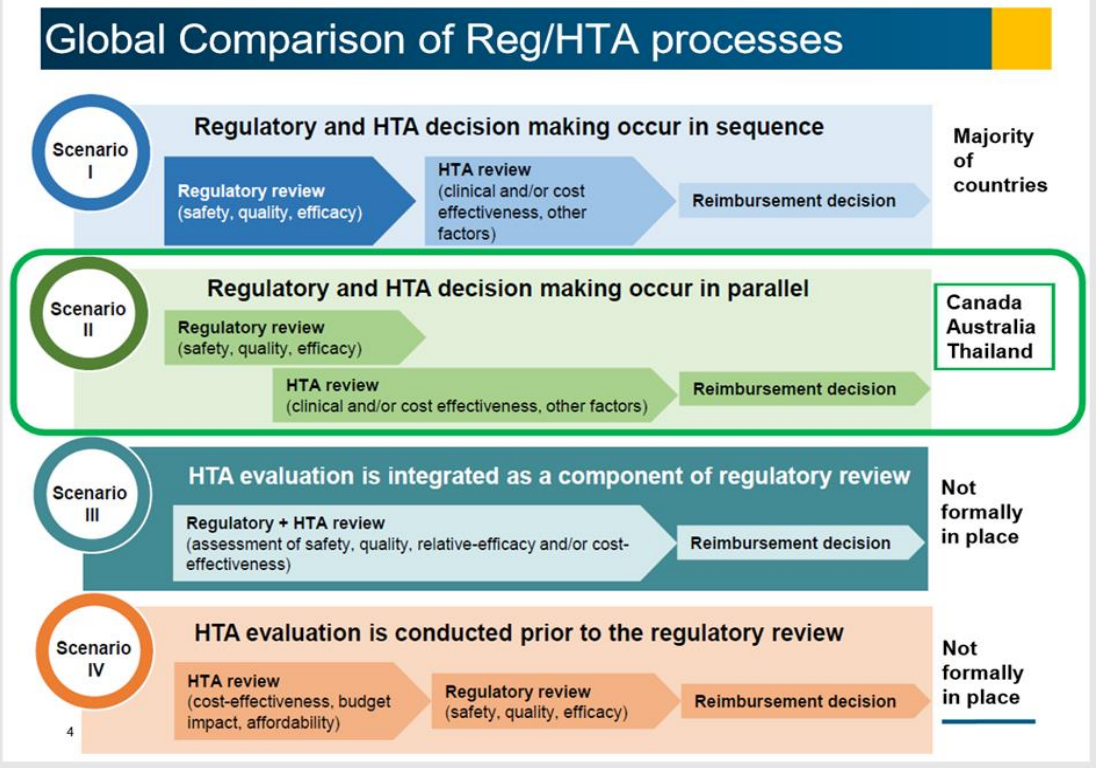


**Figure 1.2 Comparison of possible regulatory–HTA timeline processes**
***(Liberti, 2018)***

- Scenario one - Where majority of countries (including South Africa) are in the current context of medicines. In addition, in SA there is no formal national HTA entity in place yet.
- Scenario two – Only limited countries have adopted this process at the time of writing this report (this data is presented in Chapter Three).
- Scenarios three and four – No formal agreements or implementation in any country. Not likely, due to the requirement for a separate mandate of the Regulator and HTA entity. Further, in all countries where parallel review frameworks are in effect, marketing authorization is a prerequisite for any technology, before use in a clinical environment (in all formal and established regulatory systems). It is the author's opinion that this process should always be in effect i.e. marketing authorization as a prerequisite, to ensure the elements of safety, efficacy/performance and quality remain foremost in initial technology approval.

Of particular importance is that the time to submission to the HTA entity, is generally based on the anticipated time period for regulatory review to be completed. This requirement must guide the process in terms of when the submission needs to reach the HTA body, to ensure that the review period is optimized.

For example, if an NRA will require an average time period of 180 days for a technology review, and a specific HTA body takes approximately 90 days for technology review, a parallel submission to the HTA body should occur at the latest 90 days before the anticipated or expected outcome of the regulatory process, and not any period later, as this will defeat the objective of review period efficiencies

In keeping within the legislative and regulatory frameworks, the HTA approval though, cannot be formally communicated, until the regulator has completed their review process, and the product receives marketing authorization.

In briefly looking at the risks associated with the parallel review approach, one of the most important factors to consider, and impacting the HTA or payer entity primarily, would be that should a product not receive market authorization from the NRA, it would then result in a waste of resources and effort (Tsoi *et al*., 2013). In order to circumvent this risk, the HTA or coverage entity must apply a pre-determined and

consistent approach and practice, to all parallel review submissions. This approach or practice can include useful strategies such as identifying the less resource-intensive components of the review process, so that this can be done first; ensuring the concept of timely reviews is still applied, but less risk with resource wastage (Tsoi *et al*., 2013). From an approach perspective, there should be an initial assessment of technologies presented, using a defined matrix, which categorizes products into those with the greatest likelihood of attaining market authorization, which should then be prioritized for parallel reviews (Tsoi *et al*., 2013).

Market access or patient access though, may not always be improved by a parallel review process, which still requires robust and appropriate clinical evidence by both regulators and payers, to make the decision to allow the technology to be utilized (Tsoi *et al*., 2013). Therefore to improve market or patient access, it may require additional adoption of the two mechanisms to ensure that the clinical evidence needs of both the regulator and payer are met i.e. the alignment of evidentiary requirements and early dialog (Tsoi *et al*., 2013).

From all the harmonization pathways presented, parallel reviews were selected as the quintessential pathway for the local SA context, and thus formed the title of this study. Context will be provided in the subsequent chapters on the current regulatory and HTA framework within SA, to understand the potential benefit of parallel regulatory–HTA review implementation to timely patient access.

## 1.2 The South African regulatory and HTA framework

### 1.2.1 SAHPRA – Background and historical approval timelines

The NRA in South Africa is the South African Health Products Regulatory Authority (SAHPRA), having replaced the former Medicines Control Council (MCC) in 2018.

SAHPRA is a public entity separate from the National Department of Health (NDoH), created by the South African Government (SAHPRA, 2022). SAHPRA has three pillars to ensure that medicines, medical devices and *in vitro* diagnostics (IVDs) meet the requisite standards to protect the health and well-being of South Africans namely safety, efficacy/performance and quality (SAHPRA, 2022).

The medicine or pharmaceutical framework has been in place for decades, under the control of the former MCC, whilst the medical device and IVD framework is a recent development. As stipulated by Kirby (2017), medical devices are now regulated by the newly enacted Medicines and Related Substances Amendment Act, 14 of 2015 (as cited in Saidi & Douglas, 2019). The Act provides for the establishment of the SAHPRA, a body in charge of regulatory oversight for medicines, medical devices, complementary medicines, and related substances (Saidi & Douglas, 2019). Only registered products are sold in South Africa as stipulated by Khan (2017), as the regulation does not allow a manufacturer, wholesaler or distributer of medical or IVD devices to manufacture, act as a wholesaler of, or distribute, any medical device or IVD without a valid licence (as cited in Saidi & Douglas, 2019).

The regulatory framework for medical devices and IVDs is in the process of being implemented by SAHPRA and is not yet fully established. A phased implementation approach has been identified, with the first phase currently in effect, which is the licensing of medical device establishments, and will be followed by registration of medical device products in the second phase. The first phase of this process is currently underway and SAHPRA will issue a call-up plan (based on risk classification) for the registration of different categories of medical device products during the second phase. At the time of writing this report, the status as described above is still relevant.

### 1.2.2 Risk classification approach for medical devices

SAHPRA has published regulations on medical devices which are based on a four-tier, risk-based classification system for obtaining device licences for manufacturers, importers and distributors (Saidi & Douglas, 2019). These levels of risk are categorized as follows (SAHPRA, 2022):

- Class A (low risk)
- Class B (low-moderate risk)
- Class C (moderate-high risk)
- Class D (high risk).

Without a global harmonized classification system, the current issues regarding inconsistency of evidence presented to HTA entities, due to the variability in risk classification and different evidence requirements, will pose the same challenges for medical device assessment by the HTA entities in South Africa.

SAHPRA as an NRA has a responsibility to ensure public health and access to health technologies, and if this means collaborating with HTA agencies, which have been demonstrated to be the *de facto* barrier to patient access according to international findings, then this must be a strong consideration for the South African NRA to undertake.

### 1.2.3 HTA in South Africa

The South African healthcare system is currently split between the private and public sectors (MacQuilkan *et al*., 2018).

HTA is yet to be institutionalized or consistently applied in South Africa (MacQuilkan *et al*., 2018) whether public or private. There is no structured and formal utilization of HTA (Mueller, 2020). However, some decision-making bodies (e.g. private healthcare insurance companies, National Essential Medicines List Committee, and other public entities) use HTA-like methods and tools e.g. domains such as safety and efficacy (Mueller, 2020). There are also some private hospitals and provincial and hospital-based structures that conduct some form of HTA.

At present, there is no national HTA body which manages public sector funds.

Both the South African regulatory and HTA frameworks will be elaborated further in the upcoming chapters.

## 1.3 Previous research

In terms of local context and any harmonization pathways between NRAs and HTA bodies, there appears to be a lack of data in the literature that specifically addresses SAHPRA adopting any collaborative or harmonization efforts with HTA bodies, within their regulatory framework.

There is some literature which refers to the relationships between SAHPRA, a national HTA body, and the NHI strategy for universal healthcare. The 2015 NHI White Paper includes a strong policy intent for the comprehensive adoption of HTA systems (Siegfried *et al*., 2017). The document highlights the role of SAHPRA and the need for a well-functioning NRA being critical to the success of HTA in South Africa. A national HTA entity needs to be coordinated with, but independent of the NRA (Siegfried *et al*., 2017). The HTA entity is then able to make ethical decisions on technologies (no risk of adopting unsafe or poor quality products due to cost pressures), respecting marketing authorization decisions of the NRA, whilst making evidence based resource allocations (Siegfried *et al*., 2017) following the economic evaluation processes.

Another study looking at the HTA journey of various emerging economies such as South Africa and India, highlighted that resource allocation is challenging globally, however countries such as South Africa with a resource constrained context, becomes even more disadvantaged (MacQuilkan *et al*., 2018). The suggested solution would be to implement evidence based HTA processes, to ensure affordability and equity when allocating resources (MacQuilkan *et al*., 2018).

This study will assess the international initiatives related to parallel regulatory–HTA reviews (which have proven to be successful); and whether local adoption by SAHPRA can enable faster patient access to safe and cost effective medical devices.

## 1.4 Aims and objectives

Due to the global inefficiencies seen with patient access to health technologies along the regulatory–HTA framework, with HTA being the major barrier to access, various pathways to harmonization have been explored and implemented as a paradigm to improve patient access via timeline efficiencies and improvements.

Based on South Africa's current regulatory and HTA frameworks and performance, as well as looking ahead to future goals and objectives with healthcare in general, and medical devices specifically, the aim of this study was to investigate one of the

harmonization pathway's applicability to the South African context. In particular, the parallel regulatory–health technology assessment review approach, and its implications for improving patient access to medical device products in South Africa was considered.

The objectives of this study are outlined as follows:

- To review international frameworks and initiatives for parallel regulatory–HTA reviews in improving marketing authorization and access coverage.
- To assess the current regulatory and HTA framework for medical devices in South Africa, and its impact on patient access to these health technologies
- And finally, to determine whether local adoption of parallel regulatory–HTA reviews by SAHPRA and HTA bodies, will enable faster patient access to safe and cost effective medical devices.

# CHAPTER TWO – MATERIALS AND METHODS

## 2.1 Introduction

The chosen study method was best determined to be secondary data analysis using a desk review approach. Secondary analysis of qualitative data is the use of existing data to find answers to research questions that differ from the questions asked in the original research (Siegfried *et al*., 2017).

Data were analysed according to grounded theory qualitative methodology. Grounded theory is a research mechanism which was developed as a method or approach, in order to formulate a theory, that has been derived from data, systematically gathered and analysed through the research process (Khan, 2014).

This method was selected due to two unique characteristics: constant comparative analysis and theoretical sampling (Cho & Lee, 2014). This method was determined to be the most suitable, as data analysis could commence at the start of data collection, allowing for meaningful direction and guidance for interpretation and additional extraction, due to the simultaneous analysis and extraction that the methodology applies (Cho & Lee, 2014).

The concept of trustworthiness related to qualitative research requires discussion and assurance that this has been incorporated into the design, execution, extraction, analysis and formulation. Trustworthiness refers to methodological soundness and adequacy, and it is the degree to which the researcher has confidence that the respective data and findings are credible, transferable and dependable (Earnest, 2020). To ensure these key principles formed the basis of the research study, the study design followed a number of defined actions:

- Rigorous and methodological approach using defined key words.
- The use of respected sources of information and search engines.
- Multiple literature reviews which contributed to additional reliable data sources.

- All the above activities were recorded on logs depicting the flow of grounded theory evolution in data extraction following a structured, yet flexible pathway to analyse new concepts as they presented in the literature findings.
- As this was a literature review, it eliminated the risk of participant or human influence on credibility and dependability.
- In terms of transferability, the extensive research done on international frameworks and harmonization strategies, provides clear information extracted from the literature review, to determine relevance in the South African context.

All data extracted from the various research streams were applied to effectively address all the objectives as previously outlined.

In terms of objective one *(To review international frameworks and initiatives for parallel regulatory – HTA reviews in improving marketing authorization and access coverage)*, research generated was summarized in a tabulated format (Chapter 3, Table 3.1), indicating information related to the country of origin, statutory authority and / or relevant HTA entity, programme details, technology type (i.e., medicine or medical device), and source of reference.

Discussions and in-depth analysis then followed to address the subsequent objectives.

## 2.2 Keywords (vocabulary terminology)

Vocabulary terminology, or keywords, were identified for each of the following objectives to ensure that appropriate extraction of data was achieved to effectively address each subject matter.

The keywords focused on specific terminology as well as included acronyms and alternative terminology to ensure that the maximum data would be extracted.

A summary (Table 2.1) of the keywords per objective / subject matter follows:

**Table 2.1 Summary of keywords per objective(s) used for data extraction**

| Objective(s) | Keywords |
|---|---|
| To review international frameworks and initiatives for parallel regulatory – HTA reviews in improving marketing authorization and access coverage | (1) parallel OR regulatory OR health technology OR access OR coverage<br>(2) tandem OR concurrent OR simultaneous OR together OR collaborative OR integrated OR aligned OR regulatory authority OR regulator OR registration OR approval process OR HTA OR medical equipment OR health technology assessment OR approval OR turnaround time OR authorization/ authorization OR insurance<br>***Search strategy was conducted using (1) only, and then combining (1) and (2) as keywords.*** |
| To review the existing local regulatory and HTA framework and its impact on patient access of medical device products **AND** to assess current review and approval procedures of SAHPRA and HTA bodies for medical devices in South Africa | (1) HTA OR South Africa OR healthcare financing OR public healthcare OR private healthcare OR public sector OR private sector OR medical devices OR health technology OR medicines<br>(2) approval OR process OR review OR regulatory OR medicines OR medical Devices OR health technology OR SAHPRA OR MCC OR regulation OR South Africa<br>***Search strategy was conducted using (1) only, and then combining (1) and (2) as keywords.*** |

## 2.3 Electronic database search

A research log was created to document all relevant journal articles, website searches and other related search media extracted.

Once the keywords were determined and noted per objective, the literature search strategy was executed on two electronic databases which had a considerable amount of literature (Researchgate and Wiley Online) and served as the source of published literature titles.

Only English sources of information were to be included. Further, only information in the last two decades were assessed and included if the information was still relevant

to current context. The latter was a subjective interpretation, and therefore can be seen as a study limitation in terms of not having additional researchers to agree to selection.

Following each keyword application and combination (Table 2.1), the total number of records retrieved were noted (n=2371) for all objectives. These notations were done on a search strategy log, which also included all data extractions as per below (i.e. number of records included and excluded following various levels of screening or assessment).

Duplicates were removed as the search progressed (n=824).

The records were then subjected to the first level of assessment or screening, which involved analysis of the title only. Thereafter, records were excluded based on titles being irrelevant to meet study objectives, with the remaining records' abstracts analysed (n=183). Literatures sources of which the abstracts provided an indication that the article would not be beneficial to the study were further excluded.

The remaining records (n=48) were then extracted for full text assessment. After full text assessment, a number of records (n=8) were removed. The reasons for removal can be summarized as follows:

- Focused on only one harmonization pathway unrelated to parallel reviews (early dialogue or adaptive licencing) and was repetition of previous findings;
- Focused only on the HTA process, and not any regulatory collaboration;
- Focused only on real world evidence (RWE) and benefit to regulator only (no HTA inclusion);
- One study focused on an early NICE initiative with the EU on joint regulatory/HTA advice. However due to the UK exit from EU, this is no longer relevant or in effect. The study was based on a pilot with no conclusive results and due to the termination of the collaboration, was excluded with focus on other ongoing initiatives.

After the remaining full text records were screened (n=40), several additional records were identified (n=33) by exploring the source literature sources' bibliographies or by identifying meaningful citations in the source records. After full text screening of these bibliography source data records, a few more records were excluded (n=10).

## 2.4 Grey literature

The published literature records also provided meaningful grey record sources and included various websites, white papers and reports from credible institutions/entities. In addition, these 'leads' as above, were also used to institute internet searches ('google' searches) using descriptive terms as per grey sources; which resulted in a cumulative contribution of grey records (n=36). A number of these sources (n=19) were removed after screening.

## 2.5 Summary of results of literature search.

The methodology as applied above resulted in a meaningful number of records to be included in the study (n=80). The schematic process of this literature search strategy is presented in Figure 2.1.

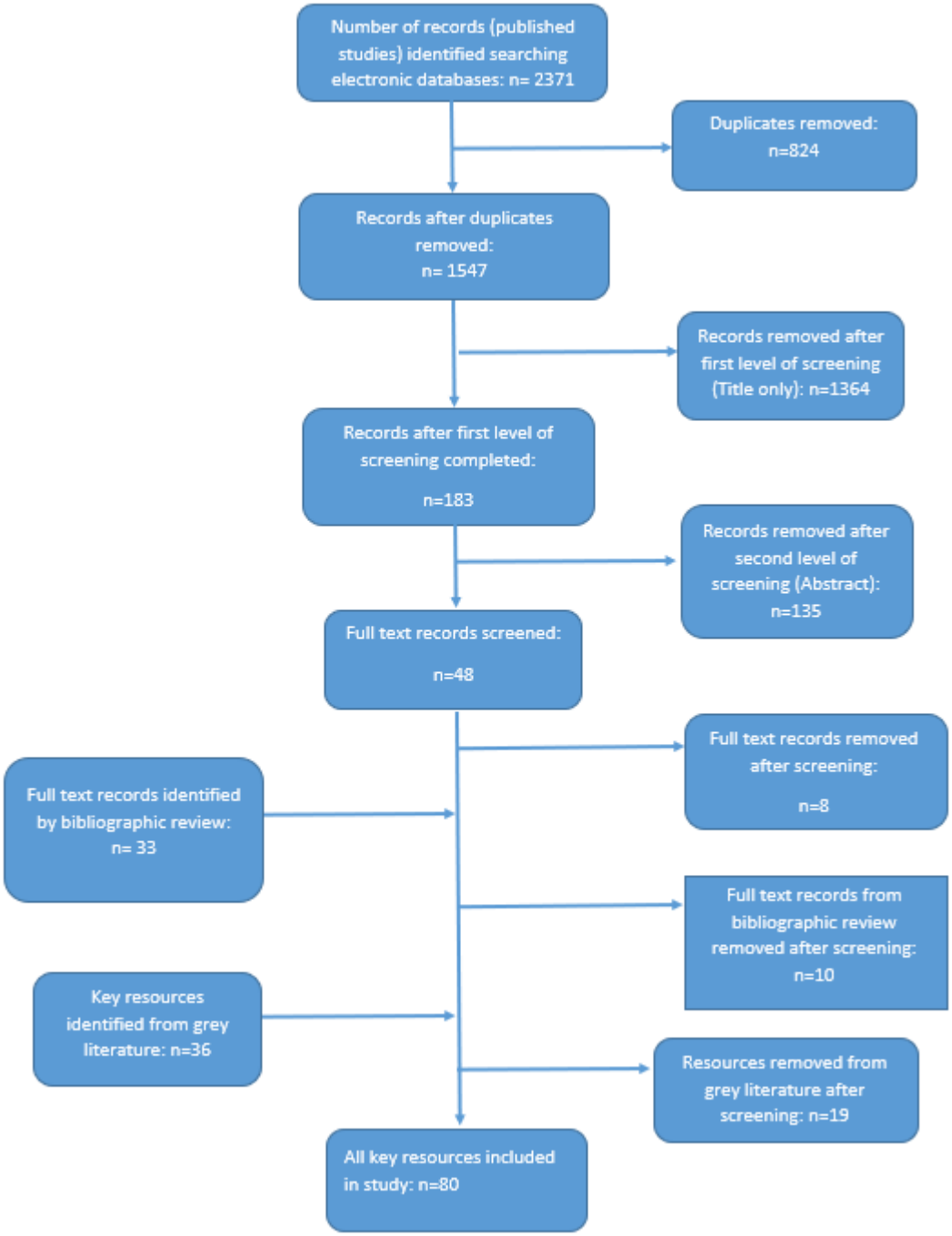


**Figure 2.1 Schematic process of the literature search strategy**

## 2.6 Methodology for comparative assessment of roll out time per country

The methodology to determine and present countries having a parallel regulatory-HTA framework (Table 3.1) has already been explained in the preceding sections. However to further expand on the concept of timely patient access to health

technologies, apart from countries applying parallel regulatory-HTA reviews, total roll out time (defined by Wang *et al*. (2019) as the review period from regulatory submission to HTA recommendation), was analysed per a defined set of countries, and also presented in chapter three (Table 3.2). The existence of a parallel regulatory-HTA framework, having efficient timelines, is not the only variable for timely patient access. Whether these systems exhibit more positive or favourable HTA recommendations (which at this point will lead to coverage or reimbursement of the product) versus negative or declined recommendations (therefore no coverage and delayed patient access), is critical to determine true efficiency and timely patient access. In keeping with the grounded theory approach, as literature sources were extracted, additional information to determine the impact of recommendations on health technologies, was analysed, discussed and an overview presented (Table 3.2).

The methodology applied to each country's comparative assessment is explained as follows:

- Only countries with information readily available on total roll out time were included, which led to countries such as the US being excluded.
- Countries were selected (Australia, Canada, Germany and Sweden) to highlight contrasting systems and percentage results on the outcomes based on HTA or coverage assessments. Two countries had parallel systems in place (Australia and Canada), one had a high percentage of negative recommendations (Germany), and the last country (Sweden) had an exceptionally high percentage of positive and positive with restriction recommendation outcomes.
- All data for this assessment was retrieved from Wang *et al*. (2019) in order to determine the roll out times, and then explore the various systems to draw meaningful conclusions.
- Only data for the years 2017 and 2018 were used, as a basis to reflect the current status, and further highlight the impact of changes made in the previous years, culminating into the recent performance seen.
- Total roll out time is divided into the regulatory review time (days) and regulatory approval to HTA recommendation (days).
- Total roll out time, regulatory review time (days) and regulatory approval to HTA recommendation (days), was calculated as an average of 2017 and 2018 data, and using the breakdown data previously discussed (Figure 3.5).

- Recommendations are the outcomes as determined by the HTA or coverage body, and can either be positive, positive with restrictions, negative or multiple (Wang *et al*., 2019). Multiple outcomes are insignificant and their results have been excluded for this analysis.
- For the purpose of this analysis, positive and positive with restrictions, are considered overall favourable recommendations / technologies.
- Recommendation outcomes was derived from Wang *et al*. (2019) and are also presented as pie diagrams (Figure 3.7) for each country, taken from the study.

Following an application of the above methodology on the selected countries, a comparative assessment could be presented in a table format (Table 3.2) highlighting the relationship (if any) between efficient roll out time (regulatory and HTA review periods) and positive HTA recommendations. As indicated, the countries presented in this particular analysis, include those with and without a parallel regulatory-HTA framework, but the basis of the analysis was more extensive than the one variable of regulatory focus, and required a broader context.

# CHAPER THREE – RESULTS OF THE REVIEW OF INTERNATIONAL FRAMEWORKS AND INITIATIVES FOR PARALLEL REGULATORY–HTA REVIEWS IN IMPROVING MARKETING AUTHORIZATION AND ACCESS COVERAGE

## 3.1 Introduction

Objective one was to review international frameworks and initiatives for parallel regulatory–HTA reviews in improving marketing authorization and access coverage.

The research included both medicines and medical devices. This was important as although the technologies are different in their attributes and specific economic evaluations, any efficiencies in patient access due to the existence of parallel review frameworks, have significant implications for medical devices as well. This thinking is supported by Frønsdal *et al*. (2012), who highlighted that any technology access improvement findings, are definitely applicable to both categories regardless if primarily medicine derived.

In terms of the relevance and applicability of a parallel regulatory-HTA review framework for medical devices, Henshall *et al*. (2011) at the Health Technology Assessment International (HTAi) Global Forum, indicated that improved interactions between regulatory and HTA and coverage bodies following market approval for medical devices and diagnostics, presented the best opportunity for efficiency in market access. The HTAi is a global organization providing guidance and conformity for any individual or entity that uses HTA or economic evaluation in their processes with the aim of developing or guiding policy and processes (htai, 2021).

## 3.2 Results and discussion

### 3.2.1 Summary presentation on international parallel regulatory–HTA review frameworks and initiatives

The findings of this research has been tabulated (Table 3.1) to provide an overview

of international frameworks and collaboration that exist between the NRA and HTA body(s). In addition, information related to programme details and technology type (medicine or medical device) are provided.

In terms of reference source (Table 3.1), all literature sources which discuss this particular harmonization pathway (parallel regulatory-HTA review or submissions) have been indicated per summary finding. The importance of adding the reference source, is to validate the findings, notably amongst the key experts in the area of regulatory–HTA efficiencies.

The presentation of the findings of international existence of parallel submissions / review frameworks (Table 3.1), leads to the next crucial assessment, which is whether this particular harmonization pathway has resulted in efficiencies in the regulatory–HTA approval timeframe.

**Table 3.1 Summary of findings: International frameworks and initiatives for parallel regulatory – HTA reviews / submissions**

| Region / Country | Regulator | HTA body / Coverage body | Name of Programme | Type of technology | Reference |
|---|---|---|---|---|---|
| **Australia** | TGA | PBAC | Parallel TGA / PBAC process | Pharmaceutical | (Liberti, 2018); (Wang *et al*., 2019); (Tsoi *et al*., 2013); (Frønsdal, 2012); (Ofori-Asenso, Hallgreen & de Bruin, 2020); (Cai, Wang, McAuslane & Liberti, 2018). |
| **Canada** | Health Canada | CADTH | CADTH pre-NOC priority review | Pharmaceutical | (Liberti, 2018); (Wang *et al*., 2019); (Tsoi *et al*., 2013); (Ciani, Wilcher, van Giessen & Taylor, 2017); (Frønsdal *et al*., 2012); (Ofori-Asenso *et al*., 2020); (Cai *et al*., 2018); (Tsoi *et al*., 2015). |
| **Canada** | Health Canada | OHTAC | MaRS Excellence in Clinical Innovation and Technology Evaluation (EXCITE) | Non-pharmaceutical | (Tsoi *et al*., 2013); (Ciani *et al*., 2017); (Tsoi *et al*., 2015); (Ciani *et al*., 2015). |
| **Thailand** | Thailand FDA | NLEM | Parallel Health Intervention & Technology Assessment Programme | Pharmaceutical | (Liberti, 2018); (Cook & Kim, 2015). |
| **United States of America (USA)** | FDA | CMS | | Non-pharmaceutical | (Wang *et al*., 2019); (Tsoi *et al*., 2013); (Ciani *et al*., 2017); (Frønsdal *et al*., 2012); (Ofori-Asenso *et al*., 2020); Zannad, F *et al*., 2017); (Tsoi *et al*., 2015). |
| **Netherlands** | Medicines Evaluation Board (MEB) | Netherlands Healthcare Institute (ZIN) | Parallel submission/ review (Pilot) | Pharmaceutical | (Ofori-Asenso *et al*., 2020); (Liebrand & Pasman, 2020); (Taylor, 2020). |

***CADTH:*** *Canadian Agency for Drugs and Technology in Health;* ***CMS:*** *Centers for Medicare & Medicaid; Services;* ***FDA:*** *Food & Drug Administration;* ***MaRS:*** *Medical & Related Sciences;* ***MEB:*** *Medicines Evaluation Board;* ***NLEM:*** *National List of Essential Medicines;* ***OHTAC:*** *Ontario Health Technology Advisory Committee;* ***PBAC:*** *Pharmaceutical Benefits Advisory Committee;* ***TGA:*** *Therapeutic Goods Administration;* ***ZIN:*** *Netherlands Healthcare Institute*

### 3.2.2 Findings per country on review timeline efficiencies with parallel review frameworks

The presence of parallel review frameworks in improving patient access to health technologies are evident in the countries that have adopted this harmonization pathway; and will now be presented by each country or system separately. The countries that were selected had easily accessible and abundant public information in order to effectively analyse their parallel regulatory-HTA review processes. The demonstrated improvements are based not only on the country's track record in terms of former sequential review process timelines, but also include comparative assessment with other countries or systems.

Roll out time refers to the total time period from regulatory submission to HTA recommendation (Wang *et al*., 2019) and includes the regulatory review period and the HTA review period. Parallel reviews, allow for an earlier submission by the manufacturer to the HTA body, in a formal agreement, whilst the regulatory review period is still underway.

Timeline efficiencies therefore refers to the efficiency in the roll out time, in reducing the time taken for regulatory review and HTA review.

#### 3.2.2.1 Thailand

The regulatory authority in Thailand is the Thailand FDA (Cook & Kim, 2015), whilst the coverage functions are determined by listing on the National Medicines Essential List (NMEL). In Thailand, Cook and Kim (2015), further indicate that in a sequential review process, the marketing authorization by the Thailand FDA can take between one and two years depending on whether the medicine is a chemical or biological agent; whilst the coverage review process to list the item on the NMEL can take between two and three years to complete. It can be done in parallel though, and this will reduce the overall time to subsidized market access (Cook & Kim, 2015). This is illustrated in Figure 3.1, as extracted from Cook and Kim (2015).

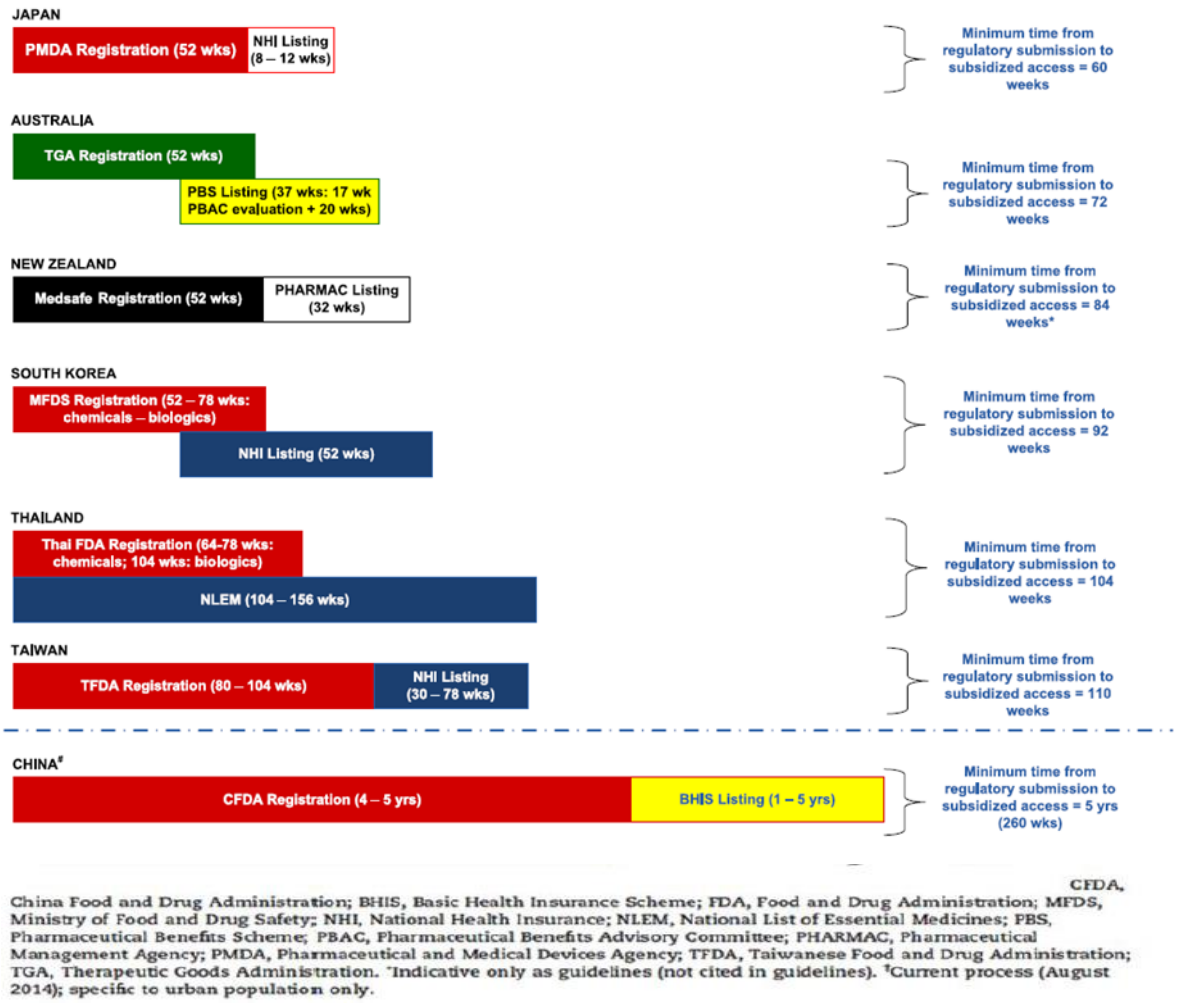


**Figure 3.1 Comparison of Thailand to other countries in time line to marketing authorization and coverage of health technologies *(Cook & Kim, 2015)***

The exact improvement in terms of weeks' reduction when using the parallel review process (Figure 3.1) is specified as a minimum of 104 weeks (two years). Had the sequential review process been undertaken, it could have taken a minimum of 156 weeks (three years) to a maximum of 260 weeks (five years) based on the information from Cook and Kim (2015), and this is therefore a remarkable improvement in an efficient access timeline by using a parallel review system.

When compared to other countries in the study performed by Cook and Kim (2015), Thailand does not have the most efficient overall review process from marketing authorization to patient access (following coverage).

In order to improve the time taken for patient access to technologies, Thailand should consider alternative harmonization pathways, and perhaps process improvements in

the current health technology / coverage system implemented, as the timeline to coverage approval decisions, is the second longest, only better than China.

#### 3.2.2.2 Australia

The NRA in Australia is the Therapeutic Goods Administration (TGA) and responsible for both drugs and medical devices, however the final marketing authorization is provided by the delegate of the Minister of Health (Frønsdal *et al*., 2012). In terms of the coverage or reimbursement authorities, there are two entities which control drugs and devices separately. The Pharmaceutical Benefits Advisory Committee (PBAC) assesses drugs with recommendations then made to the Minister on whether a drug should be listed under the national Pharmaceutical Benefits Scheme (PBS). Devices undergo a review process by the Prostheses and Devices Committee (PDC), however these reimbursement recommendations are limited to surgically implanted devices and tissues (Frønsdal *et al*., 2012).

To assess the relationship between regulatory decision and first HTA recommendation (in both timing and outcome), the Centre for Innovation in Regulatory Science (CIRS) has been collecting data on medicine new active substances (NASs), appraised between 2014 and 2018 by eight HTA agencies (Wang *et al*., 2019) in key jurisdictions. Wang *et al*. (2019) demonstrated the parallel review efficiencies (Figure 3.2) and has provided much insight, with companies having taken advantage of the parallel review mechanism in Australia, wit 68% of products undergoing this process (Figure 3.2) over the period 2014-2018.

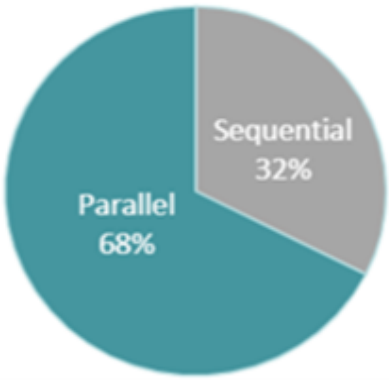


**Figure 3.2 The % of NASs in Australia that underwent parallel or sequential review processes (2014–2018)** ***(Wang et al., 2019)***

This clear preference for the parallel review process, leads to the next assessment, of whether this has resulted in efficiencies.

Wang *et al*. (2019), additionally compared key jurisdictions in terms of roll out time, to determine which country or system had the most efficient time period to HTA approval, since submission to the regulator (Figure 3.3). The eight key jurisdictions in this particular analysis included Australia, Canada, England, France, Germany, Poland, Scotland and Sweden.

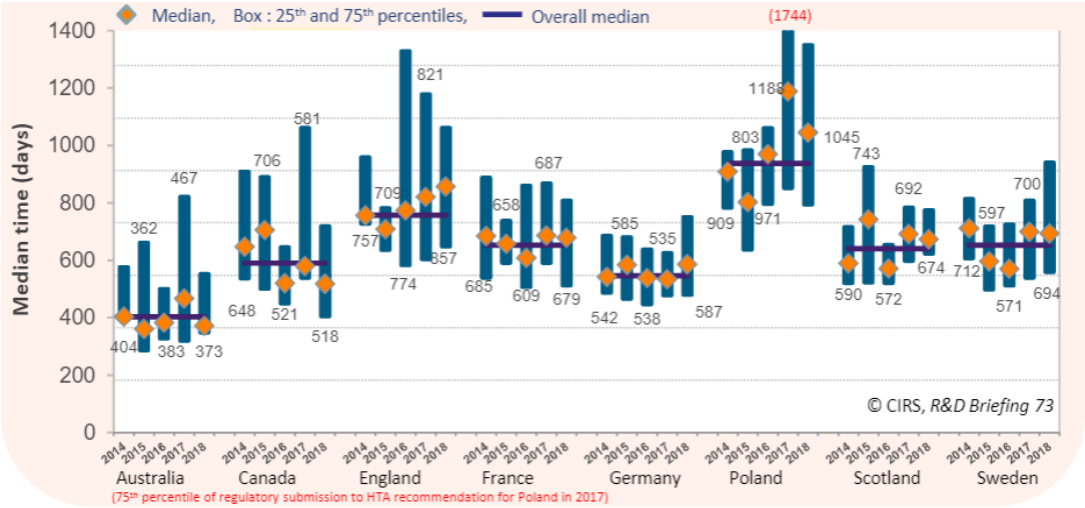


**Figure 3.3 Rollout time from regulatory submission to HTA recommendation by year of HTA recommendation *(Wang et al., 2019)***

The data shows that in 2018, the country with the quickest median roll out time from regulatory submission to HTA recommendation was achieved by Australia (373 days). This stellar performance was followed by Canada (518 days).

The third most efficient timeline following Australia and Canada, would be Germany (587 days).

Australia's regulatory and HTA review period is remarkable when benchmarked against some of the leading countries and regulatory frameworks. Their HTA review period is by far the shortest when the roll out is broken into the regulatory and HTA review periods (Figure 3.4).

Median submission to PBAC was 124 days prior to TGA approval for products that

went through parallel review, compared with a 120-day delay in HTA submission with sequential review (Wang *et al*., 2019). According to Ofori-Asenso *et al*. (2020), the efficient time period between marketing authorization and HTA recommendation or decision (median = 17 days) over the 2014-2018 review period as assessed by Wang *et al*. (2019), has been postulated as due to the TGA/PBAC parallel process.


**Figure 3.4 Breakdown of rollout time in key jurisdictions 2014-2018**
***(Wang et al., 2019)***

### 3.2.2.3 Canada

The NRA responsible for marketing authorization of both drugs and devices is Health Canada (Frønsdal, 2012). The process follows a defined pathway, with Health Canada issuing what is termed a Notice of Compliance (NOC) to the manufacturer, upon regulatory approval. The Canadian Agency for Drugs and Technologies in Health (CADTH), is the national body that conducts HTA under the Common Drug Review (CDR), and provides a reimbursement recommendation to the publically funded drug plans in all provinces and territories in Canada (except Quebec), however the price negotiations and budgetary impact considerations will still occur at provincial level for the final decision to adopt a technology (Frønsdal, 2012).

The Health Canada/CADTH parallel review process, has a clearly defined timeline. The manufacturer can make the submission to CADTH up to 180 days before the date of anticipated NOC from Health Canada (Ofori-Asenso *et al*., 2020).

This accelerates the process since the Canadian Drug Expert Committee can release its reimbursement recommendation to CDR immediately following the regulatory decision (Ofori-Asenso *et al*., 2020).

According to Wang *et al*. (2019), in 2014-2018, approximately half of the NASs submitted for HTA recommendation underwent the Health Canada/CADTH parallel review process. It is though, by comparative standards to Australia, not utilized as frequently by companies (Cai *et al*., 2018); in comparison to the 68% of NASs that followed the parallel submission process in Australia during the same period of analysis.

Canada has the second best time to market access, from the onset of regulatory submission to HTA / coverage approval, following Australia (Figure 3.3 & Figure 3.4). Therefore, it is a reasonable conclusion, that the parallel review process is driving efficiencies in patient access to health technologies.

### 3.2.3 Examination of roll out time to HTA / coverage recommendations

#### 3.2.3.1 HTA recommendation strategies

When a health technology is presented to a HTA or coverage body for approval, it will receive either an approved (favourable/positive) or declined (unfavourable/negative) status, in the form of a recommendation. The study and results from Wang *et al*. (2019), denoted the recommendations as ‘positive’, ‘positive with restrictions’ or ‘negative’; or the HTA recommendation may have different terminology applied and categorized as ‘to list’, ‘restrict’ (or ‘list with restriction’) or ‘reject’ (‘do not list’) a drug or technology for coverage (Nicod, 2017) .

The determination of whether a technology has been recommended as positive, positive with restrictions or negative, and more detail on the methodology as of these determinations as applied by Wang *et al*. (2019) can be found in Appendix A (Figure A1).

### 3.2.3.2 Analysis of total roll out time and HTA recommendations – selected countries

This analysis was conducted and adapted using the data presented in Wang *et al*. (2019). The following jurisdictions were selected for analysis: Australia, Canada, Germany and Sweden. The methodology employed by the author to derive meaningful findings can be found in chapter two (section 2.6).

A summary of the information used for data extractions follows (Figure 3.5):

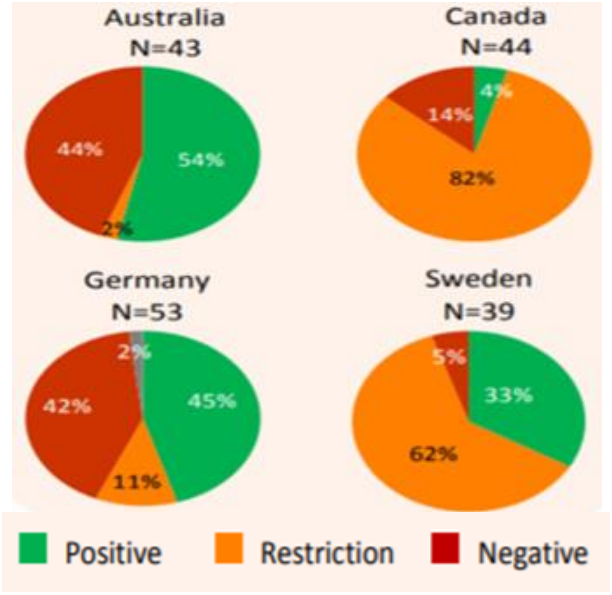


**Figure 3.5 HTA recommendations/outcomes 2017–2018 for select countries *(Wang et al., 2019)***

The outcome of this assessment is presented (Table 3.2) to illustrate the relationship (if any) between efficient roll out time and positive recommendations.

**Table 3.2 Comparative analysis of total rollout time and HTA/coverage recommendations in specific countries**

| Country | Total roll out time (days) | Regulatory review time (days) | Regulatory approval to HTA recommendation (national level) (days) | Positive % | Positive with restrictions % | Overall positive | Negative % |
|---|---|---|---|---|---|---|---|
| Australia | 420 | 362 | 72 | 54% | 2% | 56% | 44% |
| Canada | 550 | 347 | 172 | 82% | 4% | 86% | 14% |
| Germany | 561 | 417 | 120 | 45% | 11% | 56% | 42% |
| Sweden | 697 | 415 | 229 | 33% | 62% | 95% | 5% |

The following are the major findings of the roll out time and HTA recommendations:

- For the specified period of assessment, the countries with the quickest total roll out time are Australia (420 days), Canada (550 days) and Germany (561 days). Further Australia (72 days) and Germany (120 days) have the shortest timeline from regulatory approval to HTA recommendation. This does point to both efficient regulatory and HTA review frameworks, both in systems and processes. It has also been demonstrated that the parallel review process has been effective at improving patient access from the perspective of reducing overall review time (notable impact on the HTA period due to the allowance of earlier submission to the HTA entity).
- However, whilst Australia and Germany have some of the shortest total roll out times, these countries have the highest negative HTA or coverage outcomes / recommendations (Australia – 44%; Germany – 42%) versus Canada (14%), and Sweden (5%) respectively.
- One of the possible reasons for the high number of negative HTA recommendations could be due to inadequate clinical data and relevant information, presented to the HTA or coverage body, for reimbursement. The HTA or coverage entity is therefore unable to make conclusive determinations that the technology will be beneficial in the healthcare system. A suggested harmonization pathway to synchronize or align the clinical data requirements between the regulatory and HTA body, is early dialogue or parallel / joint tripartite scientific advice.
- However, it must be stated that both countries have parallel scientific tripartite

programmes at present, and this will be explored in the ensuing discussion, to try to ascertain why it has not assisted in more favourable HTA recommendations.

#### 3.2.3.2.1 Canada

As discussed earlier, Canada has a dynamic regulatory framework with the second best roll out time from market authorization to HTA approval (550 days); and third highest rate of positive recommendations (86%), after Sweden (95%) and England (92%).

The Canadian parallel regulatory–HTA review submission has assisted in reducing the overall roll out time, by allowing the submission to CADTH to occur up to 180 days before the date of anticipated NOC from Health Canada (Ofori-Asenso *et al*., 2020). Had this not been allowed, then the total roll out time, may likely have been much longer than what has been able to be achieved in the current setting.

Apart from the timing of the submissions, it must be noted that there is an optional information sharing process (with permission from the manufacturer), which has been established to permit Health Canada and CADTH to exchange information regarding a drug under review, for submissions filed with CADTH on a pre-NOC basis (Ofori-Asenso *et al*., 2020).

The high overall positivity rate (86%) of NASs is a cumulative value of positives alone (82%) and positive with restriction (4%). Canada has by far the highest positive alone value (82%) with the next best country rating following far behind, and that being Australia (54%). This is a remarkable indicator, as it shows that Canadian HTA bodies are presented with sound clinical evidence, and are comfortable to issue positive (with no restrictions) on majority of their products. This can be attributable to the conjoint regulatory advice, or parallel regulatory–health technology assessment scientific advice (PSA) undertaken on specific pharmaceutical products between Health Canada and CADTH, in a programmes known as ‘Joint pipeline meetings’ (Tsoi *et al*., 2013).

Another critical consideration to the high positivity percentage (82%), can be linked to a recent study which found that the CADTH (and other HTA bodies) were willing to accept non-comparative evidence (as opposed to the traditional RCT) in certain

situations in which treatment benefit could still be demonstrated (Vreman *et al*., 2019).

In terms of efficiency and shortest HTA review period, Canada has the third best performance (172 days) versus Australia (72 days) and Germany (120 days). This could point to looking at the HTA process in itself, where efficiencies could be explored in either process or system. However, equally important, is that approximately only half of NSAs underwent the parallel review process (Wang *et al*., 2019) in Canada. Should more manufacturers take up this pathway, one could see a reduction in the 172 day review period, due to the parallel process allowing a submission 120 days to CADTH before expected NOC from Health Canada (Ofori-Asenso *et al*., 2020).

Efficiency in patient access to health technologies, are not only limited to the speed of the process of technology market authorization, and final recommendation of the HTA i.e. the total roll out time. Efficiency in patient access, is dependent on having both a fast total roll out time, and a high percentage of positive recommendations. Having a product move quickly through the regulatory–HTA process, only to eventually be declined or negatively recommended, is not at all a productive system for the manufacturer, regulatory–HTA entities, patient or doctor.

It is therefore the author's opinion that based on the findings above and comparative analysis (Table 3.2), Canada has one of the most efficient regulatory–HTA frameworks, having the second best total roll out time (550 days), and a very high positive HTA recommendation outcome (86%). It must be noted, that efficiencies in the regulatory–HTA total roll out, could be optimized for benchmark improvements in other established regulatory frameworks.

Although this data was specific to medicines, based on the robustness of the Canadian regulatory–HTA system, one can infer that the same efficiencies would be seen with the medical device technologies. Further, it's worth noting that Canada is at the forefront of medical device parallel submission with the MaRS EXCITE programmes (Table 3.1).

#### 3.2.3.2.2 Australia

The harmonization pathway of dialogue and tripartite scientific advice initiatives, were embraced early on by Australia and started in 2011, however, the author was unable to find any recent research to support current engagements to this effect. Which points to limited use of this functionality by companies, and could explain the correlation to the high percentage of negative outcomes/recommendations.

#### 3.2.3.2.3 Sweden

The Medical Products Agency (MPA) is the NRA overseeing pharmaceuticals and health products regulation in Sweden (Frønsdal *et al*., 2012). The Dental and Pharmaceutical Benefits Agency (TLV) is an independent government body responsible for determining whether a drug should be subsidized by the National Pharmaceutical Benefit Scheme (Frønsdal *et al*., 2012).

An important element that may have aided the high percentage of overall positive recommendations (95%) as seen in Wang *et al*. (2019), can be related to a study performed by Cuche *et al*. (2014), which showed that parallel regulatory–health technology assessment scientific advice (PSA), was mandatory in Sweden. Further Tsoi *et al*. (2013) has indicated that early tripartite dialogue on scientific advice is undertaken specifically in the pharmaceutical scope in Sweden, further supporting the positive impact that PSA has had on HTA outcomes.

However of concern, is that the biggest contributor to Sweden's overall positive rate (95%), comes from positive with restrictions (62%) which accounts for almost three quarter of Sweden's overall positivity rate. In comparison to other countries, Sweden's restricted approval is not in alignment (Australia- 2%, Canada- 4%, and Germany- 11%).

Wang *et al*. (2019) indicates that the restrictions are related to subsidy or reimbursement restrictions (Appendix A, FigureA1). A contributor to positive with restriction recommendation by HTA entities, may be related to inadequate clinical evidence to demonstrate value or effectiveness of the technology at the time of assessment.

In terms of the time taken for the HTA review period specifically, Sweden fared on the higher average time end (229 days), with only England having a longer period of all countries surveyed in this exercise (337 days). Australia had the shortest HTA review period (72 days). It is a reasonable assumption, that to improve the total roll out time, Sweden should consider implementing a parallel review period, like Australia and Canada (Table 3.2), which will allow the HTA entity more time to review, and ultimately ensure quicker patient access due to a reduced overall roll out time.

#### 3.2.3.2.4 Germany

The health products regulatory authority in Germany is the BfArm (The Federal Institute for Drugs and Medical Devices). There are two HTA entities in Germany, the G-BA is the federal joint committee, and provides reimbursement recommendations for Germany. The second is the IQWiG which is the Institute for Quality and Efficiency in Health Care, which provides advice for Germany; and although is a respected international expert body, does not make coverage decisions (Cuche *et al*., 2014).

Similar to the discussion above on Sweden, as of September 1, 2012, it is mandatory for companies seeking early HTA advice from the G-BA to do so in parallel with regulatory advice from BfArm (Cuche *et al*., 2014). For companies seeking to undergo this process, Cuche *et al*. (2014) details that it is important to note that the G-BA and IQWiG have communicated that they will not alter their recommendations if regulatory requirements differ from their own due to a different understanding of "benefit". This illustrates that the HTA entities are quite steadfast in their requirements, and should these not be fulfilled, could have resulted in the high percentage of negative recommendations (Table 3.2).

Already determined and supported by Tafuri *et al*. (2019), manufacturers will be more inclined satisfy the NRA in clinical evidence requirements.

Therefore, if PSAs are provided, but manufacturers do not prioritize the requirements as outlined by the HTA bodies and favours the NRA instead, this could potentially lead to an increased number of negative recommendations by the HTA entity.

## 3.3 Conclusion

This study demonstrates the existence of parallel regulatory–HTA frameworks in multiple jurisdictions globally (Table 3.1). To validate that these collaborations represent the current efficiency and improvement thinking amongst global subject matter experts regarding health technology access, these frameworks were referenced to the numerous literature and journal articles focusing on harmonization and efficiency, which make notable mention of said programmes or collaborations.

The presence of these parallel regulatory–HTA frameworks was further explored, using literature generated and a defined methodology, to determine if they led to improvements in marketing authorization and access coverage.

Countries with parallel regulatory–HTA reviews, had the best roll out times (time taken from marketing authorization of a product, to HTA recommendation). The existence of these parallel review frameworks therefore demonstrated effectiveness as a harmonization pathway to improve the timeline to patient access of health technologies.

Patient access though is fundamentally determined by the outcomes of the regulatory process and the HTA process. HTA outcomes can be broadly summarized as favourable / positive, favourable / positive with restrictions or unfavourable / negative. Higher negative outcomes or recommendations are associated with inadequate or suboptimal clinical evidence being presented to the HTA entity for review. A country such as Australia, with parallel regulatory–HTA reviews, and the best roll out time from all the countries in the particular study (Wang *et al*., 2019), had the most number of negative recommendations from all countries. One can therefore deduce, that parallel regulatory–HTA reviews, whilst efficient in reducing the period to roll out time, does not necessitate positive HTA recommendations. These countries could then benefit from adopting alternative harmonization pathways within their frameworks, such as tripartite early dialogue or parallel regulatory–HTA scientific advice (PSA).

Canada exhibited an exceptionally efficient regulatory-HTA framework in both process efficiency and positive outcomes or recommendations.

Based on the evidence presented, this chapter has met the requirements of Objective One, demonstrating that current parallel regulatory–HTA frameworks are in existence globally, and further, has improved the roll out time of marketing authorization and patient access in terms of process optimization.

# CHAPTER FOUR - ASSESSMENT OF THE CURRENT REVIEW AND APPROVAL PROCEDURES OF SAHPRA AND HTA BODIES FOR MEDICAL DEVICES IN SOUTH AFRICA

## 4.1 Introduction

In this chapter, an assessment is undertaken of the current review and approval procedures for medical devices by SAHPRA and HTA bodies in South Africa, and the associated impact on timely patient access to health technologies.

Other elements of the healthcare system in South Africa are also considered, as it represents a very complex model in terms of having a private and public sector dichotomy.

### 4.1.1 The South African healthcare system and financing – A snapshot

The South African healthcare system is currently made up of the public and private sectors, each providing services to respective population groups, depending on their ability to either self-fund (private), or rely on State provided healthcare services (public).

The public health sector, as with most other public services in South Africa, is funded through the fiscus. The sector is also structured in line with the three spheres of government i.e. national, provincial and local (Ataguba & McIntyre, 2018), and provides primary, secondary, tertiary and academic levels of care through primary health care clinics, community health centres as well as district, regional, provincial and academic hospitals.

The private sector also offers varying levels of healthcare services from primary care to specialized hospital care. Apart from clinical services through private hospital networks, there is an array of independent healthcare professionals from varying scopes of practice offering private care e.g. doctors, physiotherapists, and pharmacists. These services are financed mainly through contributions to private health insurance (called medical schemes) with some direct household out of pocket (OOP) payments (Ataguba & McIntyre, 2018). In fact, South Africa spends a higher

share of its total health expenditure on private voluntary health insurance compared with any OECD country – including the United States (Lorenzoni & Roubal, 2016).

The significant problem that the public-private healthcare sector presents, is the separation of services to the different population groups, and the resources that each sector has to facilitate the care needed. While the public health sector accounts for about 40% of all expenditure on health, it is under pressure to deliver services to about 80% of the population (Mueller, 2020). The private sector in contrast, serves a minority of the population. Further, there is a high level of fragmentation of resources within the private sector (NDoH, n.d.).

This two-tiered system is not only inequitable, but also results in an underfunded and deteriorating healthcare infrastructure and poor management in the public sector institutions (Mueller, 2020).

### 4.1.2 NHI – South Africa's universal healthcare coverage strategy & the goal towards a national HTA body

This inequitable spread of resources resulting in suboptimal care being offered to the most vulnerable and needy in the country, has culminated in government proposing the establishment of a National Health Insurance (NHI) scheme for the country, in line with universal healthcare (UHC) objectives (Ataguba & McIntyre, 2018). Universal healthcare coverage will create the balance in resources and services, so that no individual will be prejudiced in the health care they receive, based on socio-economic status.

This balance in care and provision of services, will be executed in the form of a Health Service Package (HSP), which will ensure optimal clinical and quality outcomes, within a cost containment structure (Siegfried, Wilkinson, & Hofman, 2017). The source of income to manage the NHI fund will come from tax revenue, and this therefore demands that this fund play a central role in terms of strategic purchasing, to ensure the most cost-beneficial HSP for the entire population (Ataguba & McIntyre, 2018).

To ensure that a cost-beneficial HSP is offered that covers essential, good quality services for free, and importantly remains sustainable, will require the regulation of

healthcare costs (MacQuilkan *et al*., 2018). Strategic purchasing to ensure a value (cost and quality considered) HSP is provided to all South Africans, would require a HTA body, to make these informed and unbiased decisions.

Thus the creation and introduction of a formal national HTA agency is seen as a positive development (Siegfried *et al*., 2017). An independent national HTA agency will help address issues related to both affordability and equity when allocating resources (MacQuilkan *et al*., 2018).

The 2015 NHI White Paper has already been discussed in terms of the highlighting the importance and requirement of a national HTA body, to achieves its objectives of universal healthcare coverage. This HTA body must at all times operate within its own mandate, but be aligned with the NRA only in terms of efficiency to bring about timely patient access. SAHPRA therefore has an important role to play, in ensuring synergies between themselves and the national HTA body.

There are firm plans in place to create a national HTA structure as an independent entity under the auspices of the NDoH, as evidenced by information in SAHPRA's Annual Performance Plan for 2020- 2021; with the objective being the establishment of an independent HTA agency by April 2022 (SAHPRA, 2020).

## 4.2 Results & discussion

### 4.2.1 SAHPRA's current review and approval procedures for medical devices

SAHPRA and the current regulatory framework has already been introduced in chapter one.

The current role that SAHPRA serves for medicines and medical devices have been summarized (Table 4.1):

**Table 4.1 SAHPRA: Current regulatory processes – Drugs and medical devices**

| Element | Drugs / Pharmaceuticals | Medical Devices |
|---|---|---|
| **Regulatory authority** | SAHPRA | SAHPRA |
| **Maturity of overall framework** | Complete and established | Infancy |
| **Licencing of manufacturers, distributor and wholesalers** | Mandatory | Mandatory |
| **Registration of products** | Mandatory | Has not yet commenced (as at the time of writing this article) |
| **Controlling entity** | NDoH (South African Government) | NDoH (South African Government) |

SAHPRA's proposed regulatory framework will broadly follow a risk based approach to ensure that public health, continued access and safety remain a priority.

The NRA will, in keeping with its sound approach to medicines, implement reliance pathways in the registration of medical devices based on the approval and registration in other recognized jurisdictions e.g. Canada, US (SAHPRA, 2022).

All manufacturers and distributors of medical devices requiring registration, need to be compliant to the international quality management system specific for devices, known as ISO 13485. The verification of this compliance to ISO 13485 will be undertaken by external and legally accredited entities within the framework known as conformity assessment bodies. The manufacturer or distributor must also issue declarations of conformity (in attestation with the principles of performance and safety), for all required medical devices. A full technical dossier with all the specified requirements will be made to SAHPRA to register the medical device for use in South Africa.

In order to address the significant volume of medical devices and ensure risk management without impeding access to technologies, a call-up plan will apply the following rationale:

1. An initial review of all new class B, C and D medical devices; and
2. followed by a review of medical devices currently on the market, with an initial focus on Class D due to the highest risk associated (SAHPRA, 2022).

Until such time that SAHPRA undertakes full control of the review, approval and formal listing of medical device products, the utilization and adoption of medical device products, lies under the control of each health care entity in the private and public sectors. They may use medical devices from any company or supplier, provided that the company or supplier has the relevant SAHPRA establishment licence (applicable to risk categorization of the product) from a regulatory perspective.

This means that the review and approval process of medical devices are very much fragmented within, and between both sectors.

Medical device products are currently accessed in the public sector through a combination of national and provincial tendering processes, as well as standard listing based on a clinical requirement or demand, following an assessment process in line with their objectives.

In the private sector, each health care entity will have their own assessment process to analyse health products introduced into the market, resulting in a very heterogeneous process especially for the providers of medical devices. Health products accessed in the private sector, are also subjected to a formulary / preferred provider catalogue, and include standard listing driven by clinical requirement or demand. In the private sector, products must have some sort of international regulatory approval (requirements of which may very between entities) or conform to local standards depending on risk classification and availability of testing.

### 4.2.2 SAHPRA's impact on patient access to health technologies

The former MCC, although technically sound, struggled with efficient turnaround times. However, the regulatory function, under the authority of SAHPRA, has seen an improved performance due to the processes enhancements, targets and defined strategies implemented. The following findings will provide an overview of the performance of both the MCC and SAHPRA respectively. The context provided by the historic performance of the MCC is important, as when SAHPRA's performance is

discussed, it will serve to highlight the vastly positive impact that the current NRA leadership have had on regulatory efficiency in South Africa.

An overview of the MCC's historic performance was assessed in a study by Keyter *et al*. (2019), which sought to compare the South African NRA with other international NRAs (Australia, Canada, Singapore, and Switzerland). The MCC had two separate processes for new active substances (NASs), also referred to as new chemical entities (NCEs), in terms of reviews, which included the standard review process, and a fast track process which was assigned to eligible applications in order to expedite the registration of essential medicines (Keyter *et al*., 2019). The fast track application process does not change the review process in terms of content and analysis, but it does prioritize these particular submissions over existing applications (Keyter *et al*., 2019).

The MCC had set targets for the overall review time, for fast track applications, but not for standard reviews (Keyter *et al*., 2019). The target set for the overall review time of fast track applications was 250 calendar days (Keyter *et al*., 2019). The median approval times for fast track new active substances (NASs) applications approved in 2015, 2016, and 2017 according to Keyter *et al* (2018) were 1218, 921, and 609 calendar days, respectively (as cited in Keyter *et al*., 2019). In terms of the median review and approval timelines for standard reviews related to NAS, Keyter *et al* (2018) further indicated that over the same three year period (2015, 2016, and 2017), the NRA achieved 1175, 1641, and 1466 calendar days, respectively (as cited in Keyter *et al*., 2019). These data demonstrated that the MCC was not able to achieve the target timelines set for fast track applications (Keyter et al., 2019) despite their best intent and efforts to ensure an efficient and effective approval timeline.

For context on a global scale, the median marketing authorization timelines for TGA, Health Canada and Swissmedic, for the period 2013-2017 according to Bujat *et al* (2018), achieved 364, 350, and 487 days, respectively (as cited in Keyter *et al*., 2019).

Under SAHPRA's governance, this historic performance has been dramatically improved. For NCEs, the NRA had ensured that targets were clearly defined for standard reviews. A target of 590 working days for the 2019/2020 calendar period (SAHPRA, 2020) was the goal that the NRA worked toward achieving. Based on actual performance results for the 2019/2020 period, SAHPRA was able to achieve

that 100% of all applications processed, were reviewed within the target timeline of 590 working days (SAHPRA, 2021). Whilst it is acknowledged that the MCC data was presented as calendar days as opposed to working days, SAHPRA's recent performance is still a remarkable improvement when compared to the performance of the MCC in 2017, which had a median review period of 1466 calendar days.

SAHPRA continues to enhance its performance, with the 2022/2023 and 2023/2024 periods, having targets of 490- and 400- working days respectively; signalling ongoing commitment to optimal regulatory performance.

Despite all the demonstrated improvements, there still remains the backlog of medicine applications inherited from the MCC, and a highly complex and bountiful medical device portfolio, to add to the current regulatory workload. It would not be inaccurate to infer that the resultant delays, even with the enhanced performance, would ultimately negatively impact the access of medicines by patients in South Africa (Keyter *et al*., 2020). This will be significantly compounded with medical devices now requiring review, approval and control.

The problems and complexities experienced by SAHPRA are certainly not unique to the South African NRA, as there is an international trend according to the WHO (2014a), where NRAs of varying sizes, are under increased pressure due to a multitude of factors such as higher application volumes, diversification and increase in products requiring regulation etc. (as cited in Keyter *et al*., 2018).

Saidi and Douglas (2018) viewed the adoption of a regulatory framework for medical devices in South Africa as a positive development for the local medical device industry and the quality systems that require implementation. However, concerns have been raised by these authors, of the risk of excessive delays to approving medical device products, based on the track record of the previous MCC which had been challenged by constant backlogs and delays in bringing products to the market.

The South Africa NRA under the auspices of SAHPRA, have taken great strides to improve their regulatory performance (Keyter et al., 2019). This includes publishing regulatory timelines as a measure of performance as well as various operational strategies. However the complexity and wide-ranging portfolio of medical devices, will present progressive and new challenges, which will be mitigated to an extent by

the internal improvement strategies already under way, but also require harmonization approaches already discussed to optimize timely patient access to health technologies.

### 4.2.3 HTA current review and approval procedures for medical devices

The current HTA approval and review processes are presented (Table 4.2) and differs between public and private sector. The information (Table 4.2) has been extracted from Ataguba and McIntyre (2018) and includes elements of the author's own understanding of the HTA landscape.

**Table 4.2 HTA: Current review and approval processes – Drugs and medical devices In public and private sectors *(Ataguba and McIntyre 2018)***

| | | Drugs / Pharmaceuticals | Medical Devices |
|---|---|---|---|
| **Payer** | **Public** | South African Government (tax revenue) | South African Government (tax revenue) |
| | **Private** | Medical schemes and some Out of Pocket expenses | Medical schemes and some Out of Pocket expenses |
| **HTA agencies** | **Public** | The National EML and provincial and hospital-based structures | NHLS and provincial and hospital-based structures |
| | **Private** | Most hospital group networks, some medical schemes | Most hospital group networks, some medical schemes |
| **National independent HTA body** | **Will direct NHIF (all South Africans)** | None as yet (proposed creation 2022) | None as yet (proposed creation 2022) |

***NHLS:*** *National Health Laboratory Services;* ***EML:*** *Essential Medicines List;* ***NIHF:*** *National Insurance Health Fund*

The private healthcare sector is represented by multiple entities or role players, having a mandatory process to be followed to bring technologies to market, and has been labelled as ‘highly fragmented’ (SAMED, 2017). Individual organizations (medical schemes, hospitals) using HTA have their own rules and criteria (SAMED, 2017).

According to the South African Medical Device Industry Association (SAMED), HTA in the private sector is driven by the introduction of either a completely new technology, or when a technology at a higher cost but offering a claim of incremental benefit to a current comparator is presented (SAMED, 2017).

In the current private healthcare sector model, the hospital groups constitute the providers and the medical schemes are known as the payers, funders or coverage bodies. Patients belonging to a medical scheme, will seek treatment from the providers. The providers will deliver said service, using health technologies, and then submit a claim for reimbursement to the payer or coverage body.

HTA is therefore undertaken by both the providers and medical schemes. Within the medical schemes, the Medical Schemes Act, which empowers the medical schemes via their administrator or managed care organization, to develop reimbursement policies using HTA methodology for new technologies (SAMED, 2017).

Much like the private sector, the demand for sophisticated technologies in public sector tertiary and academic hospitals is driven by clinicians such as department heads and physicians (Mueller & Govender, 2016). Again exhibiting similarities between private and public sector trends, any technology deemed expensive or new / specialized, will be a challenge to introduce (Mueller & Govender, 2016).

HTA methodology is also fragmented and with no formal system to conduct assessments (Mueller & Govender, 2016). Those limited entities practicing HTA do so utilizing either committees which include skilled and capable professionals contracted or part-time or specialized teams within a hospital convened from time to time (Mueller & Govender, 2016).

The National Health Laboratory Services (NHLS) has a more systematic process in place, with transparent and published documentation and allowing online applications (NHLS, n.d.).

Whilst it is evident that there are effective but non standardized approaches and systems to conduct HTA in both the public and private sectors, there remains a major gap in terms of the reporting of these assessments, including a lack of uniformity in the reporting structure. Reporting of HTA evaluations, will be critical for both private and public sector entities, to ensure transparency and trust with the process that has been applied for the economic evaluation undertaken on any health technology.

The issue regarding a need for standardized reporting of economic evaluations, whether from an HTA process or research perspective, has received much global focus and attention to find a respected and homogenized approach or tool. The Consolidated Health Economic Evaluation Reporting Standards (CHEERS), originally published in 2013, has proposed a new revised format incorporating a 28-item checklist, which addresses key elements of any economic evaluation (Don Husereau *et al*., 2022). Although the CHEERS 2022 reporting tool has been developed to assist researchers undertaking health care economic evaluations, as well as provide a methodology for peer reviewers and editors in their assessment, its scope extends to all bodies engaged in HTA, to aid with uniformity and transparency.

### 4.2.4 HTA's impact on patient access to health technologies

In the private sector, the timelines to HTA approval are varied (Table 4.3) and are dependent on the specific entities undertaking the review (SAMED, 2017).

**Table 4.3 Timelines to HTA approval in the private sector *(SAMED, 2017)***

| Steps | Activity | Expected Timelines |
|---|---|---|
| 1 | Market preparation for introduction of new technology (timelines are supplier dependent) | Company determined |
| 2 | Establishment Licence (timelines undetermined) | Regulator determined |
| 3 | Private hospital groups vendor registration (timelines variable subject to information submitted and individual group requirements) | Hospital determined |
| 4 | Product (NAPPI) Code Application | 48 hours |
| 5 | Payer / Funder approvals (Approval; price negotiations; HTA) | 3-12 months 0 (where mandate exists from funder to MCO*) to 3 months |
| 6 | Hospital group approval | Hospital determined |

*MCO = Managed Care Organisation.

For the providers of health products and technologies in the country, their overall experience with the current private sector HTA process is that it is fragmented and complicated by the varying requirements from each HTA entity (SAMED, 2017).

Funder approval processes can take on average between three to twelve months, to a maximum of two years should there be extensive economic modelling required (SAMED, 2017).

Private hospital group timelines are variable and dependent on a host of factors including but not limited to issues such as current installed base of equipment, available capex and strategic objectives.

In the public sector, HTA processes dependent on the urgency and requirement, can take anywhere from a few weeks to three months (Mueller & Govender, 2016).

Depending on the type of review, additional information may be required to make an

informed assessment, usually in conjunction with the procurement officer and the staff of the clinical unit (Mueller & Govender, 2016), which includes data related to available comparators, other accessories/consumables required and the cost of the technology.

Therefore based on the above, any delays to patient access of health technology in the public sector is not due to a hurdle in the HTA process (timelines specified above), but rather will be related to budgetary pressures and lack of adequate resources to manage the amount of patients being treated within the healthcare sector.

## 4.3 Conclusions

The healthcare sector in South Africa is very complex due to the private and public sector dichotomy that presents. This has led to inequitable distribution of resources, resulting in the government's strategy to implement a NHI which will provide Universal Healthcare Coverage (UHC).

As part of effective roll out and implementation of the NHI, a national HTA body will be required to ensure funding is directed to a HSP based on value (cost and quality considered) for all South Africans.

The national HTA body and SAHPRA will work together to achieve the unified objective of NHI, however each will still operate within their mandate and independence to exert their jurisdictional responsibilities.

This relationship is a strong proponent to support the mutual and shared objective of both SAHPRA and the NHI, to ensure access to health and optimal public health outcomes for all South Africans. If this objective is made easier to achieve by harmonization pathways such as parallel regulatory–HTA reviews, to improve timely patient access, then it should be considered.

SAHPRA as the NRA has sound technical ability to review and make decisions in terms of safety, efficacy and quality for new health technologies. Their performance has been significantly improved when compared to the MCC using improvement strategies which has resulted in positive outcomes and driving regulatory function efficiency. However despite the demonstrated improvements in regulatory function, the concern is that the current performance is not optimal as yet, and there remains a backlog inherited from the MCC, which may be exacerbated by the additional workload that the medical device portfolio will present as medical device product registration commences.

The medical device category encompasses hundreds of thousands of products, and may present challenges to regulatory functionality, a phenomenon seen internationally as well.

The current HTA review and approval processes are more complicated due to the private and public healthcare sector polarity. HTA is also not yet institutionalized (MacQuilkan *et al*., 2018) or entrenched in any system, private or public. It is fragmented and subject to individual entity processes and procedures and therefore adds more complexity to any additional issues that may present. Without standardized and universal approaches to HTA, it not only makes the current process difficult but also represents a major concern in moving toward UHC and creation of the NHIF in the absence of defined process and framework. In addition, there is no reporting of HTA evaluations in both the public and private sectors, which could benefit from implementation of the CHEERS tool that can offer a much needed uniform and transparent reporting structure.

In both private and public sector, it is evident that HTA serves to ensure that value (present clinical and economic benefits) driven technologies are being utilized within their respective healthcare settings. HTA in this sense is serving the purpose of directing limited funds in both ambits, to value technologies.

HTA approval it appears, although segregated and individualized to the entity, is not the contributory factor at this stage in terms of access delays, but rather related to budget constraints.

# CHAPTER FIVE - DETERMINATION OF WHETHER LOCAL ADOPTION OF PARALLEL REGULATORY–HTA REVIEWS BY SAHPRA AND HTA BODIES WILL ENABLE FASTER PATIENT ACCESS TO SAFE AND COST EFFECTIVE MEDICAL DEVICES

## 5.1 Introduction

The determination of whether local adoption of parallel regulatory–HTA reviews by SAHPRA and HTA bodies will enable faster patient access to safe and cost effective medical devices, has been hypothesized as validated if the following would be demonstrated in this research project:

(i) Whether there exists international success data from the major regulators in improving patient access.

(ii) There exists an issue within the current South African system in terms of patient access, which could potentially benefit from implementing a process as tabulated (Table 3.1) which has illustrated various global harmonization principles.

## 5.2 Results and discussion

### (i) There is international success data from the major regulators in improving patient access

International frameworks and initiatives for parallel regulatory–HTA reviews are currently in place to improve marketing authorization and access coverage were reviewed and presented in chapter three (Table 3.1). These frameworks were further assessed in terms of how efficient the roll out time was in terms of improved patient access. This was demonstrated in Wang *et al*. (2019) where in their assessment of roll out time in some of the more established jurisdictions, it was clear that Australia and Canada had the quickest roll out times. These countries have established parallel regulatory frameworks in place, and are contributors to the efficiencies seen.

For Australia, by allowing parallel submission to PBAC (HTA body) 124 days prior to anticipated TGA (NRA) marketing authorization, this improved the HTA timeframe

review period significantly (median = 17 days). This compared with a 120 day delay in HTA submission with sequential review (Wang *et al*., 2019), is a remarkable testament to the parallel review benefit.

Canada also has data to reflect timeline improvements from sequential to parallel reviews. An analysis has shown that during the period 2014-2016 of 56 NASs as reviewed by CADTH, a stark difference was seen in the median approval times for parallel and sequential reviewed products from Health Canada to CADTH recommendation; drugs in parallel review (n=22) took 158 days, whilst drugs undergoing sequential review (n=34), had an approval timeline of 377 days (Ofori-Asenso *et al*., 2020).

There are other countries (Table 3.1) that also have established parallel regulatory–HTA frameworks in place, however these two countries were selected due to their efficient roll out times, to demonstrate that this particular objective of international systems having success from these parallel reviews, has been substantiated. The other countries have also seen the merit and efficiencies therein in this harmonization pathway and have therefore implemented same within their frameworks.

**(ii) There exists an issue within the current South African system in terms of patient access, which could potentially benefit from implementing a process in line with global harmonization principles.**

Despite significant improvements to regulatory function, the NRA may experience challenges with the addition of medical device product registration, already described in Chapter Four, including background information related to current registration status of medicines and medical devices.

SAHPRA is a forward thinking organization, which has undertaken various assessments and changes to improve efficiency in their turnaround time. The adoption of a parallel regulatory–HTA framework, as exists in Australia, Canada and the US, of which SAHPRA has current reliance mechanisms in place for medicine regulation (SAHPRA, 2022), should be considered as another step toward harmonization efforts.

Although SAHPRA has demonstrated improvements in review timelines, and continues to enhance its performance, there exists complexity in inherited backlogs and continued progress to better performance, not yet achieved. This phenomenon is not unique to the South African NRA and is a common challenge for all NRAs around the world. When medical device product registration commences, the magnitude of the medical device portfolio, which is far more expansive and complicated due to the variability of attributes that medical devices present, will impede any performance improvements achieved by the NRA. SAHPRA must therefore consider alternative harmonization pathways, to ensure continued timely patient access to health technologies.

Patient access is also defined by HTA recommendations. At present HTA is fragmented and practiced in isolated cases in both the private and public sectors. The timelines as depicted for both public and private sector HTA entities are not unreasonable (unless extensive modelling is required as with certain medical schemes, and timeline can extend up to two years). The reference to extensive modelling, further adds a question on what clinical evidence is being presented in terms of local context, and will most certainly require in depth understanding as this issue may pose similar complexities to a national HTA body.

There is no national HTA body at the time of writing this research report. South Africa has an unequal healthcare system, and in order to ensure the health of all citizens are optimized, the NHI is planned to be rolled out over the next few years. A national HTA body, an independent entity under the auspices of the NDoH, is part of the NHI implementation plan, and further referenced in SAHPRA's performance plan for 2020–2021, is planned to be created in April 2022 (SAHPRA, 2020). The formation of a national HTA body will be critical to ensuring that the NHI fund is directed to value-adding technologies (quality and cost), to ensure all citizens are covered. In order to make value based and timely adjudications on technologies, the HTA entity must have sufficient time and evidence presented to make important funding decisions and ensure timely patient access. A parallel regulatory–HTA review process will be an advantageous starting point from a roll out time efficiency perspective.

Whilst the national HTA structure is in the process of formulation, and in the interim period, consideration should be given to SAHPRA collaborating with both public and private sector HTA bodies. These HTA bodies have been applying HTA processes, albeit fragmented, to the end objective of providing value technologies to patients, which embody the best quality and clinical improvements, with limited budgets. This interaction could serve as an important learning and trial assessment for critical progression towards implementing a harmonization pathway with the national HTA body. The ultimate objective, is toward a sustainable and efficient regulatory-HTA framework, supporting key strategies of overall improvement in public health, timely health technology access (including medical devices now legislated), and NHI implementation.

This thinking is further explored by Siegfried et al. (2017) where in their discussion on the importance and integral role of a national HTA in NHI, the following recommendations were proposed for consideration: For the short-term (six to twelve months), the NDoH should consider hosting an HTA summit that should include a broad scope of current stakeholders currently contributing to HTA in South Africa, whether public or private e.g. academic hospitals, private sector medical aids and hospitals etc. This summit can bring to the fore important discussion points on the creation of an ideal national HTA agency, appropriate definition of HTA relevant to the South African context, and other vital matters (Siegfried et al., 2017).

These platforms will also allow for discussion on the important matter of current resource (human and financial) constraints experienced in both public and private sector entities, which is a consideration in implementing any parallel review regulatory-HTA process. Notably, on the part of the HTA body, if a technology fails to attain marketing authorization by the NRA, the HTA entity risks wasting valuable time and effort. As previously touched on, some of the risk mitigation strategies will be the identification and implementation of less resource-intensive components of a payer's review that can be completed earlier, and priority setting may be required to select technologies with the greatest likelihood of obtaining regulatory approval to undergo parallel review (Tsoi et al., 2013).

Although there is a risk of resource wastage within the HTA body should the regulator not approve the technology (Tsoi et al., 2013), it is the author's opinion that

parallel reviews will be the least resource intensive to implement from all the harmonization pathways (Chapter one, Table 1.6). This may require a formal agreement between the regulatory and HTA body(s) to allow submission to the HTA entity, within a specified number of days before the expected regulatory decision.

## 5.3 Conclusion

The validation of this objective i.e. whether adoption of parallel regulatory–HTA reviews will enable faster patient access to safe and cost effective medical devices, was dependent on the demonstration of the two variables below:

(i) Whether there exists international success data from the major regulators in improving patient access.
(ii) There exists an issue within the current South African system in terms of patient access, which could potentially benefit from implementing a process as tabulated (and in line with global harmonization principles).

These requirements have been substantiated by the respective findings in the foregoing chapters.

SAHPRA is in an opportune position to mitigate the regulatory impact associated with medical device product registration due to the quantum and complexity, and to opt for an appropriate harmonization pathway(s) to ensure efficient regulatory–HTA processes for timely patient access to products. With their role together with the national HTA body, in promoting public health and the roll out of NHI, this collaboration could ensure timely patient access, and the provision of quality, safety and efficacy; as well as effectiveness and cost considerations to sustainable healthcare (along with other HTA objectives), are made available in an efficient manner.

Consideration should be given to collaboration between SAHPRA and current public and private sector HTA bodies, to start the process of shared learnings to develop a framework, to enable the National HTA body to be readily functional once established. This thinking has been supported by another literature source (Siegfried et al., 2017).

With no national HTA mechanism or entity yet in place, South Africa is also well positioned to learn from the experiences of other countries and to establish an HTA

framework that delivers the components of HTA in a way that meets the needs of NHI and the National Development Plan (Siegfried *et al*., 2017).

In crafting the parallel regulatory-HTA framework, SAHPRA will need to take the lead (until the national HTA body is fully functional) on determining some initial crucial steps, for effective implementation.

Although there is a risk of resource wastage within the HTA body should the regulator not approve the technology (Tsoi et al., 2013), it is the author's opinion that parallel reviews will be the least resource intensive to implement from all the harmonization pathways (Chapter one, Table 1.6). This may require a formal agreement between the regulatory and HTA body(s) to allow submission to the HTA entity, within a specified number of days before the expected regulatory decision.

Additionally, as harmonization efforts do require resources in order to overhaul current processes and systems (in both the regulatory and HTA spaces), parallel reviews may be a sensible approach to consider as the first pathway implementation in SA, as it may represent the least resource intense and easiest pathway to implement. This is because it is primarily process based, in terms of timing and submissions. Once perfected, consideration can then be applied to the other pathways, in terms of what will be the next progressive harmonization step to improve patient access

# CHAPTER SIX – LIMITATIONS AND RECOMMENDATIONS

## 6.1 Limitations

The study has several limitations.

During the literature search, only English sources of information were included. There could therefore have been foreign language articles overlooked which could have added more value and content. Further, date ranges from the last two decades were assessed and only included if the information was still relevant to current context. The latter was a subjective interpretation, and therefore can be seen as a study limitation in terms of not having additional researchers to agree to selection.

This study did not discuss in detail or focus on the barriers to implementation of the harmonization of the regulatory-HTA framework. These barriers have been alluded to previously and include issues such as legal, organizational and resource-related issues (Ofori-Asenso, 2020).

Many initiatives related to framework efficiencies, extracted from research articles, were based on medicines and therefore some may consider irrelevant. However the research findings have also supported the applicability of solutions presented, to both medicines and medical devices, with the latter having greater relevance by nature of their attributes and functionality.

Although we have discussed the various harmonization pathways, there has not been assessment of applicability of all the various options within the South African context. Bearing in mind that the various pathways may have certain dependencies e.g. parallel reviews will improve roll out time, but adding early dialogue or tripartite discussion will increase the number of positive HTA recommendations. However a more rational approach will be to start with one element such as parallel regulatory–HTA reviews (due to resource constraints etc.), implement, master, and then consider the other pathways for continued efficiency enhancements.

### 6.2 Recommendations

The following recommendations are proposed:

- The collaboration of current private and public sector HTA bodies with SAHPRA has been discussed and raised as an important potential relationship which could provide critical learnings for effective implementation of a SAHPRA–National HTA body for NHI purposes or harmonization pathways. SAHPRA should consider creating a working committee between these existent HTA entities to explore and formulate a precursor model which can be perfected and ready to implement when the national HTA body is created in tandem, SAHPRA should also respectfully request that the NDoH make strategic appointments to leadership roles at the national HTA agency, so that a proactive and constructive collaborative relationship can be formed from the onset.
- This working committee between public and private sector HTA bodies, could also benefit from the discussion and adoption of a standardized reporting structure of all healthcare economic evaluations, such as the CHEERS 28-item checklist which will add transparency and trust to the HTA process.
- During these collaborative engagements, focus must be directed to gather more information on the shortcoming associated with parallel review, notably the wastage of resources on the HTA entity perspective, and determination of the risk mitigation strategies thereof.

# CHAPTER SEVEN – CONCLUSION

A literature search strategy was conducted using a defined set of keywords and terminology on electronic databases, and additional resources were retrieved from the primary data sets that were extracted to enable continued and meaningful findings and discussion.

The regulatory–HTA process and all stakeholder roles were discussed in great detail to provide an overview of the critical roles that each entity plays in bringing health technologies to patients.

The differentiation between medicines and medical device notably from an economic evaluation context was analysed. Current challenges related to the timeline and clinical evidence generation related to medical devices were then examined, including the solutions to these issues, broadly referred to as harmonization pathways between the NRA and HTA body(s). The focus of these harmonization pathways was parallel regulatory–HTA reviews for application in the South African context.

Existent international frameworks were presented and showed efficiencies in total roll out time (i.e. time from marketing authorization to HTA recommendation) versus other countries lacking these parallel review structures. This efficiency in roll out time implies improved patient access to technologies due to reduced delays in the approval time at the HTA body.

However timely patient access is not only dependent on efficient regulatory approval, but also on the all-important HTA or coverage recommendation, which will ultimately grant patient access. This reimbursement or coverage process can impact timely patient access, both by the speed of the process as well as the type of recommendation provided to a technology (positive, positive with restriction, or negative). The recommendation is contingent on the completeness of clinical evidence presented, and implementing an alternative harmonization pathway such as tripartite dialogue, would ensure higher number of positive recommendations by the HTA body, thus ensuring patient access to devices. A combination of harmonization pathways may be required to achieve efficiencies throughout the regulatory–HTA framework.

The South African healthcare system exists as a dichotomy of public and private sectors. The healthcare sector financing, resources and current challenges resulting in inequitable healthcare to the majority of the South African population was reviewed.

The government's strategy to inequitable healthcare, is the roll out of universal healthcare coverage, known as NHI. The NHI will need a national HTA body to direct funds to value technologies for all South Africans. SAHPRA and the national HTA body will work together, still within their respective mandates and independence, to achieve the objectives of public health and NHI coverage, under the auspices of the NDoH. Thus timely patient access to health technologies, will require a formidable synergy and relationship between these two entities. This important element presents another reason for harmonization and parallel reviews to be considered. HTA in South Africa is fragmented in both public and private sectors, and practiced in certain spheres only. There is no national HTA body at present, with plans to create an entity in 2022.

SAHPRA is a respected NRA for their technical skills and sound evaluation processes to ensure listing of medicines with the most favourable safety, quality and efficacy standards. They have also undertaken global harmonization initiatives for medicine reviews, such as reliance models with other NRAs to improve efficiency and therefore understand the important of harmonization. Additionally, significant performance improvement measures have been put into place to operationalize efficiencies in approval time frames, and have demonstrated remarkable achievements in driving efficiency in the review periods. However the challenge that will present is related to the impending commencement of the review and approval of medical devices, a substantial and complex portfolio.

SAHPRA may need to adopt harmonization pathways to ensure efficient regulatory–HTA processes for timely patient access to products. Their role alongside the national HTA body, with the common shared goal of promoting public health and the effective implementation of the NHI, will ensure collaboration toward timely patient access, and the provision of quality, safety, efficacy; as well as effectiveness and cost management (along with other HTA objectives), are executed in an efficient manner.

It was demonstrated that SAHPRA should consider adoption of parallel

regulatory–HTA reviews to improve access to all health technologies, including medical devices, as there exists global implementation and success. Further, this harmonization pathway will align to SAHPRAs strategic objectives to support the national HTA body and government's strategy toward universal healthcare coverage, via NHI.

SAHPRA has a pivotal responsibility to play in the success of the national HTA body. Both SAHPRA and the national HTA body will be reporting into the NDoH, thus it will be a seamless relationship, easy to collaborate for the best interests of the country, and yet will be able maintain their mandate and independence within each statutory entity.

Therefore parallel reviews as the first pathway to achieving efficient patient access to all health technologies, not only medical devices, is a sound consideration. It is the author's opinion that this pathway will prove the less resource intensive, and easiest to implement, due to the current regulatory and HTA systems governing medical devices, being at a stage of infancy (medical device product reviews and national HTA body creation). Against this backdrop, an easier and more agile collaboration can be formed de novo, as there are no historic processes to change, and a structure can be mapped as a joint approach to shared objectives. Each entity though will continue to function within their respective mandates.

There must be an analysis of the barriers to any harmonization pathway implementation, notably within the local context, as this could be a significant obstacle for any potential collaboration, including the wastage of resources from a HTA perspective should the NRA decline a technology. In preparation for a SAHPRA–National HTA body alliance, there needs to be consideration given to immediate dialogue and workshops between existing public and private sector HTA bodies and the NRA, for learnings and future collaboration with the national HTA entity. This platform could also serve to adopt a uniform strategy for all entities on the reporting structure of economic evaluations, such as the CHEERS 28-point checklist. It would be ideal if appointments can immediately be made to the National HTA leadership structure, to ensure early and effective synergies are enhanced.

The link between framework efficiency and government policy and objective support in the form of NHI implementation, has also been discussed.

SAHPRA should provide consideration to adopting a parallel regulatory–HTA review framework, as this may have a positive improvement to timely access to medical devices in South Africa.

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# 9 APPENDIX

## Appendix A

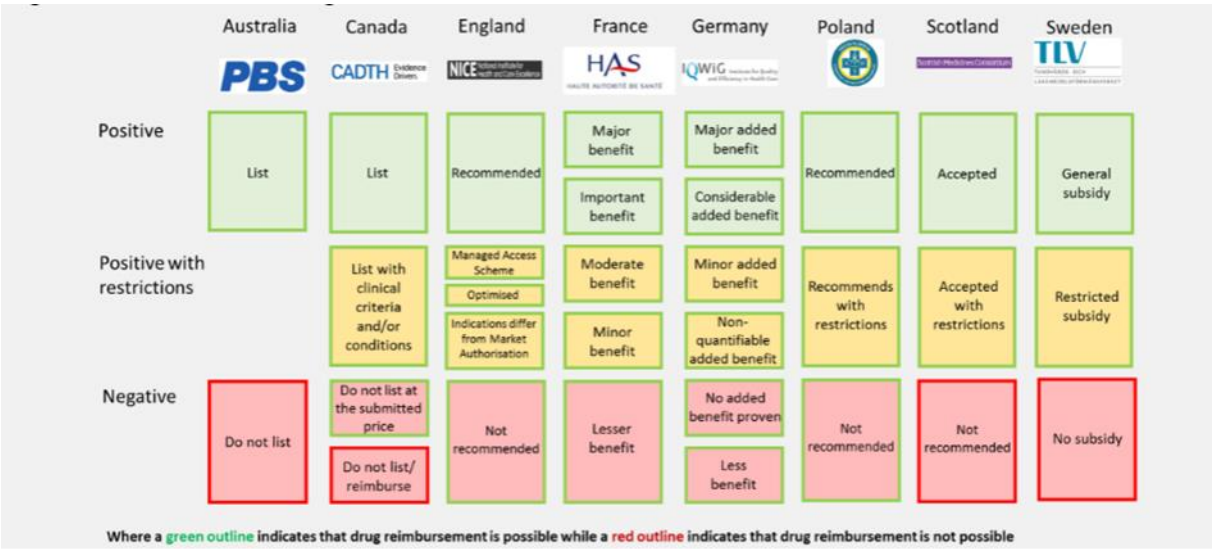



Figure A1: Methodology for health technology determination (Wang *et al*., 2019)

## Appendix B

## Ethics Waiver

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

**Office of the Deputy Vice-Chancellor (Research & Innovation)**

04/01/2022

Ref: W-CBP-220104-01

**TO WHOM IT MAY CONCERN**

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

**Investigator:** Ms U Raghununan
Student No. (if appropriate): 9904081
Staff No. (if appropriate):

**Supervisor:** Professor MP Danckwerts

**School:** Therapeutic Sciences
**Department:** Pharmacy and Pharmacology

Medical School
University

**Project title:** *Parallel Regulatory-HTA reviews: Implications for improving access to medical devices in South Africa*

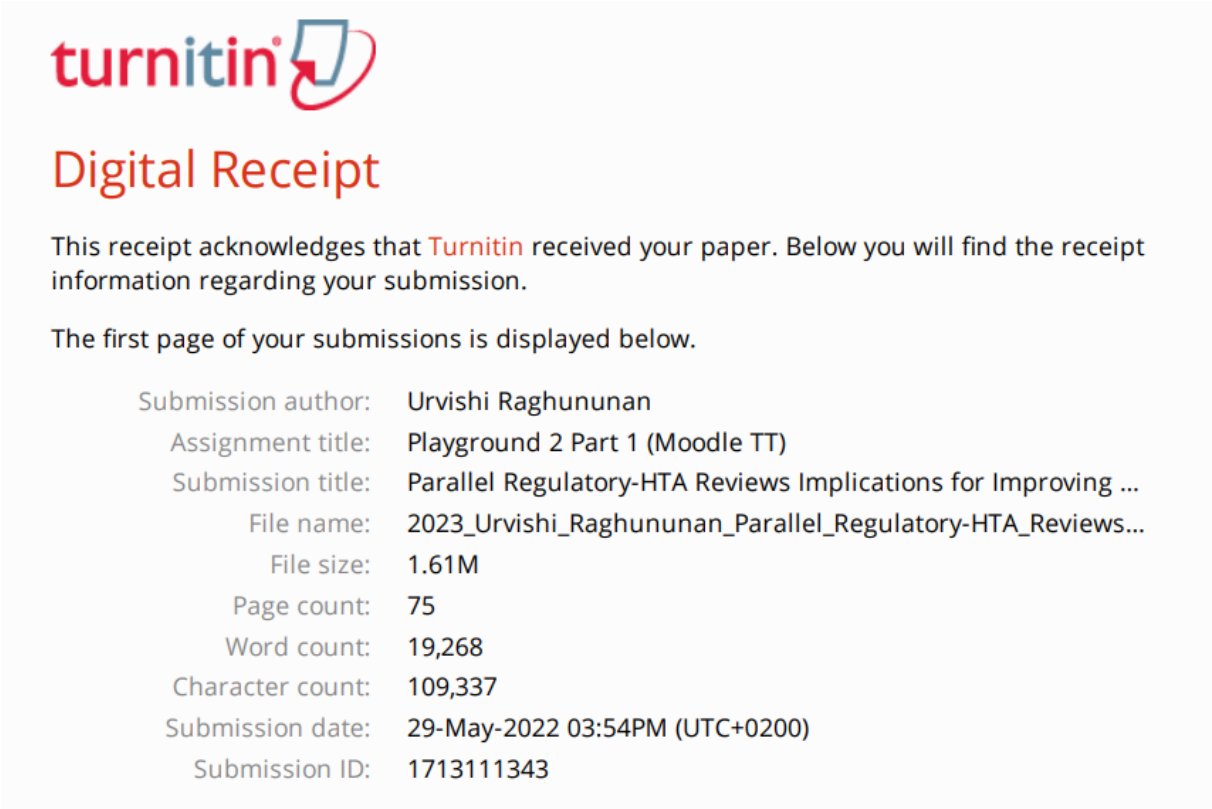
**Reason:** Review of information in the public domain
No human participants will be involved in the study

Dr N Naran
Co-Chairperson: Human Research Ethics Committee (Medical)

Research Office Secretariat:
Third Floor, Phillip Tobias Building, corner of St Andrews and York Roads, Parktown, Johannesburg 2193
Postal address: Private Bag 3, Wits 2050
Tel Nos: +27 (0)11 717 1234/1252/2656/2700
Office E-mail: HREC-Medical.ResearchOffice@wits.ac.za
Website:
https://www.wits.ac.za/research/researcher-support/research-ethics/ethics-committees/

**APPENDIX C**

**Turn It In Report – Similarity Index**



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