DEVELOPMENT OF MULTI-CRITERIA DECISION ANALYSIS (MCDA) FRAMEWORK FOR FORMULARY LISTING DECISIONS OF ONCOLOGY DRUGS IN MALAYSIA

HAARATHI A/P CHANDRIAH

UNIVERSITI SAINS MALAYSIA

2025

DEVELOPMENT OF MULTI-CRITERIA DECISION ANALYSIS (MCDA) FRAMEWORK FOR FORMULARY LISTING DECISIONS OF ONCOLOGY DRUGS IN MALAYSIA

by

HAARATHI A/P CHANDRIAH

Thesis submitted in fulfilment of the requirements
for the degree of
Doctor of Philosophy

April 2025

ACKNOWLEDGEMENT

First and foremost, I would like to offer my heartfelt gratitude and praise to the Almighty for His countless blessings and guidance, which have enabled me to successfully complete this thesis. I would like to express my deepest gratitude to my research supervisor, Professor Dr. Asrul Akmal Shafie for his immense support and guidance that led me to completion of this research. Additionally, it has been an honour to be under the co-supervision of Professor Dr. Rob Baltussen whose invaluable insights had been instrumental in introducing me to MCDA. I cannot find words to express my gratitude to my cherished colleagues in USM. Their assistance, encouragement, and kindness, created a positive atmosphere in which I was able to thrive. Special mention goes to Dr. Azuwana Supian, Siti Fauziah Abu, Dr. Shamala Balan, Dr. Annushiah Vasan, Jacqueline Wong, Noor Syahireen, Sivaraj Raman, Dr. Ng Chin Hui and Khairu Hazwan. They will forever have a special place in my heart. My appreciation also extends to Dr. Azuana Ramli, Ms Nik Nuradlina, Ms Kamarun Neasa Begum and our fellow oncologist Dr. Muthukkumaran Thiagarajan and Dr. Vaishnavi Jeyasingam. I am also grateful to the Formulary Management Branch, Pharmacy Practice and Development Division MOH for their immense support in this research. This thesis would also not have been possible without the financial support from the Federal Training Award Scheme (HLP) by the Ministry of Health and MAKNA Cancer Research Grant. I am also indebted to my family, whose sacrifices had made me the person I am now. Special mention goes to my pillar and support throughout this journey and life, my husband Krishna Murthiy. And finally, I would like to dedicate this study to all the cancer patients in Malaysia.

TABLE OF CONTENTS

LIST OF TABLES

Page

LIST OF FIGURES

Page

LIST OF ABBREVIATIONS

AE	Adverse event
AHP	Analytical Hierarchical Process
AMSTAR	A Measurement Tool to Assess Systematic Reviews
APPL	Approved Product Purchase List
ASCO	American Society of Clinical Oncology
ATC	Anatomical Therapeutic Chemical
BIA	Budget Impact Analysis
BHIS	Basic Health Insurance Scheme
CADTH	Canadian Agency for Drugs and Technologies in Health
CBA	Cost Benefit Analysis
CDF	Cancer Drug Fund
CEA	Cost-effectiveness Analysis
CMA	Cost Minimization Analysis
CRD	Centre for Review and Dissemination
CSMBS	Civil Servant Medical Benefit Scheme
CUA	Cost Utility Analysis
CTLA-4	Cytotoxic T-lymphocyte Antigen 4
CVR	Content Validity Ratio
DCA	Drug Control Authority
DCE	Discrete Choice Experiment
DEC	Dossier Evaluation Committee
DFS	Disease Free Survival
DMARDs	Disease Modifying Anti-Rheumatic Drugs
DPIS	Drug and Poison Information Services
DTC	Drug and Therapeutics Committee
DWC	Drug Working Committee
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicine Agency
EML	Essential Medicines List

ESMO	European Society for Medical Oncology
EVIDEM	Evidence and Value Impact on Decision Making
FDA	Food & Drug Administration
FGD	Focus Group Discussion
GDP	Gross Domestic Product
HER-2	Human Epidermal Growth Factor 2
HITAP	Health Intervention and Technology Assessment Program
HRQOL	Health-related Quality of Life
HTA	Health Technology Assessment
ICER	Incremental Cost Effectiveness Ratio
INAHTA	International Network of Agencies for Health Technology Assessment
IPD	Individual Patient Data
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
KKM	Kementerian Kesihatan Malaysia
KM	Kaplan Meier
LMIC	Low- and Middle-Income Country
LOI	Letter of Intent
LOA	Letter of Acceptance
LOR	Letter of Rejection
MACBETH	Measuring Attractiveness by a Categorical Based Evaluation Technique
MAUT	Multi Attribute Utility Theory
MAVT	Multi Attribute Value Theory
MCBS	Magnitude of Clinical Benefit
MCDA	Multi Criteria Decision Analysis
MNMP	Malaysia National Medicines Policy
MO	Medical Officer
MOH	Ministry of Health
MOHMF	Ministry of Health Medicines Formulary
MOHMFP	Ministry of Health Medicines Formulary Panel
MREC	Medical Research and Ethics Committee

MRCI	Medication Review Complexity Index
MSKCC	Memorial Sloan Kettering Cancer Centre
NCCN	National Comprehensive Cancer Network
NCD	Non-communicable Disease
NEML/NLEM	National Essential Medicines List/ National List of Essential Medicine
NHB	Net Health Benefit
NHI	National Health Insurance
NHIA	National Health Insurance Administration
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network Meta-Analysis
NMRR	National Medical Research Register
NMUS	National Medicine Use Survey
NPRA	National Pharmaceutical Regulatory Agency
NSCLC	Non-Small Cell Lung Cancer
NSPCC	National Strategic Plan for Cancer Control
ORR	Objective Response Rate
OS	Overall Survival
PASc	Patient Access Scheme
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
pCODR	pan-Canadian Oncology Drug Review
PD	Progressed Disease
PD-1/PD-L1	Programmed cell death protein 1/programmed death ligand 1
PE	Pharmacoeconomics
PFS	Progression Free Survival
PHARMAC	Pharmaceutical Management Agency
PNDF	Philippines National Drug Formulary
PPDD	Pharmacy Practice and Development Division
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis

PSP	Pharmaceutical Services Programme
QALY	Quality Adjusted Life Years
R&D	Research & Development
RECIST	Response Evaluation Criteria in Solid Tumours
SAM	Special Approval Medicine
SAW	Simple Additive Weighted
SMARTS	Simple Multi Attribute Rating Tool with Swing Weights
SR	Systematic Review
SSS	Social Security Scheme
DWC	Drug Working Committee
TKI	Tyrosine Kinase Inhibitor
TNF	Tumour Necrosis Factor
TTP	Time to Progression
UK	United Kingdom
US	United States
VAS	Visual Analogue Scale
VBM	Value Based Medicine
VIF	Variance Inflation Factor
WHA	World Health Assembly
WHO	World Health Organization
WTP	Willingness to Pay

LIST OF APPENDICES

PEMBANGUNAN RANGKA KERJA ANALISIS KEPUTUSAN BERBILANG KRITERIA (MCDA) BAGI KEPUTUSAN PENYENARAIAN DRUG ONKOLOGI DALAM FORMULARI DI MALAYSIA

ABSTRAK

Peningkatan insiden kanser dan penghasilan ubat-ubatan inovatif baru yang berkos tinggi, menjadi antara faktor kepada pengurangan akses kepada ubat-ubat kanser di Malaysia. Ini merupakan satu cabaran besar kepada perkhidmatan kesihatan awam. Proses penyenaraian ubat-ubatan kanser dalam formulari ubat kebangsaan dan penetapan harga ubat adalah penting dalam memastikan akses kepada ubat-ubat ini. Namun, isu-isu semasa tempatan yang berkaitan dengan harga dan akses ubat kanser masih belum diketahui. Tambahan pula, pendekatan sedia ada iaitu Penilaian Teknologi Kesihatan (HTA) untuk penyenaraian ubat kanser ke dalam formulari dianggap masih kurang lengkap kerana ia tidak sepenuhnya mencakupi dimensi-dimensi penilaian yang sepatutnya. Oleh itu, objektif utama tesis ini adalah bagi membangunkan rangka kerja Analisis Keputusan Berbilang Kriteria *(MCDA)* untuk penilaian ubat kanser. Selain itu, isu-isu lain berkaitan akses kepada ubat kanser juga turut dikaji. Semakan dokumen dan analisis data sekunder menggunakan data penyenaraian formulari dari tahun 2011 hingga 2018 telah dilaksanakan bagi mengenal pasti cabaran yang berkaitan dengan akses kepada ubat kanser. Dalam membangunkan rangka kerja *MCDA*, satu tinjauan keratan rentas melibatkan pelbagai pihak berkepentingan telah dijalankan untuk menentukan kriteria keutamaan bagi menentukan keputusan formulari. Di samping itu, satu senarai kriteria penentu keputusan telah dihasilkan melalui kaedah Delphi yang diubahsuai. Seterusnya, perbincangan kumpulan fokus (FGD) dijalankan bagi menentukan kriteria penentu

keputusan dan pemberatnya. Teknik *Multi-Attribute Rating Technique with Swing weights* (SMARTS) digunakan untuk menetapkan pemberat. FGD kedua diadakan bagi menguji rangka kerja yang dihasilkan dengan menggunakan satu kajian kes penyenaraian dua ubat (erlotinib, afatinib) dari kumpulan penghalang kinase tirosin sebagai rawatan jalur pertama kanser paru-paru jenis *non-small cell*. Para pakar membuat penilaian berdasarkan bukti yang diperoleh melalui kajian sistematik dan analisis impak bajet. Kemudian, keputusan dibuat menggunakan pendekatan standard HTA, dan diikuti dengan pendekatan MCDA-HTA. Dapatan kajian ini menunjukkan bahawa sebahagian besar perbelanjaan adalah untuk ubat antikanser terapi bersasar. Malaysia didapati mempunyai liputan akses ubat kanser yang lebih baik berbanding Thailand dan Philippines. Hasil kajian juga menunjukkan bahawa walaupun Formulari Ubat KKM menyenaraikan ubat-ubatan kanser dengan kadar yang baik, kadar penolakan bagi keputusan formulari masih tinggi. Keberkesanan ubat telah dikenalpasti sebagai faktor utama sesuatu ubat dapat disenaraikan dalam formulari. Metodologi kajian yang digunakan dalam pembangunan MCDA terbukti dapat dilaksanakan. Pihak berkepentingan berpendapat pendekatan MCDA adalah lebih baik kerana kaedah ini mempunyai proses yang lebih teratur, konsisten, dan telus di samping dapat memastikan penyertaan semua pakar dalam proses penentuan keputusan. Rangka kerja yang dihasilkan juga dianggap berjaya mencapai tujuan yang diinginkan dan berpotensi untuk membantu dalam penentuan keputusan. Kesimpulannya, perbelanjaan tinggi bagi ubat kanser kekal menjadi satu kebimbangan dan penggunaan MCDA untuk penilaian ubat kanser bagi tujuan penyenaraian formulari telah berjaya dibangunkan.

DEVELOPMENT OF MULTI-CRITERIA DECISION ANALYSIS (MCDA) FRAMEWORK FOR FORMULARY LISTING DECISIONS OF ONCOLOGY DRUGS IN MALAYSIA

ABSTRACT

Given the increasing incidence of cancer in the country and the introduction of new high-cost innovative medicines, ensuring access to cancer drugs remains a significant public health challenge. National formulary listing and drug pricing play crucial roles in ensuring access to these drugs. The current issues surrounding cancer drug prices and access in the country are not known. Moreover, the existing Health Technology Assessment (HTA) approach for value assessment of cancer drugs for formulary listing is considered to be lacking in comprehensiveness as it does not fully capture other dimensions of value such as disease severity. Therefore, this thesis aims to develop a Multi Criteria Decision Analysis (MCDA) framework for value assessment of cancer drugs while concurrently investigating other issues related to access to cancer drugs. Documents review and secondary data analysis using formulary listing data from year 2011 to 2018 was conducted to identify challenges related to cancer drug access. In developing the MCDA framework, a cross-sectional survey involving multiple stakeholders was conducted to determine preferences for formulary decision criteria. Following this, through a modified Delphi, agreement on decision criteria was reached. Subsequently, a focus group discussion (FGD) was conducted to finalize the decision criteria and their weights. The Simple Multi-Attribute Rating Technique with Swing weights (SMARTS) was employed for assigning weights. A second FGD was held to test the framework using case-study of listing two tyrosine kinase inhibitors (erlotinib and afatinib) for first-line treatment of

non-small cell lung cancer. Experts rated the drugs based on evidence from a systematic review and budget impact analysis. Decisions made first using the standard HTA approach was compared with the MCDA-HTA approach. The study on access revealed that a considerable proportion of cancer drug expenditure was attributed to targeted therapies. Malaysia had highest coverage of cancers drugs compared to Thailand and Philippines. The MOH Medicines Formulary provided good coverage for cancer drugs, but the rejection rate for formulary decisions was high. Drug effectiveness was identified as a key factor influencing successful formulary listing. The methods employed in developing the MCDA framework were deemed feasible. Stakeholders preferred the MCDA approach as it offered a more structured, consistent, and transparent process that ensured the participation of all experts in the decision-making process. The framework was deemed successful in achieving its intended purpose and was considered a potential tool to guide decision-making. In conclusion, high cancer drug expenditures have been identified as a concern. A MCDA tool for assessing the value of cancer drugs for formulary decisions has been successfully developed.

CHAPTER 1

INTRODUCTION

1.1 Epidemiology and economic burden of cancer

Cancer is a major public health challenge posing significant social and economic burden on healthcare systems worldwide. The global burden of cancer is increasing with an estimated 19.3 million new cancer cases and 10 million cancer deaths in 2020, making it the second leading cause of death globally (Ferlay et al., 2021, Sung et al., 2021). The increasing trend in the incidence of cancer from 18.7 million cases registered in 2010 (Global Burden of Disease Cancer Collaboration, 2022) to 19.3 million in 2020 is concerning, and the disease burden is expected to reach 28.4 million cases by 2040. The most common cancers worldwide are breast, lung, colorectal, prostate and stomach cancer (Sung et al., 2021) .

Cancer incidence rates vary by region where Asia was reported to have the highest incidence as well as cancer mortality rates (Sankaranarayanan et al., 2014, Sung et al., 2021, Rajappa et al., 2023). In Malaysia, a total of 168,823 new cases of cancer were reported between 2017 and 2021 versus 115,238 new cases for the period of 2012-2016 (Azizah et al., 2019, Mohd Anis et al., 2024). In 2022, a total of 51,650 new cases were reported with more cases in females (51.8%) compared to males (48.2%) (Ferlay et al., 2024). Breast cancer, colorectal cancer and lung cancer remained the most common cancers in the overall population from the period of 2007 until 2021 (Azizah et al., 2016, Azizah et al., 2019, Mohd Anis et al., 2024). The three most common cancers among males were colorectal, lung, and prostate while in females, breast, colorectal, and lung cancer were the most common (Azizah et al., 2019, Mohd Anis et al., 2024). Cancer remains as one of the principle causes of death in both Ministry of Health (MOH) and private hospitals in Malaysia (Health

Informatics Centre Planning Division, 2016, Health Informatics Centre Planning Division, 2022)

Cancer is known to have substantial economic burden on patients, society and healthcare systems. In 2010, the total annual economic cost of cancer was estimated to be US$ 1.16 trillion which was more than 2% of the total global gross domestic product (GDP) (Stewart and Wild, 2014). In Malaysia, according to MOH report on health cost of non-communicable diseases (NCDs) (focusing on three NCD categories: cardiovascular diseases, diabetes and cancer), the estimated health care cost for cancer in 2017 was MYR1.34 billion which accounted for 13.89% of the total cost incurred for all three NCDs (Ministry of Health Malaysia, 2022). Hospitalisation cost was the main contributor (MYR 727.73 million; 54.30% of total cancer cost) followed by medicines cost (MYR 408.10 million; 30.45%) (Ministry of Health Malaysia, 2022).

The Malaysian National Cancer Registry 2012 -2016 reported that a large proportion of patients are diagnosed at late stage of disease which is associated with significantly poor outcomes and more costly care (Azizah et al., 2019). Additionally, a large proportion of cancer patients are diagnosed during their most productive and economically active ages. In 2017, the cost of productivity loss due to premature deaths was estimated to be MYR 1.5 billion, while productivity loss due to absenteeism and presenteeism totalled MYR 114 million and MYR 211 million respectively (Ministry of Health Malaysia, 2020). Apart from productivity losses, cancer also had high burden of disease cost totalling MYR 30.73 billion resulting from disability and loss of healthy life years due the disease. The MOH reported that the NCD-related (three NCD categories: cardiovascular, diabetes and cancer) disease burden cost accounted for 7.35% of GDP in 2017 (Ministry of Health Malaysia, 2020, Ministry of Health Malaysia, 2022).

The social and economic impact of cancer will continue to rise driven by ageing population and growth, in addition to lifestyle changes. Therefore, it requires continuous attention and investment in prevention, screening and treatment strategies. Though it is imperative that the national cancer control strategies consider the full spectrum of interventions from prevention to palliation, ensuring access to cancer drugs has gained a lot of attention in recent years (Hofmarcher et al., 2021).

1.2 Access to cancer drugs: Challenges in the era of new innovative therapies

Cancer management requires a multidisciplinary care where medicines play an essential core role, along with surgery and radiotherapy. Cancer treatment has evolved significantly with the introduction of new innovative cancer drugs (Arruebo et al., 2011). Advances in cellular and molecular biology have made it possible to target a patient's unique tumour biology using the targeted therapies. Targeted therapies act on predefined molecular pathways specific for cancer cells and their selectiveness for a target molecule was found to result in better effectiveness and safety profile in comparison to standard chemotherapy (Ross et al., 2004). Therefore, identifying molecular targets followed by synthesis of corresponding targeted therapies emerged as one of the main concepts in the development of new cancer drugs (Lee et al., 2018). This has led to expansion in the number of licensed targeted therapies available in the market. For example, between 2000 and 2008, the United States Food and Drug Administration (US FDA) approved five targeted therapies for solid tumours. However, from 2009 to 2017, the number of approved targeted therapies surged to 24 (Batta et al., 2020). The cancer treatment landscape became more promising with the recent introduction of immunotherapies called immune checkpoint inhibitors (anti PD-

1, anti PD-L1, and anti CTLA-4) (Emens et al., 2017). These drugs help inhibit "immune system brakes" and reactivate the patient's immune system to attack the cancer cells. These agents are characterised by broad clinical activity, durable response rates, and distinct side effects which is different compared to standard chemotherapy and targeted therapies (Emens et al., 2017, Oiseth and Aziz, 2017).

While these innovations have achieved advances in survival and other clinical outcomes, ensuring access to these cancer drugs remains a public health challenge. This is evidenced through the major disparities in access to cancer drugs across European countries (Cheema et al., 2012, Mihajlović et al., 2015, Jönsson et al., 2016, Uyl-de Groot et al., 2020). Conversely, in the low- and middle-income countries (LMICs) the focus has been on access to essential cancer drugs since many of these countries struggle to provide access to basic cancer treatments (Cherny et al., 2017b, Fundytus et al., 2021). Hence, in LMICs ensuring access to innovative therapies is more of an aspiration for the future. Consequently, global attention on access to cancer drugs has been increasing and evident with the World Health Assembly (WHA) passing a landmark resolution on cancer prevention and control. The 2017 Cancer Resolution calls on Member States to ensure comprehensive approach through national cancer control plans, where providing access to cancer services including timely access to cancer medicines and vaccines was emphasised (World Health Organization, 2017a).

Although cancer drugs are not the major contributor of overall cancer care costs, the proportion spent on pharmaceuticals is increasing. In the United States in 2015, the total cost of cancer drugs rose to US$37.8 billion from US$15.9 billion in 2010 (Aitken and Kleinrock, 2016). Based on Malaysian Statistics on Medicine reports, oncology drugs are one of the top ten therapeutic classes contributing to high

drug expenditure in the country though not classified as drug classes with highest utilization (Ministry of Health, 2014).

High cost of treatment due to spiralling prices of new cancer therapies is a key factor threatening access to cancer drugs (World Health Organization, 2018). Cancer drug prices have almost doubled from an average of US$5000 per month to more than US$10,000 per month (Figure 1.1). In 2015, the median price of 13 cancer drugs approved by the US FDA was US$145,000 annually (Kantarjian and Patel, 2017). The treatment cost is expected to rise further with the introduction of immunotherapy. For instance, the treatment cost per patient with pembrolizumab, an anti PD-1 was estimated to reach almost US$ 1 million per year depending on the dosing regimen used (Prasad et al., 2017). The situation is further complicated by regulatory approvals and recommendations for combining immunotherapy with either chemotherapy or targeted therapy. This approach, while promising, will inevitably affect both healthcare spending and affordability (Morrissey et al., 2016, Zhu et al., 2021). The global oncology spending has been forecasted to exceed US$ 260 billion by 2025 where immuno-oncology will represent 20% of the global oncology spending (IQVIA Institute for Human Data Science, 2021).

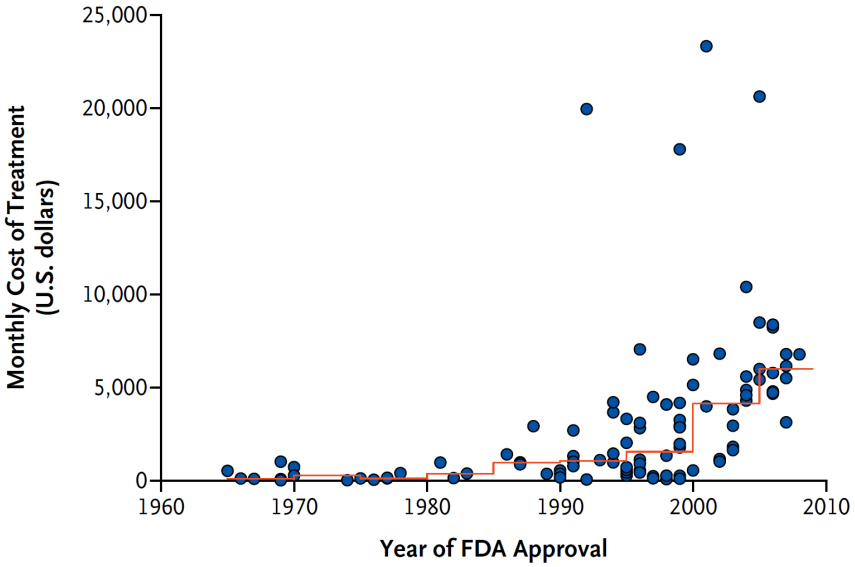

Figure 1.1 Monthly cost of cancer drugs in US at the time of approval by FDA from 1965-2008
Note: Figure source from Bach, 2009

1.3 Access to cancer drugs in Malaysia

Access to drug treatment is just one component in the overall strategy for cancer care. Nevertheless, it is an important component as treatment access has major impact on patients' lives. As such, discussions regarding access to cancer drugs have been gaining public attention in Malaysia with media reporting on the high costs of these drugs specifically the new innovative drugs (Boo, 2016).

The Ministry of Health Medicines Formulary (MOHMF) which is a list of medicines approved to be used in MOH facilities is seen as an important indicator of access for treatment in the public sector (Pharmaceutical Services Division, 2015). The MOHMF has been in public scrutiny with claims that the public hospitals lack access to cancer drugs as no immunotherapies and only limited targeted therapies are available in the formulary due to concerns on cost-effectiveness. Additional concern was that the listing of a cancer drug in the MOHMF does not guarantee patients will receive the treatment as it depends on budget availability (Boo, 2016).

This issue was also reflected in a study by (Lim et al., 2014b) who found that only 19% of 172 patients younger than 70 years with HER-2 positive breast cancer stage I-III received the targeted therapy trastuzumab within 1 year of diagnosis. The limited access was attributed to its high cost and insufficient public funding for the treatment. While access to innovative cancer drugs were the highlights of these local reports, international publications reported Malaysia as not having access to essential cancer drugs which are the basic medicines required for cancer treatment (Bazargani et al., 2014). Such reporting is concerning but there is no local report confirming this scenario.

Though there are concerns regarding the limited number of innovative cancer drugs in the MOHMF which affects access, the MOH does provide access to treatment that are not available in the MOHMF via Special Approval Medicine (SAM) pathway which require approval by the Director General of Health (Eisah et al., 2016). This pathway for access is only allowed when patient has failed all alternative treatment available in the MOHMF, or when existing alternatives in the MOHMF is contraindicated or patient is intolerant to the available treatment.

1.4 Value assessment and reimbursement decisions of cancer drugs: International scenario

As the costs of cancer treatments continue to rise, their value is increasingly being questioned by patients, clinicians, payers and policy makers. The argument is whether the high drug prices justify their clinical benefit and are they worth to be reimbursed (Kantarjian et al., 2013, Cohen, 2017). Thus, decision makers are faced with growing pressure to ensure optimal reimbursement decisions are made to maximize health gains from the limited resources available, and ensure patients get

access to treatment of value (Godman et al., 2018). This has raised the need to define value concerning cancer treatment and implement value-based models for reimbursement decisions (Danzon and Taylor, 2010, Given et al., 2016, Gyawali and Sullivan, 2017, Mathew et al., 2022).

Many countries have developed Health Technology Assessment (HTA) processes to value clinical and economic aspects of new cancer drugs. HTA is a multidisciplinary approach to policy analysis, studying the medical, social, ethical, and economic implications of development, diffusion, and use of health technology (Velasco Garrido et al., 2010, Henshall et al., 2014). Agencies such as the National Institute for Health and Clinical Excellence (NICE) in United Kingdom, Canadian Agency for Drugs and Technologies in Health (CADTH) in Canada, and Pharmaceutical Benefit Advisory Committee (PBAC) in Australia are some of the leading exponents of HTA (O'Donnell et al., 2009, Novaes and Soárez, 2016). In Australia, Canada and United Kingdom, drug reimbursement decisions are driven by therapeutic value and economic outcomes reported using economic evaluations (Drummond and Sorenson, 2009, Hailey, 2009, Menon and Stafinski, 2009, Akehurst, 2010). Economic evaluation is defined as the comparative analysis in terms of both costs and consequences of a new drug in comparison to current standard of care (Drummond et al., 2015).

Economic evaluation appeared to be an influential element in these assessments and reflects the current definition of value in healthcare which is “health outcomes achieved per dollar spent” ie. value for money. However, value assessment based on economic evaluation also known as cost-effectiveness analysis (CEA) is argued to have several limitations. First, literatures have highlighted several barriers which hamper the use of CEA in decision making (Brousselle and Lessard, 2011).

These barriers can be summarised as being research-related such as timely availability, lack of credibility, insufficient methodological quality, while the decision context-related barriers are capacity of decision makers to understand and interpret economic evaluation, and attitudes towards economic evaluations including concerns about the basis of the analyses and relevance to decision context (Jönsson et al., 2014, Miller et al., 2014, Tsoi et al., 2015, Yothasamut et al., 2009).

Second, the cost per quality adjusted life years (QALY) is the common outcome used in CEA of cancer drugs. QALY has been reported to have limitations in adequately capturing changes in health that are relevant for cancer (Devlin and Lorgelly, 2017, Garau et al., 2011). There are also concerns that it may not fully capture the benefits of new cancer drugs since not all relevant factors, such as disease severity, rarity of disease, the limited availability of other treatment options and budget impact are taken into account in this parameter (Devlin and Sussex, 2011, Devlin and Lorgelly, 2017). Third, the use of standard HTA criteria (effectiveness, safety and cost effectiveness) pose particular challenges for reimbursement decisions of treatment for advance cancers as these drugs often have only surrogate outcomes, are life-extending rather than curative, and are expensive (Cohen, 2017, Kemp and Prasad, 2017). This increases the cost-effectiveness ratio, potentially making the drug to be not cost-effective, and increasing the likelihood of its rejection for reimbursement (Devlin and Parkin, 2004, Kaczyński et al., 2015). There are also equity issues around the weight that should be given to extension of life in terminal cancer patients relative to other patients' needs (Jonsson, 2013, McHugh et al., 2015) .

In general, the current HTA approach for value assessment that considers both clinical benefits and economic considerations is considered to lack comprehensiveness as it does not fully capture other dimensions of value such as disease severity (Devlin

and Sussex, 2011). It can be argued that other factors such as equity, patient and societal values, and budgetary constraints are factored in by decision makers during the deliberations occurring at appraisal and decision-making phase (Baji et al., 2016). However, these factors are considered subjectively and may not be considered always in a standardized manner, thus introducing inconsistency in the decision-making process (Peacock et al., 2009, Devlin and Sussex, 2011, Diaby and Goeree, 2014). Additionally, the deliberative process in HTA involves various stakeholders. Each of the stakeholders attaches implicit and different value judgements to the decision-making criteria, which are not fully transparent in the deliberative process. In this sense the deliberative process fails to consistently aggregate the evidence gathered through the HTA process (Devlin and Sussex, 2011, Diaby and Goeree, 2014). Hence the standard HTA approach for reimbursement decisions is deemed to lack transparency and consistency.

1.5 Value assessment and formulary listing decisions in Malaysia

Malaysia has a dichotomous healthcare system consisting of both public and private sectors. The public health care system is funded by the government through general taxation revenue with the MOH being the main provider of health care services in the country (Safurah et al., 2013).

The journey of ensuring access to a medicine in the country begins with drug registration and issuance of marketing authorisation by the Drug Control Authority (DCA). The DCA is empowered by The Control of Drugs and Cosmetics Regulation (CDCR) 1984 to implement drug registration and issue marketing authorisation. The National Pharmaceutical Regulatory Agency, a division under the Pharmaceutical Services Programme (PSP) is the regulatory body which serves as the Secretariat to

the DCA (Thatte et al., 2009, Sani et al., 2020). Post-registration, the private sector gets immediate access to a medicine. However, in the public sector especially in the MOH, a drug must be listed in the MOHMF before it can be used in the MOH facilities.

The objective of the MOHMF is to ensure only efficacious, safe and cost-effective drugs are used in MOH facilities (Shafie et al., 2019). It stands as a strategy under the Access to Medicines component of the Malaysian National Medicines Policy (MNMP). This core component in the MNMP aims to ensure adequate, continuous and equitable access to quality, safe, effective and affordable medicines towards achieving optimal health outcomes (Pharmaceutical Services Division, 2022b).

The MOHMF listing process begins with submission of formulary listing application by the applicant (Pharmaceutical Services Division, 2015). Prior to year 2016, the process involved a multistage approval before the application is received and processed by the Secretariat at Pharmacy Practice and Development Division (PPDD) under PSP and the applicants were MOH healthcare providers (Figure 1.2). However, a new formulary listing process was implemented in 2016 after recognizing the setbacks in the existing process. In the new system, a single channel submission is provided where submissions are done by the pharmaceutical companies or MOH stakeholders direct to the PPDD (Figure 1.3) (Pharmaceutical Services Division, 2015). There are three categories of applications which can be submitted by the pharmaceutical companies:

a) Dossier D1 – Proposal to list a new medicine or to add indication for an existing medicine in the formulary

b) Dossier D2 - Proposal to add or amend formulation/ dosage form/ strength of medicines listed in the formulary.

c) Dossier D5 - Proposal to delist approved medicine(s)/ indication(s) from the formulary

Application to change the category of prescriber for existing medicine in the formulary can only be submitted by MOH healthcare providers via submission of Dossier D3.

The application for listing a new medicine or indication (dossier D1) into the MOHMF requires mandatory submission of a Budget Impact Analysis (BIA) and if feasible, a local pharmacoeconomic (PE) evaluation (Pharmaceutical Services Division, 2015). PE evaluation is the terminology for economic evaluation of pharmaceuticals. The submission of local PE studies is not a mandatory requirement given the challenges encountered to conduct local PE studies (Tarn et al., 2008, Shafie et al., 2019). Nevertheless, the submission of local PE studies is highly encouraged and consequently the Pharmacoeconomics Guideline for Malaysia was published to guide PE research in Malaysia (Pharmaceutical Services Division, 2012) .

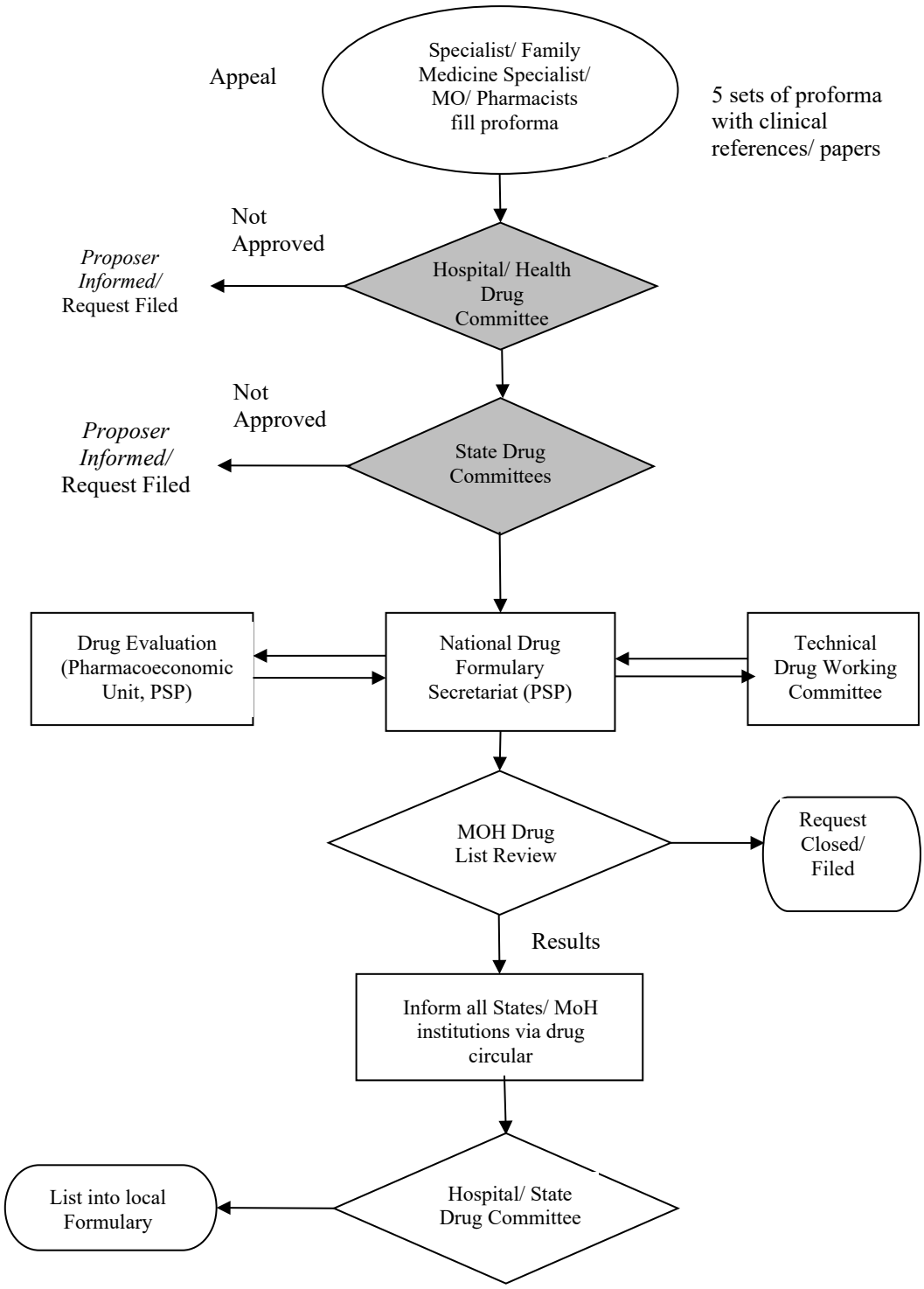

Figure 1.2 MOH Medicines Formulary listing process before year 2016

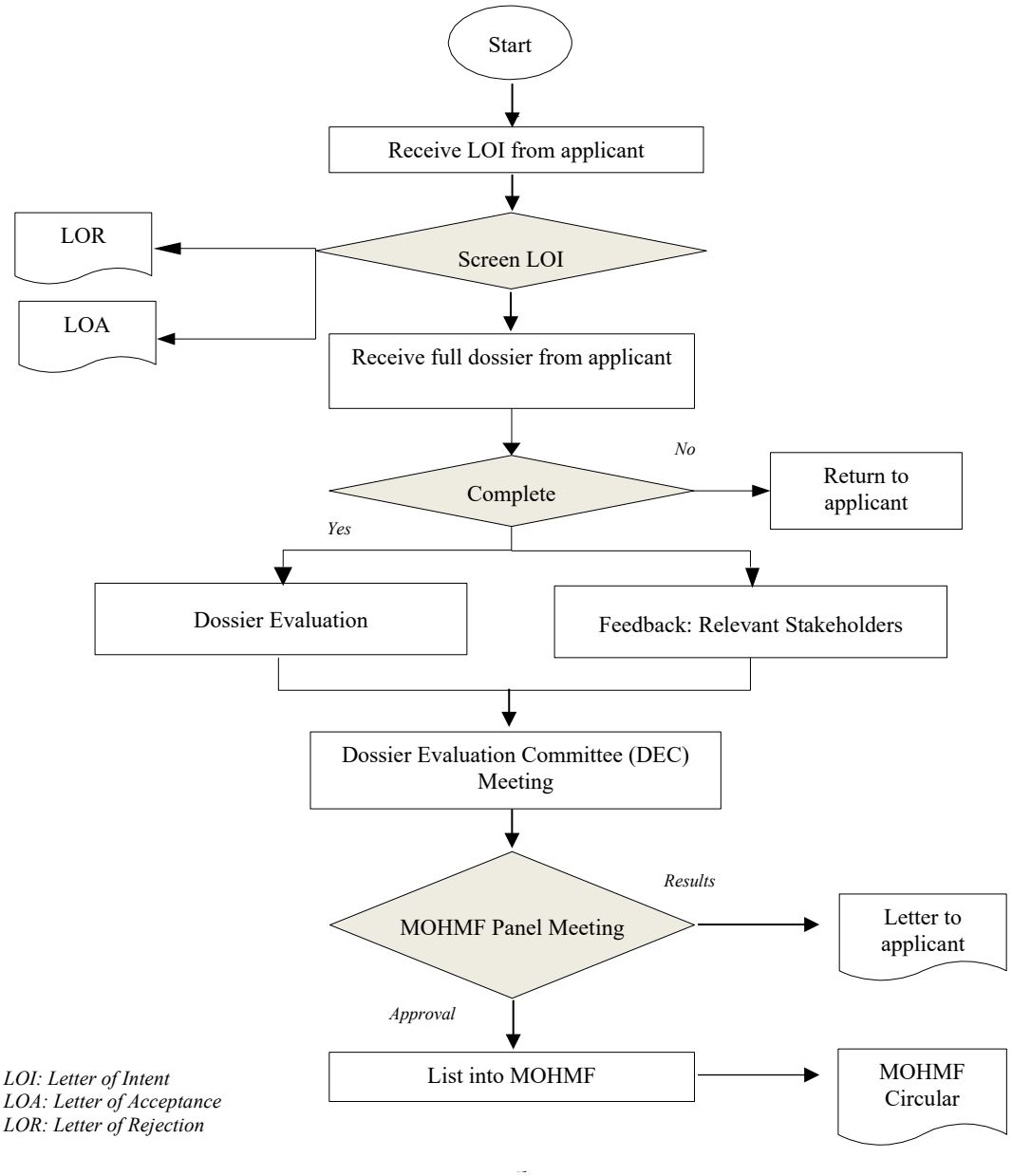

Figure 1.3 MOH Medicines Formulary Listing Process after year 2016

Similar to other jurisdictions, the MOH in Malaysia has adopted HTA framework to inform formulary listing decisions which consider the 'traditional' criteria of safety, efficacy, effectiveness, and cost-effectiveness for the value assessment of medicines (Shafie et al., 2019). Assessments are done for all categories of application (to introduce a new medicine, add or alter specifications for an existing medicine in the MOHMF, and remove listed medicine), either as rapid reviews or mini-HTAs depending on the category of dossier application. The Formulary Management Branch of the PPDD reviews all evidence submitted by the pharmaceutical company and also conducts an in-house assessment. Currently, all drugs including cancer drugs undergo the same process from the submission of application up to listing into the Formulary. There are no separate requirements for dossier submission or considerations for formulary listing decisions of cancer drugs in MOH.

The formulary listing process involves several committees with different roles. First, there are expert committees called Drug Working Committee (DWC) established for 22 clinical disciplines in MOH. The DWC is responsible in providing technical inputs and recommendations for formulary decisions as well as ensuring rational use of medicines within their clinical disciplines. Second is Dossier Evaluation Committee (DEC). The outcomes of the drug assessment by PPDD are first presented to the Dossier Evaluation Committee (DEC), an appraisal committee within PSP which provides recommendations for formulary decisions. The final assessment outcomes and recommendations by both the DEC and DWC of relevant clinical disciplines are presented to the MOH Medicines Formulary Panel, a national level committee responsible for MOHMF listing decisions. The panel deliberates on the

findings of the assessment and considers recommendation of the two committees before a decision is made by consensus (Shafie et al., 2019).

The MOHMF Panel is chaired by the Director General of Health with members including the Senior Director of Pharmaceutical Services, Deputy Director General of Health for Medical Services, eight senior consultants from various disciplines in the public services and four senior pharmacists from the public services. The Formulary Management Branch of the PPDD is the secretariat for this committee and coordinates the process for formulary listing (Shafie et al., 2019).

As the formulary listing process applies the standard HTA framework, the limitations highlighted with the use of such approach applies for the MOH setting as well. Thus, it triggers the need for use of alternative decision frameworks encompassing of more value dimensions which can complement the traditional HTA. In this context, multi-criteria decision analysis (MCDA) concept has been explored for use in HTA to guide decision making.

1.6 Multi-Criteria Decision Analysis (MCDA) for decision making

MCDA serves as an approach and a set of techniques developed in the domain of decision theory, designed to aid in problem solving. It is a sub discipline of operations research and has wide applications in engineering, energy management, and environmental sciences (Devlin and Sussex, 2011). This technique recognises that decision makers consider multiple and often conflicting criteria during decision-making processes. It allows clarification of the factors (criteria) being considered in the decision and their relative importance (weight) (Belton and Stewart, 2002).

In MCDA, the criteria affecting a decision are identified and weighted using explicit and transparent techniques (Thokala and Duenas, 2012). The different

treatment strategies related to a decision context are scored against each of the identified criterion and weighting is used to provide summary scores for comparative purposes, thus allowing prioritization of different treatments. MCDA is increasingly embraced by healthcare decision makers as a promising approach to improve decision making such as reimbursement/coverage decisions, especially in healthcare systems where there is reluctance to primarily use a single decision metric such as incremental cost effectiveness ratio (ICER) from an economic evaluation (Marsh et al., 2014, Devlin and Lorgelly, 2017). This approach also helps to provide structure and transparency in the decision-making process, which in principle improves accountability and consistency of decision making (Baltussen and Niessen, 2006).

In view of its benefits of providing a consistent framework for decisions by explicitly incorporating various value dimensions and encouraging the inclusion of various stakeholders from different perspectives, it is seen as an alternative to address the current shortcomings of HTA approach based on economic evaluation. Thus, it has potential for application in MOHMF listing decisions considering the complexity of the decision for formulary listing where multiple criteria need to be considered while ensuring consistency and transparency of the process.

1.7 Problem statement and study justification

Innovation in cancer treatment has offered great promise for patients (Lee et al., 2018). However, even after approval by national regulatory bodies, access to such treatment has been a challenge for many countries (Cheema et al., 2012, Pujolras and Cairns, 2015). In Malaysia, access to both new innovative cancer therapies as well as essential cancer drugs have been a concern (Boo, 2016, Bazargani et al., 2014). Despite reporting's on access issues, the extent of the problem is unclear with no

concrete evidence at country level regarding cancer drug expenditures, availability and accessibility. Given the serious impact of treatment access on patients' lives, this is an important gap that needs to be investigated to ascertain degree of the problem and to guide formulation of remedial measures.

Access to cancer drugs is affected by the reimbursement/formulary listing status. In reality, ensuring optimal use of limited resources has become the strategy of interest for policy makers where value-based decision making plays a role in reimbursement/formulary listing decisions. In Malaysia, numerous efforts have been emphasised in the National Cancer Control Programme to combat the cancer crisis, which are directed at prevention, early detection, improved treatment and palliative care (Disease Control Division, 2015). Noteworthy is that one of the objectives under the National Strategic Plan for Cancer Control (NSPCC) 2016-2020 was to establish Value-Based Medicine (VBM) as a strategy to maintain sustainability of treatment through the conduct of HTA based on economic evaluation. This strategy continues as part of the NSPCC 2021-2025, highlighting the focus given to value assessment of cancer drugs (Disease Control Division, 2015, Disease Control Division, 2021). Although the recommendation to use economic evaluation for value assessment of cancer drugs is in line with approaches in other countries, the barriers and challenges that come with its use apply to Malaysia as well, and strategies to overcome these barriers are needed for successful use of economic evaluation in the MOHMF decision making (Tarn et al., 2008, Shafie et al., 2019, Ku Abd Rahim et al., 2020). Additionally, it is cautioned that an unfavourable cost-effectiveness result may potentially affect formulary listing of a drug and hamper access to treatment (Kaczyński et al., 2015).

Although many jurisdictions are proponents of using HTA based on economic evaluation for determining value of cancer drugs, the described barriers and limitations related to its use need to be addressed before it can be implemented in MOHMF decisions. Nevertheless, there are other important shortcomings of this approach which also need attention. First, the standard HTA process used for MOHMF does not formally capture other value dimensions besides cost and clinical benefits. Second, the subjective deliberations by decision makers during the MOHMF listing process affects transparency and consistency of the decisions. This is due to the lack of clear guidelines on which criteria are relevant and how important they are in the decision-making process. Given these shortcomings, it is essential that an alternative decision framework capable of capturing broader set of values as well as improve transparency and consistency of the decision-making process is developed for use in MOH.

MCDA has emerged as a potential approach for value assessment and can act as a valuable decision-making tool by overcoming the setbacks in the traditional HTA (Marsh et al., 2014). However, the practical application of this approach in oncology is scarce in comparison to other areas of health care, particularly in Asian countries (Adunlin et al., 2015, Campolina et al., 2022). These limited studies that have used MCDA for value assessment of cancer drugs have primarily been conducted in developed countries. Furthermore, current studies are limited to simulation applications with no formal comparison between MCDA approach and the traditional HTA (Angelis et al., 2017, Angelis, 2018).

The paucity of evidence on the potential for MCDA implementation in developing countries and its role in the HTA process is an area which requires more research. This research aims to fill this gap by exploring the use of MCDA for value assessment of cancer drugs in a middle-income country with a different healthcare

system and social values. Social values are known to influence healthcare decisions and outcomes (Armstrong and Swartzman, 2001, Rajkumar, 2021, Leong et al., 2022). In Malaysia, a collectivist culture plays a crucial role in decision-making, where decisions are often made with consideration for the well-being of the family or community, rather than focusing solely on the individual. Additionally, Malaysia's multicultural society, with its diversity of religious beliefs, can shape preferences and acceptance of healthcare policies and decisions (Jogulu and Ferkins, 2013, Jahn Kassim and Alias, 2016, Lee et al., 2022). This cultural context contrasts with more individualistic societies such as Europe, where personal autonomy in healthcare decisions tends to be more emphasized (Trang, 2024). These sociocultural differences can lead to varied research outcomes, underscoring the importance of conducting this study.

1.8 Study objectives

1.8.1 General

The main aim of this research is to develop a MCDA framework for value assessment of oncology drugs and determine its applicability for formulary listing decisions.

1.8.2 Specific

The specific objectives of this study are:

a) To determine trends in oncology drug expenditure and issues related to access of oncology drugs in the Ministry of Health, Malaysia

b) To identify factors influencing formulary listing decisions of oncology drugs in the Ministry of Health, Malaysia

c) To identify decision criteria relevant for formulary decisions of oncology drugs

d) To develop a formulary decision support framework for oncology drugs using Multi-criteria Decision Analysis (MCDA) approach

e) To test the applicability of the MCDA framework for formulary listing decisions of oncology drugs in the Ministry of Health

1.9 Significance of study

This study addresses a critical gap in understanding the challenges related to treatment access and aims to improve access to cancer treatments in Malaysia, a middle-income country that faces significant challenges in ensuring equitable access to both innovative and essential cancer drugs. By exploring these issues, the study sheds light on the level of access and the barriers to access, and provides insights on potential strategies that can be designed to improve access to cancer drugs. Additionally, it provides valuable insights into the feasibility of using multi-criteria decision analysis (MCDA) as an innovative tool for the value assessment of cancer drugs, targeted to be employed at the macro level for formulary decision-making. Notably, this is the first study to compare formulary decision-making based on a standard health technology assessment (HTA) approach using economic evaluation versus one based on MCDA. Moreover, it is the first study in Malaysia to explore use of MCDA in the context of multistakeholder involvement from the Ministry of Health.

1.10 Operational terms

Several fundamental concepts and terms used in this thesis are defined in Table 1.1.

Table 1.1 Operational terms and definitions used in the thesis

Terms	**Operational definitions**
Oncology	Is the branch of medicine that specialises in the diagnosis, treatment and prevention of cancer. In this thesis, the term 'oncology' and 'cancer' are used interchangeably according to the context.
Innovative cancer drugs	Refers to cancer drugs classified as targeted therapies primarily the tyrosine kinase inhibitors and monoclonal antibodies.
Reimbursement	The term 'reimbursement' is used in this thesis to reflect national drug policy decisions to provide access to treatment. However, in the context of Malaysia with a different health care system, this term refers to the MOH Medicines Formulary decisions which is a national level drug policy decision.
Multi-criteria Decision Analysis	A decision-making tool used to evaluate and compare different treatment options based on multiple criteria
Economic evaluation	Defined as the comparative analysis in terms of both costs and consequences of a new drug in comparison to current standard of care
Patient Access Scheme	Is a type of scheme offered by pharmaceutical companies with the aim to reduce the financial burden on patients and health care, or both, and improve patient access to medicine
Compulsory Licensing	A legal mechanism that allows government to permit a third party, typically a generic drug manufacturer, to produce and sell a patented product without the consent of the patent holder

CHAPTER 2

LITERATURE REVIEW

2.1 Disparities in access to cancer drugs

The global burden for cancer has been increasing, particularly in the LMICs with Asia having 50% of the global cancer burden. Therefore, ensuring access to cancer drugs is crucial to reduce cancer mortality and enhance patient survival(Jemal et al., 2011, Sankaranarayanan et al., 2014, Sung et al., 2021, Rajappa et al., 2023). Global attention on access to cancer drugs has been increasing and is evident with the World Health Assembly (WHA) passing a significant resolution on cancer prevention and control. The 2017 Cancer Resolution urges member states to adopt comprehensive approach through national cancer control plans, with particular emphasis on ensuring access to cancer services, including timely access to cancer medicines and vaccines (World Health Organization, 2017a). Access to medicines can be defined in various ways and in general encompasses availability and affordability. Availability refers to the extent to which medicines are available in the market for their intended use. Conversely, affordability pertains to the extent to which prices of medicines align with the purchasing capacity of patients or a health care system (Abbas et al., 2020).

Disparities in access to cancer drugs have been reported in several studies. An international study by Cheema et al. (2012) assessed the variability in reimbursement of 10 targeted therapies by public payers in several countries from Europe, United States, Canada, Australia and New Zealand. A vast variation was observed in reimbursement rate across these countries ranging as low as 25% to full reimbursement (100%). The low reimbursement was attributed mainly to the drugs not being cost-effective (Cheema et al., 2012). A substantial difference in access was also noted by Cherny et al. (2016) between developing countries of Eastern Europe

compared to the more developed Western Europe. The disparity was seen particularly for new and expensive targeted therapies, which was less profound for essential cancer drugs found in the WHO EML (Cherny et al., 2016a).

The WHO Model List of Essential Medicines (WHO EML) serves as a valuable guide for countries, particularly LMICs to prioritise effective medicines. In its 2015 update, the WHO EML included a substantial number of 16 new cancer drugs, which includes three targeted therapies; trastuzumab, rituximab and imatinib (Mayor, 2015). Studies investigating the alignment between cancer drugs included in a country's national medicines list and those recommended by the WHO EML have shown variability across LMICs. The number of cancer drugs incorporated in a country's list correlated with its income group (Bazargani et al., 2014, Robertson et al., 2016, Cuomo and Mackey, 2017). Malaysia was among the countries investigated in these studies. Notably, Bazargani et al. (2014) reported that Malaysia had no access to any essential cancer drugs, while Cuomo et al. (2017) reported an 8.33% concordance between the Malaysia NEML and the WHO EML. These two studies produced conflicting results, and there are no studies in Malaysia to confirm these findings. It is important to note that the study by Robertson et al. (2016) provided regional results without specific findings pertaining to Malaysia.

A survey conducted across 63 countries has revealed a significant lack of availability of cancer drugs listed on WHO EML in low- and low-middle income countries. These drugs were found to be accessible only at out-of-pocket expense. The issue on availability was more prominent for new, high-cost targeted therapies. Overall, accessibility was reported as a major concern in both low-income and middle-income countries in Asia, including Malaysia (Cherny et al., 2016b, Eniu et al., 2019).