HEALTH POLICIES AND PROGRAMS FACILITATING ACCESS TO HIGH-COST ANTICANCER DRUGS

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นโยบายสุขภาพและโครงการที่ช่วยเพิ่มการเข้าถึงยามะเร็งที่มีราคาแพง

นายฉันทวัฒน์ ปฏิกรณ์

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ผู้ป่วยเข้าถึงยามะเร็งได้อย่างจำกัดเนื่องจากเป็นยาราคาแพง การที่ผู้กำหนดนโยบายจะตัดสินใจเรื่องการเบิกจ่ายยามะเร็งราคาแพงจำเป็นจะต้องมีข้อมูลหลายด้านจากทั้งในประเทศและต่างประเทศสนับสนุน การศึกษานี้เป็นการทบทวนวรรณกรรมอย่างเป็นระบบ โดยรวบรวมข้อมูลจาก PubMed Embase และ Web of Science ตั้งแต่วันที่ 8-11 ตุลาคม พ.ศ.2561 เพื่อสืบค้นวรรณกรรมที่ตีพิมพ์ในวารสารที่มีการประเมินโดยผู้เชี่ยวชาญ ตีพิมพ์เป็นภาษาอังกฤษ ตั้งแต่ปี พ.ศ. 2543-2561 วรรณกรรมจะถูกคัดเข้าหากมีการบรรยายถึงนโยบายสุขภาพหรือโครงการที่ช่วยเพิ่มการเข้าถึงยามะเร็งที่มีราคาแพง แก่นสาระ และรายละเอียดของนโยบายและโครงการที่ทำให้การเข้าถึงยามะเร็งราคาแพงในแต่ละประเทศจะถูกรวบรวม และสรุปตามระดับรายได้ของประเทศ นอกจากนี้ยังมีการศึกษาเชิงคุณภาพด้วยวิธีการสัมภาษณ์แบบเจาะลึกในผู้ให้ข้อมูลหลักในประเทศไทยเพื่อศึกษาสถานการณ์การเข้าถึงยามะเร็งที่มีราคาแพง และเปรียบเทียบระหว่างสิทธิการรักษา 3 ประเภท

จากการสืบค้นด้วยกุญแจคำที่กำหนดพบวรรณกรรมทั้งหมด 2,112 เรื่อง โดยเป็นบทความที่ใช้ได้ 113 เรื่อง จาก 178 ประเทศ จากการวิเคราะห์พบ 4 แก่นสาระของเรื่องได้แก่ การเบิกจ่ายและการกำหนดราคายา การบริหารจัดการการเข้าถึงยาราคาแพงรูปแบบอื่น ความยืดหยุ่นของกฎสิทธิบัตร และโครงการช่วยเหลือผู้ป่วย เนื่องจากยามะเร็งมีราคาแพงเกินกว่าที่ผู้ป่วยจะรับผิดชอบค่าใช้จ่ายด้วยตนเอง พบว่าทุกประเทศใช้วิธีการกำหนดรายการยาเบิกจ่าย นอกจากนี้สำหรับประเทศที่มีรายได้น้อยและปานกลาง มักพบว่ามีการจัดโครงการช่วยเหลือผู้ป่วยที่ริเริ่มโดยบริษัทยา สำหรับประเทศที่มีรายได้สูง มีการใช้กลยุทธ์เพิ่มเติมเพื่อจัดการกับความไม่แน่นอน และความไม่คุ้มค่าของการใช้ยามะเร็งราคาแพงเหล่านี้ เช่น การใช้ชุดข้อตกลงที่ช่วยเพิ่มการเข้าถึงยา และการจัดให้มีกองทุนพิเศษสำหรับยามะเร็งที่มีราคาแพงเป็นต้น

ในส่วนของการเข้าถึงยามะเร็งราคาแพงในประเทศไทยและการเปรียบเทียบการเข้าถึงยามะเร็งราคาแพงของผู้ป่วย 3 สิทธิการรักษา ซึ่งทำการสัมภาษณ์ระหว่าง กรกฎาคม-พฤศจิกายน พ.ศ. 2561 โดยมีผู้ให้ข้อมูล 9 ราย พบว่าแก่นสาระจากการสัมภาษณ์เชิงลึกประกอบด้วย 6 แก่นสาระตามวิธีการเข้าถึงยามะเร็งที่มีราคาแพง เช่น บัญชียา จ(2) โครงการเบิกจ่ายตรงยามะเร็งราคาแพง และ โครงการช่วยเหลือผู้ป่วยเป็นต้น การเข้าถึงยามะเร็งที่มีราคาแพงโดยหลักแล้วขึ้นอยู่กับนโยบายการเบิกจ่าย และการกำหนดราคายาในประเทศ ผู้ป่วยทั้งสามสิทธิการรักษาสามารถเข้าถึงยามะเร็งราคาแพงได้โดยหากยาดังกล่าวอยู่ภายใต้บัญชียาหลักแห่งชาติ โดยเฉพาะบัญชียา จ(2) หากมีการสั่งใช้ยาที่ไม่อยู่ในบัญชียาหลักแห่งชาติ ผู้ป่วยจะต้องออกเงินค่ายาด้วยตนเอง สำหรับผู้ป่วยสิทธิสวัสดิการรักษาพยาบาลข้าราชการสามารถเข้าถึงยามะเร็งราคาแพงได้มากกว่าผู้ป่วยอีก 2 สิทธิการรักษา ผ่านโครงการเบิกจ่ายตรงยามะเร็งราคาแพง แต่อย่างไรก็ตามโครงการนี้มีข้อจำกัดในด้านจำนวนยาที่ครอบคุลม และกระบวนการขออนุมัติก่อนสั่งและจ่ายยา นอกจากนี้โครการช่วยเหลือผู้ป่วยยังมีส่วนช่วยอย่างมากในการช่วยเหลือผู้ป่วยที่จ่ายเงินเอง ให้สามารถเข้าถึงยามะเร็งที่มีราคาแพงได้ แต่โครงการเหล่านี้มีการบริหารจัดการที่หลากหลายเป็นภาระต่อผู้ให้บริการอย่างมาก นอกจากนี้ยังพบว่าเริ่มมีการใช้ชุดข้อตกลงที่ช่วยเพิ่มการเข้าถึงยาในประเทศไทย ซึ่งเป็นการปรับกลยุทธจากโครงการช่วยเหลือผู้ป่วยซึ่งทีปัญหาเรื่องความยั่งยืนของโครงการ ข้อจำกัดของทรัพยากร มาเป็นการบริหารจัดการที่ทั้งผู้ให้ประกันและบริษัทยามีข้อตกลงที่ชัดเจนและโปร่งใสมากขึ้น เป็นการแบ่งเบาภาระจากความไม่แน่นอนและความเสี่ยงจากการใช้ยากับบริษัทยาอีกด้วย

สาขาวิชา	เภสัชศาสตร์สังคมและบริหาร	ลายมือชื่อนิสิต .....
ปีการศึกษา	2561	ลายมือชื่อ อ.ที่ปรึกษาหลัก .....

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Access to anticancer drugs is limited mainly due to their high cost. To support policymakers in Thailand to develop policies and programs to facilitate better access to high-cost anticancer drugs, global and local evidence are needed. A systematic review of literature was conducted using PubMed, Embase and Web of Science between October 8-11, 2018 to identify peer-reviewed articles published in English from 2000 to 2018. Studies were included if they described health policies or programs facilitating access to high-cost anticancer drugs. Using thematic *synthesis, policies and programs were summarized by themes and by income classification of countries.* In addition, a qualitative in-depth interview was conducted with key informants in Thailand to study access to high-cost anticancer drugs across three health benefit schemes. The search identified 2112 studies, of which 113 studies in 178 countries were included in this review. Four themes of policies and programs were identified: Reimbursement and pricing policies, Alternative funding models for high-cost drugs, Procurement, Flexibility of patent law and Assistance programs. Access to high-cost anticancer drugs mainly depends on individual country's pricing and reimbursement policies as the costs of these drugs are beyond patients' affordability. Low- and middle-income countries mainly facilitate patient access through pharmaceutical industry-initiated patient assistance programs. In high-income countries utilized various strategies to overcome uncertainties and relatively poor cost-effectiveness of these drugs, for example, Managed Entry Agreements (MEAs) and dedicated fund for anticancer drugs. Interviews were conducted between July 2018 and November 2018 with 9 informants in Thailand. Six key themes emerged from the analysis synthesized by patient access to high-cost anticancer drugs under different programs and drug formularies. For example, E2 access program under National List of Essential Medicines (NLEM), Oncology Prior Authorization (OCPA), and Patient Access Programs (PAPs). Patients under the three health benefit schemes can access to high-cost anticancer drugs listed in NLEM especially E2 access program. Prescription of non-NLEM drugs requires out-of-pocket payments from patients. Civil servant medical benefit schemes patients have better access to high-cost drugs compared to the other two schemes, through the OCPA. However, OCPA has limited number of reimbursed drugs as well as strict prior authorization process. PAPs also play major role in supporting self-paying patients, but they have to be simpler in order to reduce burdens to the healthcare professionals. The use of MEAs is found to be introduced to Thailand which is the further step to deal with sustainability of PAPs, which have limited budget. MEAs are written contractual agreements between payers and pharmaceutical companies to ensure transparency and could share the risk of uncertainties among these parties

Field of Study:	Social and Administrative Pharmacy	Student's Signature .....
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CHAPTER I

INTRODUCTION

1.1 BACKGROUND AND RATIONALE

Access to anticancer drugs is limited mainly due to their high cost. The cost of anticancer drugs has been increasing concomitantly with the paradigm shift in cancer therapies from the use of traditional intravenously-administered chemotherapy to innovative targeted cancer therapy. The median annual price of anticancer drugs has been increasing from 12,000 United States dollar (US$) to more than US$120,000 over the past two decades.[5] However, these innovative cancer therapies often offered relatively small benefits in contrast to their high costs.[115] The global expenditures on cancer therapies and supportive care drugs reached US$113 billion in 2016, increasing from US$107 billion in 2015. These global expenditures were expected to increase to more than US$137 billion by 2021 as a result of more innovative therapies in the market.[116] Healthcare systems have to control the cost of cancer care while balancing access to anticancer drugs for patients needing them. Limited access to high-cost anticancer drugs is not only an issue in developing Low- and Middle-Income Countries (LMICs), [1, 5] but also in developed high-income countries.[117, 118] Each country manages access to anticancer drugs differently due to different backgrounds and economies of health systems. Previous studies mostly summarized policies and programs facilitating access to high-cost anticancer drugs in a single country[117, 119] or a group of countries,[1, 5, 118, 120] but summary of these disseminated evidences is absent.

Thailand, an upper middle-income country, is also trying to enable patient access to innovative high-cost drugs while containing the growing healthcare expenditures from the increasing cost of innovative drugs, especially anticancer drugs. In Thailand, under the Universal Health Coverage (UHC), there are three main health insurance schemes covering all of Thailand's population; the Civil Servant Medical Benefit Scheme (CSMBS) for government employees, the Social Security Scheme (SSS) for private sector employees and the Universal Coverage scheme (UC) for those not enrolled to the previous schemes.[121] Variations in access to high-cost anticancer drugs across the three health benefit schemes in Thailand were shown in three previous studies. First, CSMBS patients (67%) were more likely to received new drugs for lung cancers compared with UC scheme (19%) and SSS patients (10%).[122] Second, it was found that the survival of patients with diffuse large B-cell lymphoma under UC scheme was inferior to CSMBS patients. Lack of access to rituximab was the principal factor accounting for the inferior survival time in UC scheme patients, because rituximab was not listed in the National List of Essential Medicines (NLEM) at that time.[123] Third, there was a variation in the extent of coverage of imatinib, a drugs listed in NLEM, across three health benefit schemes because the payer of

each scheme implemented differently.[119] However, a qualitative study of access to high-cost anticancer drugs in Thailand is absent.

To support policymakers in Thailand to develop policies and programs to facilitate better access to high-cost anticancer drugs, global and local evidence are needed. A systematic review of literature was conducted to summarize existing policies and programs facilitating access to high-cost anticancer drugs in different countries. In addition, a qualitative in-depth interview was conducted with key informants from selected tertiary hospitals, cancer centers, patient advocacy groups and pharmaceutical companies in Thailand to study access to high-cost anticancer drugs across the three health benefit schemes.

1.2 RESEARCH QUESTIONS

1.2.1 What are the existing health policies and programs implemented in different countries to facilitate access to high-cost anticancer drugs?

1.2.2 What is the situation of access to high-cost anticancer drugs across the three health benefit schemes?

1.3 OBJECTIVES

1.3.1 To systematically review existing health policies and programs implemented in different countries to facilitate access to high-cost anticancer drugs

1.3.2 To study access to high-cost anticancer drugs across the three health benefit schemes in Thailand

1.4 EXPECTED BENEFITS

Results from the two study objectives will support policymakers to develop proper policy and program options to improve access to high-cost anticancer drugs in Thailand. Systematic review will show global evidences of programs and policies being implemented around the world which could be an option to be implemented in Thailand in the future. In-depth interview will show local evidences of access problem in each and between health benefit schemes in real life practices which will be the gap for improvement for policy makers.

CHAPTER II

LITERATURE REVIEW

2.1 BURDEN OF CANCER

Cancer is a group of diseases that can affect any part of the body. Cancer occurs when cells abnormally divide without control and invade nearby tissues. Since cancer cells do not have any function, they disturb normal activities of normal cells.

Cancer is a leading cause of morbidity and mortality worldwide, with 14.1 million new cancer cases, 32.6 million people living with cancer and 8.2 million deaths in 2012.[124] Cancer is the second leading cause of death worldwide with 8.8 million deaths in 2015.[125] Cancer is estimated to be increasing with aging population and population growth. The incidence rate of cancer cases increased by 33% between 2005 to 2015, 16.4% from an aging population, 12.6% from population growth and 4.1% from increasing age-specific incidence rates.[126]

Cancer can be treated with effective therapies including surgery, radiation and anticancer drugs. Anticancer drugs include chemotherapy, hormone therapy and targeted cancer therapy. Chemotherapy is a small molecule drug intended to stop the growth of cancer cells by directly killing or stopping them from dividing. Most chemotherapy affects normal cells which results in adverse drug reactions such as nausea, vomiting, hair loss or bone marrow suppression. Hormone therapy is anticancer drugs which slow or stop the growth of cancer which uses hormone to grow. Targeted cancer therapy or targeted therapy is a drug that specifically interferes with specific molecular targets involved in the growth, progression and spread of cancer cells thus, leaving normal cells unharmed. As a result of advances in cancer screening, early detection and effective cancer therapies, cancer patients have improved outcomes and increased survival time.[127]

Cancer care costs a lot of expenditures to the society. The global expenditures on cancer therapies and supportive care drugs reached US$113 billion in 2016, increasing from US$107 billion in 2015. These global expenditures were expected to increase to more than US$137 billion by 2021 as a result of more innovative therapies in the market.[116] In 2009, cost of cancer care in 27 European countries was €51 billion which accounted for 4% of the European healthcare expenditure. Half of cost of cancer care was from inpatient care. This was followed by drug expenditure which accounted for €13.5 billion or 27% of cost of cancer care.[128] As in the United States (US), cost of cancer care was estimated to be US$124 billion in 2010.[129]

Even though the cost of anticancer drugs is not the highest element of the total cost of cancer care, the cost of anticancer drugs has been increasing concomitantly with the paradigm shift in cancer therapies from the use of traditional intravenously-administered chemotherapy to

innovative targeted cancer therapy. The median annual price of anticancer drugs has been increasing from US$12,000 to more than US$120,000 over the past two decades. As of 2016, 631 anticancer drugs were in late phase of the research and development pipeline, of which, targeted cancer therapy accounted for 90%.[116] These innovative cancer therapies often offer relatively small benefits in contrast to their high costs. The survival benefits of 71 anticancer drugs approved by the United States Food and Drug Administration (US FDA) for solid tumors between 2000 and 2014 were relatively small with median Progression-Free Survival (PFS) of 2.1 months and median Overall Survival (OS) of 2.5 months.[115] Healthcare systems have to control the cost of cancer care, because more patients will get diagnosed with cancer in the future along with innovative, but expensive anticancer drugs launched into the market.

2.2 REASONS AND CONSEQUENCES OF HIGH-COST ANTICANCER DRUGS

High-cost drugs have not been explicitly defined as an exact amount of money. The following literature review will try to define "high-cost anticancer drugs". A study conducted by Faden and colleagues in 2009, defined an anticancer drugs drug with an annual cost of more than 50% or greater than the Gross Domestic Production (GDP) per capita to be considered as expensive.[118] Before 2000, new anticancer drugs were introduced with annual treatment cost at 34% of United Kingdom (UK) GPD per capita. The annual treatment cost of anticancer drugs increased to 53% in 2000-2004 and 67% of UK GDP per capita in 2005-2009.[130] The median annual price of anticancer drugs has been increasing from US$12,000 to more than US$120,000 over the past two decades.[5] This median annual price of anticancer drugs exceeded many countries' GDP per capita in 2000.[131] Therefore; high-cost anticancer drugs in this review will be defined as anticancer drugs approved since 2000.

The approved anticancer drugs are priced highly to reflect costs of lengthy research and development of successful and unsuccessful drugs. Moreover, anticancer drugs for rare cancers are high-priced given that the number of patients is relatively small. The high prices of drugs for rare cancers encourage pharmaceutical companies to do further drug research and development. Anticancer drugs are priced differently from drugs for other chronic diseases, because the nature of the disease is life-threatening.[5] The willingness to pay of patients and physicians are higher for anticancer drugs and they accept to pay for high-priced anticancer drugs, even though the benefits of drugs are limited to small prolongation of survival of months. [115, 132]

High costs of anticancer drugs directly affect the patients. High costs of anticancer drugs place a substantial financial burden upon them especially from high out-of-pocket (OOP) payment or cost-sharing. The financial toxicity from cancer care can lead to delay to treatment, non-compliance to prescribed treatment, exhaustion of savings and medical bankruptcy.[132]

Effective policies and programs should be developed and implemented to address financial toxicity in cancer patients and their families.

2.3 ACCESS TO HIGH-COST ANTICANCER DRUGS

Access to healthcare has been a complex expression with various concepts and interpretations. The most recent study in 2013 conducted by Levesque and colleagues defined access to healthcare as "the opportunity to identify healthcare needs, to seek healthcare services, to reach, to obtain or use healthcare services and to actually have the need for services fulfilled". Normally, access to healthcare can be determined by factors such as availability, price and quality of health services.[133]

Access to drugs is defined according to the definition from Gammie and colleagues as "the enabling of individuals in their financial and physical ability to obtain and receive relevant care".[134] Access to drugs can be determined by extent of coverage, reimbursement status and price.[135] These three factors determine access to drugs by their affordability.

Access to high-cost anticancer drugs, which is determined by extent of coverage, reimbursement status and price, is mainly limited due to their high costs of treatment.[1, 5] Therefore, policies or programs intended to control or lower the costs could facilitate access to high-cost anticancer drugs.

Limited access to high-cost anticancer drugs is not only an issue in developing Low- and Middle-Income Countries (LMICs), [1, 5] but also developed high-income countries.[117, 118] Each country manages access to anticancer drugs differently due to different backgrounds and economies of health systems. It was estimated in 2011 that only 15% of patients, who lived in low- and middle-income countries in the Southeast Asian Nations (ASEAN), had access to anticancer drugs compared with 55% of patients in Singapore, a high-income country in Southeast Asia.[1] In low-income countries, where there are very limited resources and facilities, major strategies to improve access to anticancer drugs are to establish an effective health system and fundamental investment in basic healthcare infrastructure, education and man power.[136] In middle-income countries, where facilities are more available than in low-income countries, strategies to lower the price of anticancer drugs are the main focus to make the anticancer drugs more favorable and more cost-effective. Strategies to facilitate access to high-cost anticancer drugs in LMICs are use of generics and biosimilars, compulsory licensing, differential pricing policies, access programs, risk-sharing agreements and collective negotiation and procurement.[1, 5, 119] Moreover, many countries in LMICs have adopted Health Technology Assessment (HTA) in their reimbursement and coverage decision, to make better decisions to allocate limited budget to high-cost anticancer drugs.[1, 5] In high-income countries, lack of access to high-cost anticancer

drugs is due to lack or adequacy of insurance, financial burden of insurance and differences in reimbursement status across countries especially newer drugs.[137] To facilitate access to high-cost anticancer drugs in high-income countries, various strategies have been implemented such as Managed Entry Agreements (MEAs), Patient Assistance Program (PAP), co-pay assistance foundation and funding and financial support. [117, 118]

Previous studies mostly summarized policies and programs facilitating access to high-cost anticancer drugs in a single country[117, 119] or a group of countries.[1, 5, 118, 120] One study conducted by Gammie and colleagues in 2015, systemically reviewed legislation, regulations and policies enabling availability and accessibility of orphan drugs in 35 countries across the world. Therefore, a systematic review of literature can be done to summarize the disseminated evidences of policies and programs facilitating access to high-cost anticancer drugs in different countries.

2.4 HEALTH POLICIES AND PROGRAMS FACILITATING ACCESS TO HIGH-COST ANTICANCER DRUGS

The following is the review of health policies and programs initiated and complementarily to facilitate access to high-cost anticancer drugs.

Reimbursement and coverage decision

Insurance systems have been established in order to pool the resources and provide financial protection for the population in the country while in the same time maintaining the sustainability of the health system. Reimbursement and coverage of high-cost drugs are widely considered as the main determinants of access.[134] The responsible bodies have to decide the insurance benefits and the extent of coverage for their population and decide which treatments and procedures should be funded or subsidized by the government. For anticancer drugs, each drug normally has to passed through two-step evaluations submitted by the pharmaceutical companies. First, the anticancer drug has to gain the market approval by the country regulator and after that the government will decide whether to fund or not fund. With the use of Health Technology Assessment (HTA), policymakers can make better decisions to allocate limited healthcare budget under uncertainty of evidences. HTA working groups make reports to the policymakers, including cost-effectiveness analyses, budget impact and/or reimbursement recommendations. Normally, policymakers assess whether the treatment is cost-effective or cost-ineffective by using the Incremental Cost-Effectiveness Ratio (ICER), reported as the incremental cost per Quality-Adjusted Life Years (QALYs) gained compared with the comparator, against country's willingness to pay threshold. The willingness to pay threshold of each country varies, but normally complies with the recommendation of the World Health Organization (WHO). WHO

recommends that willingness to pay is based on each country's GDP per capita. If the treatment's ICER falls under three times the GDP per capita, the treatment is considered cost-effective, if not it is considered cost-ineffective.[117] However, the reimbursement and coverage decisions are made by considering drug values including benefits (clinical efficacy), risks (safety profile), cost-effectiveness, budget impact, clinical practice guidelines, burden of disease, severity of disease and the number of affected patients. Therefore, even if a drug is cost-ineffective, but it shows value to the policymakers, it can get positive reimbursement and coverage decision. Also, the government may negotiate with the pharmaceutical company to lower the price of anticancer drugs to be cost-effective under the country's willingness to pay threshold. [5, 117]

If the policymakers cannot make decision because of uncertainty of the high-cost anticancer drugs, Managed Entry Agreements (MEAs) may be used. MEA is an agreement between drug manufacturers and payers (for example, the government) with the objective to reduce the impact of uncertainty from clinical-effectiveness data, pharmacoeconomic evaluations and budget impact analysis and high price of new drugs. The MEAs are one of the policy options to make decision whether to fund expensive drugs. MEAs may be known by different names such as Risk-Sharing Agreement (RSAs), Performance-based Risk-Sharing Agreements (PBRSAs), Coverage with Evidence Development (CED), access with evidence development, conditional licensing or Patient Access Schemes (PAS). For example, CED is a reimbursement condition that a drug may gain a reimbursement status with condition which requires the pharmaceutical companies to further collect clinical data in order to make definite reimbursement decision in the future. [137, 138]

Advantage of reimbursement and coverage decision policy is that the patients have better access to the high-cost anticancer drugs, because the cost of anticancer drugs is funded or subsidized. On the other hand, disadvantages of reimbursement and coverage decision policy are delayed access from the time-consuming process of review and barrier to access of treatments receiving negative reimbursement and coverage decision. If the treatment receives negative decision, patients have to pay OOP in order to buy the treatment. [117, 139]

Pricing

The government can control pricing of high-cost anticancer drugs by using flexible value-based pricing and differential pricing. Flexible value-based pricing is to price a drug flexibly according to drug's value. This means that a drug with better clinical effectiveness and benefit, such as new indication, can be priced higher than a drug with declining clinical effectiveness. Price discrimination, also known as differential pricing or tiered pricing, is to price drug differently according to each country's income and willingness to pay. This means that for the same drug, high-income countries will have to pay much higher, but it will be more affordable for the lower-

and middle-income countries. The major disadvantage of this policy is parallel importing of drugs from the lower- and middle-income countries to high-income countries. [1, 5]

Centralized procurement

Centralized or pool procurement is the process that a single body is negotiating and procuring drugs from pharmaceutical manufacturers and subsequently distributing to the providers. This gives higher negotiating power because of single buyer and high-volume purchase, instead of each healthcare provider purchasing drugs for their own facility. Therefore, the pharmaceutical manufacturers can offer lower price or discounts. [5, 119]

Use of generic and biosimilar drugs

Use of generic and biosimilar off-patent drugs can save a substantial amount of national health expenditures. Generic drug is a copy version of the same chemical entity manufactured by other companies once the patent of the originator expires. The generic drugs can substitute the original brands given that they have to be proved to be bioequivalent to the referenced product, which is tested by pharmacokinetic study. On the other hand, biosimilar is not merely a copy version of original brand biologic drug because biologic drug is a complex protein molecule. Therefore, biosimilar has to be proved to be bioequivalence by conducting a clinical trial testing that it can really substitute the referenced product. [1, 5]

Compulsory licensing

The World Trade Organization (WTO) Trade-Related Aspects of Intellectual Rights agreement (TRIPs) allows any country with public urgent need to issue a compulsory license without consent from patent holder to produce a generic drug. Also, the Doha Declaration allows countries without competency of producing its own generic drug to import from other countries. Before issuing a compulsory licensing, government may request a voluntary licensing from pharmaceutical manufacturer. Compulsory licensing can save a substantial amount of national health expenditures. [1, 5]

Patient assistance program

Most of the strategies described above are meant to facilitate access to cost-effective high-cost anticancer drugs or those receiving positive reimbursement and coverage decision. However, access to high-cost anticancer drugs receiving negative or restrictive recommendation is different. Negative recommendation means that a drug is rejected from the reviewing process in reimbursement and coverage decision and consequently rejected from the reimbursement list. While, restrictive recommendation means that the government will fund or subsidize the cost of drug under certain conditions such as specific indication or patient characteristics. Access to these drugs can be facilitated by pharmaceutical companies' program called Patient Assistance Program (PAP). PAP may be known as compassionate access program or patient access program. Under PAP, pharmaceutical companies may give patients high-cost anticancer drugs for free, subsidized or discounted. Major disadvantage of PAP is that each program makes unpredictable decision with eligibility criteria for patient selection. [1, 117, 139]

Funding and financial assistance

Funding is another source of financial support for patients who suffered from financial toxicity of high-cost anticancer drugs. Source of funding may come from government budget under healthcare financing or donations or non-governmental organizations or foundations. For example, in England, the Cancer Drug Fund (CDF) is established to allow access to anticancer drugs which are 1) waiting for reimbursement decision, 2) receiving negative recommendations and 3) used in off-label indications.[57] Funding decision is made by hospital committee or local governmental organizations or non-governmental organizations whether to fund or subsidize treatments not listed in the reimbursement list. On the other hand, for drugs listed in the reimbursement list, patients may need financial assistance because of high cost sharing. Major disadvantage is unpredictable decision and delayed treatment due to processes of getting funds. [118, 140]

2.5 CURRENT SITUATION IN THAILAND

Healthcare system

Thailand, an upper middle-income country, is trying to enable patient access to innovative high-cost drugs while containing the growing healthcare expenditures. Healthcare expenditures in Thailand was US$13,182 million in 2013 which nearly two-fold increased from US$7,032 million in 2012. Cost of drugs accounted for approximately 46% of healthcare expenditures as of 2006.[121]

In Thailand, under the Universal Health Coverage (UHC), there are three main health insurance schemes covering all of Thailand's population; the Civil Servant Medical Benefit Scheme (CSMBS) for government employees (7.6% of the population in 2013), the Social Security Scheme (SSS) for private sector employees (16.1%) and the Universal Coverage Scheme (UC) for those not enrolled to the previous schemes (76.3%).[121] These three schemes guarantee access to basic healthcare services including drugs listed on the National List of Essential Medicines (NLEM). As of 2018, drugs listed on NLEM can be divided into five categories with two sub-categories; A, B, C, D, E1 and E2. Category A includes basic drugs that every healthcare facility must make available. Category B includes alternative or second line drugs of those in category A. Category C includes drugs prescribed only by specialists. Category D includes drugs used only for specific indications. Category E is divided into two sub-categories. Sub-category E1 includes drugs used only for specific indications in special government programs. Sub-category E2 or E2 access program includes high-cost drugs.[141] E2 access program, was introduced in 2008 to improve access to high-cost drugs, which resulted in increasing number of patients receiving high-cost drugs and improvement in clinical outcomes. Also, the implementation of E2 access program involves enlisting high-cost drugs to the NLEM which resulted in lower prices and decreasing total healthcare expenditures.[121]

However, access to drugs not listed on NLEM (non-NLEM drugs) is different. Patients under SSS and UC scheme have to pay out-of-pocket payments while patients under CSMBS receive those treatment for free.[119, 121]

Burden of cancer

As of 2012, there are 123,800 new cases diagnosed with cancer and 85,00 deaths from cancer in Thailand.[142] Cancer care costs a substantial burden to Thailand's healthcare system. The National Health Security Office (NSHO), the payer of UC scheme, reported that NHSO reimbursed Thai Baht (THB) 6,662 million for cancer care; THB 1,356 million for outpatients and THB 5,526 million for inpatients during 2015-2017. This accounted for 6% of total NHSO's

budget.[143] Healthcare expenditures is expected to increase along with the increasing cost of innovative drugs, especially anticancer drugs.

Health policies and programs facilitating access to high-cost anticancer drugs

Only one health policy or program alone cannot effectively facilitate access to high-cost anticancer drugs. Different stakeholders have implemented various complementary policies and programs to facilitate access to targeted cancer therapies including NLEM, E2 access program, compulsory licensing, pooled purchasing, price negotiation and PAP. As a result of these strategies, the number of patients treated with selected targeted cancer therapies significantly increased between 2001 and 2012.[119] As of NLEM 2018, there are 8 anticancer drugs in E2 access program.[141] **(Table 1)**

Table 1 Anticancer drugs in E2 access program

Anticancer drugs	Indications
Thyrotropin alfa	Well differentiated thyroid cancer
Docetaxel	Early or metastatic breast cancer in patients with heart diseases Advanced non-small cell lung cancer Metastatic prostate cancer
Imatinib	Chronic myeloid leukemia in chronic stable phase Advanced or metastatic gastrointestinal stromal tumors
Nilotinib	Chronic myeloid leukemia in patients who cannot use imatinib
Dasatinib	Chronic myeloid leukemia in patients who cannot use imatinib or nilotinib
Rituximab	Diffused large B-cell lymphoma
Trastuzumab	Early stage breast cancer
Letrozole	Hormone receptor positive breast cancer

The NHSO has established “Protocol CA” which are criteria used for healthcare providers for the reimbursement of cancer services. The Protocol CA describes qualifications of healthcare providers and treatment protocols for different cancers. Qualifications of healthcare providers include qualified and available facilities, effective drug system and well-trained personnel. Treatment protocols describe cancer managements that healthcare professions should follow to get their services reimbursed. In 2017, NSHO announced that they will increase the coverage of cancer care from 8 cancer disease groups, and 11 protocols in 2013 to 11 cancer disease groups, and 21 protocols in 2018.[144] At first, Protocol CA was established for UC scheme patients only. However, the Social Security Office (SSO), the payer of SSS, announced that healthcare providers

also have to comply with the Protocol CA in order to get reimbursement for cancer services for SSS patients.[145] The Protocol CA covers only NLEM drugs. So, the patients under three health benefit schemes should be able to access to anticancer drugs indifferently.

CSMBS patients can access to high-cost anticancer drugs through reimbursement program called Oncology Prior Authorization (OCPA). OCPA has been established since 2005 to facilitate access to high-cost anticancer drugs, not listed on NLEM or indications not listed on NLEM and reduce unnecessary cost of hospital admission. Since 2005, there were 6 anticancer drugs in OCPA. Healthcare providers have to follow the OCPA's qualifications and criteria in order to get reimbursement.[146] In 2018, the Comptroller General's Department (CGD), the payer of CSMBS, announced that 9 anticancer drugs will be included in OCPA due to advances in medical knowledge and health technology.[147] Detailed information of anticancer drugs in OCPA and their indications is summarized in **Table 2**. 10 out of 16 indications of OCPA drugs are not listed in Thai NLEM 2018.[141] Therefore, CSMBS patients have better access to high-cost anticancer drugs compared with SSS and UC scheme patients.

Previously, CSMBS patients whose physician prescribed non-NLEM anticancer drugs did not have to pay drug cost because drug cost was covered by CSMBS. However, CGD announced that from February 14, 2018 onwards non-NLEM anticancer drugs in the high-cost anticancer drugs list **(Table 3)** will not be covered under the benefits of CSMBS and CSMBS patients whose physician prescribes these drugs have to pay the cost of drugs by themselves and get reimbursement from their original affiliation.[147] As previously mentioned, normally CSMBS patients received non-NLEM drugs for free, but in case of anticancer drugs, only OCPA drugs will be covered. However, CSMBS patients still have better access to high-cost anticancer drugs compared with SSS and UC scheme patients, because more anticancer drugs are covered.

Table 2 Anticancer drugs in Oncology Prior Authorization (OCPA) program

	Oncology prior authorization (OCPA)						Remarks
	2005			2018			
	Anticancer drugs	Indication	Indication in NLEM	Anticancer drugs	Indication	Indication in NLEM	
1	Imatinib	Chronic myeloid leukemia	Yes	Imatinib	Chronic myeloid leukemia	Yes	
		Gastrointestinal stromal tumor	Yes		Gastrointestinal stromal tumor	Yes	
					Acute lymphocytic leukemia, Ph+	No	Non-NLEM additional indication
2	Rituximab	Diffuse large B cell lymphoma	Yes	Rituximab	Diffuse large B cell lymphoma	Yes	
					Follicular lymphoma	No	Non-NLEM additional indication
					Mantle cell lymphoma	No	Non-NLEM additional indication
					Marginal zone lymphoma	No	Non-NLEM additional indication
					Chronic lymphoblastic leukemia, Ph+	No	Non-NLEM additional indication
3	Trastuzumab	Metastatic breast cancer	No	Trastuzumab	Metastatic breast cancer	No	
					Early breast cancer	Yes	NLEM additional indication
4	Erlotinib	Non-small cell lung cancer	No	-	-	-	Removed from OCPA
5	Gefitinib	Non-small cell lung cancer	No	Gefitinib	Non-small cell lung cancer	No	
6	Bevacizumab	Metastatic colorectal cancer	No	Bevacizumab	Metastatic colorectal cancer	No	
7				Nilotinib	Chronic myeloid leukemia	Yes	Additional OCPA drugs with NLEM indication
8				Dasatinib	Chronic myeloid leukemia	Yes	Additional OCPA drugs with NLEM indication
					Acute lymphocytic leukemia, Ph+	No	Additional OCPA drugs with non-NLEM indication
9				Bortezomib	Multiple myeloma	No	Additional OCPA drugs with non-NLEM indication
10				Sunitinib	Gastrointestinal stromal tumor	No	Additional OCPA drugs with non-NLEM indication

Table 3 List of high-cost anticancer drugs announced by the Comptroller General's Department in 2018

Oncologic anticancer drug	Hematologic anticancer drugs
1. Afatinib	1. Alemtuzumab
2. Aflibercept	2. Azacitidine
3. Atezolizumab	3. Basiliximab
4. Cabazitaxel	4. Bendamustine Hydrochloride
5. Degarelix	5. Brentuximab
6. Denosumab	6. Carfilzomib
7. Erlotinib	7. Clofarabine
8. Ipilimumab	8. Daratumumab
9. Nab-paclitaxel	9. Darbepoetin alfa
10. Nintedanib	10. Decitabine
11. Nivolumab	11. Nivolumab
12. PEG-filgrastim	12. Obinutuzumab
13. Pembrolizumab	13. Plerixafor
14. Pertuzumab	14. PEG-filgrastim
15. Radium-223	15. Pomalidomide
16. Ramucirumab	16. Ponatinib
17. Regorafenib	17. Pralatrexate
18. Sorafenib	18. Romiplostim
19. Temsirolimus	19. Ruxolitinib
20. Trastuzumab Emtansine	
21. Vinorelbine oral	
22. Darbepoetin alfa	

Access to high-cost anticancer drugs in Thailand

Access to high-cost anticancer drugs in Thailand were investigated in three previous studies. The percentage of patients receiving new drugs for lung cancer was significantly different among three health benefit schemes during 2003 to 2005. CSMBS patients (67%) were more likely to receive new drugs compared with UC scheme (19%) and SSS patients (10%).[122] It was found that the survival of patients with diffuse large B-cell lymphoma under UC scheme was inferior to CSMBS patients in the period of 2003 to 2006. The 6-year progression-free survival (PFS) was superior for CSMBS patients compared with UC scheme patients (34.2 vs. 23.2%, p =0.005), with a median follow-up of 24.6 months. Lack of access to rituximab was the principal factor accounting for the inferior survival time in UC scheme patients, because rituximab was not

listed in NLEM at that time.[123] This showed that there were variations in access to high-cost anticancer drugs between patients under UC scheme and CSMBS which resulted in inferior health outcomes. Also, in case of imatinib, there is a variation in reimbursement of drug cost across three schemes even though imatinib has been listed in NLEM since 2008. Given that the medicines listed in the NLEM have to be accessible to all patients, payer of each scheme implemented differently. UC scheme patients received treatment for free under Glivec International Patient Assistance Program (GIPAP), SSS patients received treatment with 50% price reduction and CSMBS patients received treatment for free under fee-for-service payment.[119] This showed variations in access because of differences in extent of coverage of imatinib across three health benefit schemes at that time.

All of the previous studies were quantitative studies and there is no qualitative study on access to high-cost anticancer drugs across the three health benefit schemes in Thailand. Therefore, this will be the gap of knowledge to be studied.

CHAPTER III

METHODOLOGY

In the absence of systematic review, to understand how each country manages access to high-cost anticancer drugs, a systematic review of literature was conducted to identify, review and summarize existing health policies and programs implemented in different countries to facilitate access to high-cost anticancer drugs **(STUDY OBJECTIVE I)**

In addition, to study access to high-cost anticancer drugs across the three health benefit schemes in Thailand, a qualitative in-depth interview was conducted with key informants from selected tertiary hospitals and cancer center and pharmaceutical companies in Thailand. **(STUDY OBJECTIVE II).**

3.1 SYSTEMATIC REVIEW OF LITERATURE (STUDY OBJECTIVE I)

The process of conducting this systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[148] A protocol of this review was registered at PROSPERO – International Prospective Register of Systematic Reviews - CRD42018068616.

3.1.1 Definition of terms

For the purpose of this review, definition of terms used were as followed;

Anticancer drugs were defined as drugs developed to treat cancer, which included chemotherapy, hormone therapy and targeted cancer therapy. Supportive cancer drugs such as antiemetic drugs, painkillers or hematopoietic stimulating factors and preventive cancer drugs such as vaccines were excluded from this review.

High-cost drugs had not been explicitly defined as an exact amount of money. A study conducted by Faden and colleagues in 2009, defined a drug with an annual cost more than 50% or greater than the Gross Domestic Production (GDP) per capita to be considered as expensive.[118] Before 2000, new anticancer drugs introduced with annual treatment of 34% of United Kingdom (UK) GPD per capita. The annual treatment cost of anticancer drugs increased to 53% in 2000-

2004 and 67% of UK GDP per capita in 2005-2009.[130] The median annual price of anticancer drugs has been increasing from US$12,000 to more than US$120,000 over the past two decades.[5] This median annual price of anticancer drugs exceeded many countries' GDP per capita in 2000.[149] Therefore; high-cost anticancer drugs in this review were defined as anticancer drugs approved since 2000 and anticancer drugs that were described as expensive, high-cost, highly priced or costly in the articles.

Policy was defined as rule, and financial or administrative order made or implemented by governments, non-government organizations or payers that influenced access to high-cost anticancer drugs.

Program was defined a set of structured activities or tools or projects made or implemented by governments, non-government organizations, payers, and pharmaceutical companies that influenced access to high-cost anticancer drugs.

Access to drugs was defined as the enabling of individuals in their financial and physical ability to obtain and receive high-cost anticancer drugs. Access is normally defined as *Availability* and *Affordability.* However, availability of anticancer drugs within a country is not always related to affordability. Therefore, this review defined access only as Affordability of high-cost anticancer drugs which will be determined by extent of coverage, reimbursement status and price.

3.1.2 Search strategy and selection criteria

The literature search was undertaken between October 8, and October 11, 2018 to identify published articles regarding health policies and programs facilitating access to high-cost anticancer drugs in different countries. Searches were undertaken in three electronic databases including PubMed, Embase and Web of Science. Search strategy was developed by CP under supervision by ST and PA. Search strategy used the combination of terms including "Policy", "Program", "Access", "Cancer" and "Drugs" (full search strategy is in the **Appendix**). The search for grey literatures was not done in this review.

Inclusion criteria were peer-reviewed studies including original articles, reviews, systematic reviews and meta-analyses, commentaries and editorial which were published from 2000 to 2018 in English language. We included studies if they described health policies or programs facilitating access to high-cost anticancer drugs. Exclusion criteria were unable to identify specific countries,

letters, news and proposed or recommended policies or programs that had not been implemented at the time of publication.

After duplicates were removed, one reviewer (CP) screened abstracts and titles for relevance. The full-text articles were obtained by CP and independently selected by two reviewers (CP and ST) against eligibility criteria. Excluded articles were described with reasons for exclusion. Discrepancies were resolved through a consensus discussion with the third reviewer (PA).

3.1.3 Data extraction and quality assessment

One reviewer (CP) extracted data from selected studies in a piloted data extraction form in an Excel spreadsheet. The selected studies were divided among the second and third reviewer (ST and PA) for cross-check of extracted data. Discrepancies were resolved through a consensus discussion among three reviewers. The following data were extracted: author(s), year of publication, article type, objective of article, country, and details of policies and programs which included objective, established year, initiator, responsible organization and desirable and undesirable impacts.

3.1.4 Quality assessment for risk of bias

There was no quality assessment for risk of bias of selected articles because this systematic review was descriptive in nature.

3.1.5 Data analysis

Thematic synthesis was done by adding new types of policy or program and relevant sub-types until no more themes were identified and saturation was reached. Types and sub-types were classified by objective of the policies and programs. Countries identified in the articles were then be classified by region and by the World Bank's income levels as high-, middle- or low-income country.[150] Results were summarized and presented by themes of policies and programs facilitating access to high-cost anticancer drugs in identified countries

3.2 QUALITATIVE IN-DEPTH INTERVIEW (STUDY OBJECTIVE II)

Qualitative study was conducted to investigate access to high-cost anticancer drugs across the three health benefit schemes in Thailand which reflected real practices and gap of policy or program implementation. An individual face-to-face in-depth semi-structured interview was conducted with key informants, including physicians, nurses and pharmacists from selected tertiary hospitals and cancer centers, pharmaceutical companies and cancer patient advocacy groups in Thailand.

3.2.1 Definition of terms

Definition of terms related to ***Study objective 2*** was described as followed;

Anticancer drugs were defined as drugs developed to treat cancer, which included chemotherapy, hormone therapy and targeted cancer therapy. Supportive cancer drugs such as antiemetic drugs, painkillers or hematopoietic stimulating factors and preventive cancer drugs such as vaccines were excluded from this study.

High-cost anticancer drugs were defined as anticancer drugs in E2 access program **(Table 1)**, OCPA **(Table 2)** and list of non-NLEM high-cost anticancer drugs. **(Table 3)**

Access was defined as the enabling of individuals in their financial and physical ability to obtain and receive high-cost anticancer drugs. Access to high-cost anticancer drugs was determined by extent of coverage, reimbursement status and price.

Variations in access to anticancer drugs was defined as differences in reaching and obtaining (or delay in obtaining) and in the type and intensity of anticancer drugs received across three health benefit schemes.

3.2.2 Drugs of interest

This study focused on specific anticancer drugs approved for solid tumor as an example to primarily explore access to these drugs in Thailand. These anticancer drugs allowed interviewees to give more detailed information than asking about every high-cost anticancer drug. High-cost anticancer drugs were selected from anticancer drugs in E2 access program **(Table 1)**,

OCPA **(Table 2)** and list of non-NLEM high-cost anticancer drugs **(Table 3)** with criteria as follows.

Selection criteria

1. Targeted cancer therapy
2. Approved for solid tumors
3. Used in outpatient setting

The selected high-cost anticancer drugs were then classified into 4 groups by reimbursement program

1. Drug listed on both E2 access program and OCPA: Trastuzumab for breast cancer
2. Drug listed only on E2 access program: Letrozole for breast cancer
3. Drug listed only on OCPA: Gefitinib for lung cancer
4. Drugs not listed neither E2 access program nor OCPA: Erlotinib for lung cancer

3.2.3 Interviewees

Interviewees in this study were key informants, including physicians, nurses and pharmacists from selected tertiary hospitals and cancer centers, pharmaceutical companies and cancer patient advocacy groups in Thailand. Participants were included if they have information or experience with any of the drugs of interest.

Healthcare professionals can provide information reflecting access to high-cost anticancer drugs across three health benefits because they decide which drugs to be given to their patients under different limitations of each health benefit scheme. Pharmaceutical companies can provide detailed information that was not available publicly for example patient assistance programs which normally were unwritten agreements between pharmaceutical companies and payers or providers. Patient advocacy group can provide patients' perspective data on access to high-cost anticancer drugs. This research focused on patient's, provider's and industrial prospective. Therefore, payers and policymakers who develop policies and programs were not target interviewees in this research.

The selected hospitals were tertiary hospitals which had medical oncologists who had experiences with high-cost anticancer drugs. Pharmaceutical companies were selected based on the availability of selected high-cost anticancer drug products in Thailand. Participant approaches were as follows. Health care providers – the researcher contacted head of pharmacy department of a hospital via e-mail to ask for participation. After the interview with head of pharmacy department of selected hospital, snowball sampling was done to further recruit key informants who were physicians, pharmacists or nurses.

Pharmaceutical companies – the researcher contacted target participants who were market access managers or product managers to ask for participation. After the interview with head of pharmacy department of selected hospital, snowball sampling was done to further recruit key informants in pharmaceutical companies.

Cancer patient advocacy groups - researcher contacted responsible person to ask for participation. After the interview, snowball sampling was done to further recruit key informants in the patient advocacy groups.

Sample size was not specified. The interview stopped when data saturation was reached, defined as no new information was provided during interviews.

3.2.4 Ethical considerations

Study protocol was approved by the Ethics Review Committee for Research involving Human Research Subjects, Health Science Group, Chulalongkorn university. Interviewees were informed with verbal and written consent form prior to participation. Interview process and interviewee identity were kept confidential.

3.2.5 Semi-structured interview guide

Semi-structured interview guide was developed to qualitatively examine access to high-cost anticancer drugs and differences of access between health benefit schemes and between hospitals. Interview guide was as follows.

1. What is your role in the health system?
    a. Provider: Physician

b. Provider: Nurse

c. Provider: Pharmacist

d. Industry: Pharmaceutical company

e. Patient: Patient Advocacy Group *(Answer questions no. 1,2,4,5 and 6)*

2. Which of the following high-cost anticancer drugs that you have experiences with?

   a. Trastuzumab

   b. Letrozole

   c. Gefitinib

   d. Erlotinib

3. Information of ____ (drug answered in question 2)?

   a. Hospital formulary

   b. Indication

   c. Available drug strength

   d. Brand (Original brand, Generic brand)

   e. Extent of coverage

4. What are the processes needed for patient to get _____ (drug answered in question 2)? Each process will be further asked for clarification and completeness of information.

   a. Universal coverage scheme patients

   b. Social security scheme patients

   c. Civil servant medical benefit scheme patients

5. How long does patient have to wait to get _____ (drug answered in question 2)?

6. Who paid the cost of ____ (drug answered in question 2)?

7. For ineligible patient, how can they get ____ (drug answered in question 2)?

   a. How many patients who were ineligible?

   b. Were the eligibility criteria appropriate?

3.2.6 Data collection

Interviewees were interviewed individually. Each interviewee was interviewed for 1 time only. Interviews were audio recorded, and transcribed verbatim. Transcript was sent to interviewee for verification. Data collection stopped when data saturation was reached, defined as no new information was provided during interviews. Interview process was as followed;

1. Greet the interviewee
2. Briefly describe the steps of the interview process
3. Obtain informed consent
4. Asked for permission to record audio and take notes
5. Turn on audio recorder
6. Verify informed consent orally with the audio recorder on
7. Conduct the interview according to the developed semi-structured interview guide with further asking for clarification and completeness of data
8. Turn off the audio recorder and thank the participant
9. Ask for potential informants (snowball sampling)
10. Reimburse the participant in accordance with study protocol

3.2.7 Data analysis

Collected data were analyzed by content analysis to examine access to high-cost anticancer drugs across three health benefit schemes and gap of policies and programs implementation. Results were then summarized by reasons of variations in access, such as differences in extent of coverage or differences in number of anticancer drugs covered by health benefit scheme.

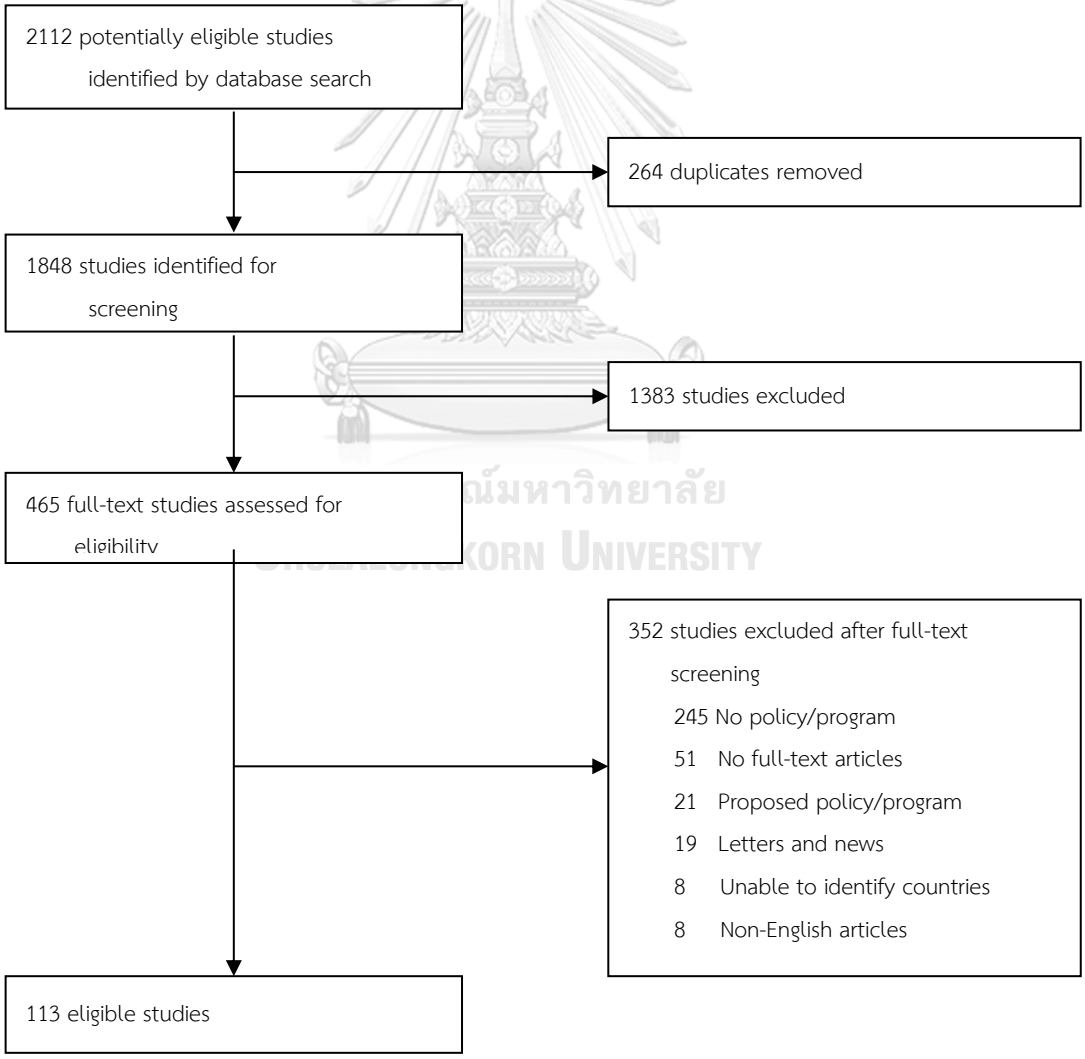
CHAPTER IV

RESULTS

4.1 RESULTS FROM SYSTEMATIC REVIEW OF LITERATURE (STUDY OBJECTIVE I)

The search identified 2112 studies, of which 264 duplicates were removed. Titles and abstracts of 1848 studies were screened for relevance, 1383 studies were excluded. 465 full-text articles were obtained and assessed against eligibility criteria. 352 studies were excluded with reasons shown in **Figure 1.** The remaining total of 113 studies were included in this review.

Figure 1 *Study-selection flow*



The included 113 studies involved 178 countries and comprised of 55 high-income countries (31%), 49 upper middle-income countries (28%), 45 lower middle-income countries (25%) and 29 low-income countries (16%). Ninety-nine studies described health policies and programs implemented in high-income countries, followed by 27 studies in upper middle-income countries, 15 studies in lower middle-income countries and 5 studies in low-income countries.

Our review of 113 studies generated 4 themes with 20 sub-themes. These themes and sub-themes described the implementation of health policies and programs by various stakeholders to influence and facilitate patient access to high-cost anticancer drugs as shown in **Table 4.** The absence of policies or programs in countries indicated that the policies and programs were not identified in literatures. However, the policies and programs might or might not be implemented in the countries. The impacts of policies and programs were not summarized, because studies were varied in methodologies with different context of individual countries. Existing health policies and programs found were summarized in each of the included countries by the emergent themes and sub-themes in **Table 5.**

Table 4 Themes and sub-themes of policies and programs facilitating access to high-cost anticancer drugs

Themes	Sub-themes
Reimbursement and pricing policies	National reimbursement decision, Local reimbursement scheme, List of essential medicines, Health Technology Assessment, Price negotiations, External reference pricing, Internal reference pricing, Value-based pricing, Price regulation, Copayment reduction, Insurance scheme for the poor, Centralized purchasing, Collective negotiation and procurement
Alternative funding models for high-cost drugs	Managed Entry Agreements, Adjusted cost-effectiveness threshold, Orphan drugs, Dedicated funds for anticancer drugs
Flexibility of patent law	Compulsory licensing
Assistance programs	Patient Assistance Programs, Assistance foundations

Table 5 Health policies and programs facilitating access to high-cost anticancer drugs

Country	Reimbursement and pricing policies													Alternative funding models for high-cost drugs				Flexibility of patent law	Assistance programs	
	National reimbursement decision	Local reimbursement scheme	List of essential medicines	Health Technology Assessment	Price negotiation	External reference pricing	Internal reference pricing	Value-based pricing	Price regulation	Copayment reduction	Insurance scheme for the poor	Centralized purchasing	Collective negotiation and procurement	Managed entry agreements	Adjusted cost-effectiveness threshold	Orphan drugs	Dedicated funds for anticancer drugs	Compulsory licensing	Patient Assistance Programs	Assistance foundations
High-income countries																				
Argentina[1, 3-6]	/		/	/									/						/	
Australia[2, 3, 7, 9, 15, 18, 24, 26-38]	/			/	/									/	/	/	/			
Austria[7, 39, 54]	/													/						
Bahamas[4]																				
Bahrain[6]			/																	
Barbados[6, 11]			/																/	
Belgium[1, 7, 18, 19, 27, 39, 67, 69, 73]	/			/	/	/	/							/			/			
Canada[2, 3, 15, 26, 27, 29-31, 34, 35, 37, 51, 56, 63, 100-107]	/	/		/	/									/			/		/	

Country	Reimbursement and pricing policies													Alternative funding models for high-cost drugs				Flexibility of patent law	Assistance programs	
	National reimbursement decision	Local reimbursement scheme	List of essential medicines	Health Technology Assessment	Price negotiation	External reference pricing	Internal reference pricing	Value-based pricing	Price regulation	Copayment reduction	Insurance scheme for the poor	Centralized purchasing	Collective negotiation and procurement	Managed entry agreements	Adjusted cost-effectiveness threshold	Orphan drugs	Dedicated funds for anticancer drugs	Compulsory licensing	Patient Assistance Programs	Assistance foundations
Chile[1-5]	/		/	/									/						/	
Croatia[7, 13, 14, 17, 18]	/			/										/						
Cyprus[3, 7]	/																			
Czech Republic[7, 13, 14, 18, 39]	/													/						
Denmark[4, 7, 15, 27, 35]	/			/													/			
Estonia[7, 13, 14, 18, 73]	/			/	/	/								/						
Finland[4, 7, 19]	/			/																
France[1, 7, 15, 19, 26, 27, 30, 35, 39, 42, 47, 51, 54, 67, 69, 87]	/			/	/	/	/			/				/		/	/			
Germany[7, 15, 19, 27, 47, 51, 54, 67, 69]	/			/	/	/	/							/			/			
Greece[7, 110]	/																			

Country	Reimbursement and pricing policies													Alternative funding models for high-cost drugs				Flexibility of patent law	Assistance programs	
	National reimbursement decision	Local reimbursement scheme	List of essential medicines	Health Technology Assessment	Price negotiation	External reference pricing	Internal reference pricing	Value-based pricing	Price regulation	Copayment reduction	Insurance scheme for the poor	Centralized purchasing	Collective negotiation and procurement	Managed entry agreements	Adjusted cost-effectiveness threshold	Orphan drugs	Dedicated funds for anticancer drugs	Compulsory licensing	Patient Assistance Programs	Assistance foundations
Hong Kong[9, 15, 16]	/			/													/			/
Hungary[7, 13, 14, 18, 19]	/			/										/						
Iceland[7]	/																			
Ireland[1, 7]	/			/																
Israel[7, 19]	/													/						
Italy[4, 7, 19, 31, 39, 43, 54, 61, 64, 67, 70]	/	/		/	/	/	/							/						
Japan[3, 4, 9]	/								/											
Kuwait[3]	/																			
Latvia[7, 13, 14, 18]	/													/						
Lithuania[7, 13, 14, 18]	/													/						
Luxembourg[1, 7, 39]	/			/										/						

Country	Reimbursement and pricing policies													Alternative funding models for high-cost drugs				Flexibility of patent law	Assistance programs	
	National reimbursement decision	Local reimbursement scheme	List of essential medicines	Health Technology Assessment	Price negotiation	External reference pricing	Internal reference pricing	Value-based pricing	Price regulation	Copayment reduction	Insurance scheme for the poor	Centralized purchasing	Collective negotiation and procurement	Managed entry agreements	Adjusted cost-effectiveness threshold	Orphan drugs	Dedicated funds for anticancer drugs	Compulsory licensing	Patient Assistance Programs	Assistance foundations
Malta[6, 7]	/		/																	/
Monaco[1]	/			/																
Netherlands[1, 2, 7, 15, 19, 26, 27, 35, 39, 43, 47, 50, 67-69, 111, 112]	/			/	/	/	/							/	/	/	/			
New Zealand[3, 5, 37, 38]	/			/										/			/			
Norway[4, 7]	/			/																
Oman[3, 6]	/		/																	
Palau[6]			/																	
Panama[4]																			/	
Poland[7, 13, 14, 18, 67, 69, 113]	/			/	/	/	/							/			/			
Portugal[4, 19, 69, 114]	/			/																

Country	Reimbursement and pricing policies													Alternative funding models for high-cost drugs				Flexibility of patent law	Assistance programs	
	National reimbursement decision	Local reimbursement scheme	List of essential medicines	Health Technology Assessment	Price negotiation	External reference pricing	Internal reference pricing	Value-based pricing	Price regulation	Copayment reduction	Insurance scheme for the poor	Centralized purchasing	Collective negotiation and procurement	Managed entry agreements	Adjusted cost-effectiveness threshold	Orphan drugs	Dedicated funds for anticancer drugs	Compulsory licensing	Patient Assistance Programs	Assistance foundations
Qatar[3]	/																			
Saudi Arabia[3]	/																			
Seychelles[4, 6, 11, 23]																			/	
Singapore[3, 9, 26]	/																		/	
Slovakia[7, 13, 14, 17]	/			/																
Slovenia[7, 13, 14, 17, 18]	/			/										/						
South Korea[1, 3, 9, 37]	/			/	/	/								/	/	/				
Spain[4, 7, 19, 54, 69, 95]	/	/		/																
Sweden[7, 15, 19, 26, 27, 29, 35, 67, 69, 73, 88]	/	/		/	/		/	/						/	/		/			
Switzerland[4, 7]	/			/																
Taiwan[1, 9, 108, 109]	/			/																

Country	Reimbursement and pricing policies													Alternative funding models for high-cost drugs				Flexibility of patent law	Assistance programs	
	National reimbursement decision	Local reimbursement scheme	List of essential medicines	Health Technology Assessment	Price negotiation	External reference pricing	Internal reference pricing	Value-based pricing	Price regulation	Copayment reduction	Insurance scheme for the poor	Centralized purchasing	Collective negotiation and procurement	Managed entry agreements	Adjusted cost-effectiveness threshold	Orphan drugs	Dedicated funds for anticancer drugs	Compulsory licensing	Patient Assistance Programs	Assistance foundations
Trinidad and Tobago[6]			/																	
United Arab Emirates[3]	/																			
United Kingdom[1, 5, 7, 15, 17-19, 24, 26-31, 34-37, 39-74]	/			/	/			/	/					/	/	/	/			
United States[3, 7, 27, 30, 31, 34, 35, 47-49, 58, 61, 65, 71, 78-93]	/			/	/					/	/			/			/		/	/
Uruguay[3, 5, 6]	/		/	/									/							
Upper middle-income countries																				
Albania[4, 7, 10, 11, 13, 17]	/																		/	

Country	Reimbursement and pricing policies													Alternative funding models for high-cost drugs				Flexibility of patent law	Assistance programs	
	National reimbursement decision	Local reimbursement scheme	List of essential medicines	Health Technology Assessment	Price negotiation	External reference pricing	Internal reference pricing	Value-based pricing	Price regulation	Copayment reduction	Insurance scheme for the poor	Centralized purchasing	Collective negotiation and procurement	Managed entry agreements	Adjusted cost-effectiveness threshold	Orphan drugs	Dedicated funds for anticancer drugs	Compulsory licensing	Patient Assistance Programs	Assistance foundations
Algeria[3, 6]	/		/																	
Armenia[6, 7]	/		/																/	
Azerbaijan[4, 10, 11, 24]	/			/															/	
Belarus[4, 7, 10, 11, 14, 24]	/		/																/	
Belize[6]			/																	
Bosnia and Herzegovina[7, 13, 17, 18]	/													/						
Botswana[4, 6]			/																/	
Brazil[1, 3, 5-7, 24, 43, 96]	/		/	/	/								/	/						
Bulgaria[7, 13, 14, 17, 18]	/													/						

Country	Reimbursement and pricing policies													Alternative funding models for high-cost drugs				Flexibility of patent law	Assistance programs	
	National reimbursement decision	Local reimbursement scheme	List of essential medicines	Health Technology Assessment	Price negotiation	External reference pricing	Internal reference pricing	Value-based pricing	Price regulation	Copayment reduction	Insurance scheme for the poor	Centralized purchasing	Collective negotiation and procurement	Managed entry agreements	Adjusted cost-effectiveness threshold	Orphan drugs	Dedicated funds for anticancer drugs	Compulsory licensing	Patient Assistance Programs	Assistance foundations
China[1, 3, 4, 6-9]	/	/	/						/	/	/			/					/	
Colombia[3-6]	/		/	/	/								/						/	
Costa Rica[4]																			/	
Dominican Republic[3, 4, 6]	/		/																/	
Ecuador[3-6]	/		/										/						/	
Fiji[4, 6, 10, 11]			/																/	
Gabon[6, 10, 11]			/																/	
Guatemala[4]																			/	
Guyana[5, 6]			/																	
Iran[3, 6, 97]	/		/	/																
Iraq[3, 6]	/		/																	

Country	Reimbursement and pricing policies													Alternative funding models for high-cost drugs				Flexibility of patent law	Assistance programs	
	National reimbursement decision	Local reimbursement scheme	List of essential medicines	Health Technology Assessment	Price negotiation	External reference pricing	Internal reference pricing	Value-based pricing	Price regulation	Copayment reduction	Insurance scheme for the poor	Centralized purchasing	Collective negotiation and procurement	Managed entry agreements	Adjusted cost-effectiveness threshold	Orphan drugs	Dedicated funds for anticancer drugs	Compulsory licensing	Patient Assistance Programs	Assistance foundations
Jamaica[6, 12]	/		/																/	
Jordan[3, 6]	/		/																	
Kazakhstan[3, 4, 7]	/																		/	
Lebanon[3, 6]	/		/																	
Macedonia[7, 13, 17]	/																			
Malaysia[1, 4, 6, 9, 77]	/		/	/															/	
Maldives[6]	/		/																	
Marshall Islands[6]			/																	
Mauritius[4, 10, 11]																			/	
Mexico[3-6, 98]	/		/	/							/								/	
Montenegro[7, 13, 17]	/																			

Country	Reimbursement and pricing policies													Alternative funding models for high-cost drugs				Flexibility of patent law	Assistance programs	
	National reimbursement decision	Local reimbursement scheme	List of essential medicines	Health Technology Assessment	Price negotiation	External reference pricing	Internal reference pricing	Value-based pricing	Price regulation	Copayment reduction	Insurance scheme for the poor	Centralized purchasing	Collective negotiation and procurement	Managed entry agreements	Adjusted cost-effectiveness threshold	Orphan drugs	Dedicated funds for anticancer drugs	Compulsory licensing	Patient Assistance Programs	Assistance foundations
Namibia[4, 6]			/																/	
Nauru[6]			/																	
Paraguay[4-6]			/										/						/	
Peru[3-6]	/		/										/						/	
Romania[7, 13, 14, 17, 18]	/													/						
Russia[7, 8, 14, 76]	/		/								/								/	
Serbia[7, 13, 14, 17, 18, 68]	/			/										/						
South Africa[3, 4, 6, 27, 94]	/		/	/	/														/	
St. Lucia[4, 10]																			/	
St. Vincent and the Grenadines[6]			/																	

Country	Reimbursement and pricing policies													Alternative funding models for high-cost drugs				Flexibility of patent law	Assistance programs	
	National reimbursement decision	Local reimbursement scheme	List of essential medicines	Health Technology Assessment	Price negotiation	External reference pricing	Internal reference pricing	Value-based pricing	Price regulation	Copayment reduction	Insurance scheme for the poor	Centralized purchasing	Collective negotiation and procurement	Managed entry agreements	Adjusted cost-effectiveness threshold	Orphan drugs	Dedicated funds for anticancer drugs	Compulsory licensing	Patient Assistance Programs	Assistance foundations
Suriname[3-5, 10, 11]	/												/						/	
Thailand[1, 3-7, 9, 20-22]	/		/	/	/							/					/	/	/	
Tonga[6]			/																	
Turkey[3, 4, 7]																			/	
Turkmenistan[7]	/																			
Tuvalu[6]			/																	
Venezuela[3-6]	/		/										/						/	
Lower middle-income countries																				
Angola[6]			/																	
Bangladesh[4, 6]			/																/	
Bhutan[6, 10, 11]			/																/	

Country	Reimbursement and pricing policies													Alternative funding models for high-cost drugs				Flexibility of patent law	Assistance programs	
	National reimbursement decision	Local reimbursement scheme	List of essential medicines	Health Technology Assessment	Price negotiation	External reference pricing	Internal reference pricing	Value-based pricing	Price regulation	Copayment reduction	Insurance scheme for the poor	Centralized purchasing	Collective negotiation and procurement	Managed entry agreements	Adjusted cost-effectiveness threshold	Orphan drugs	Dedicated funds for anticancer drugs	Compulsory licensing	Patient Assistance Programs	Assistance foundations
Bolivia[4-6]			/										/							
Cabo Verde[6]			/																/	
Cambodia[4, 6, 10, 11]			/																/	
Cameroon[4, 6, 10, 11]			/																/	
Republic of the Congo[4, 6, 10, 11]			/																/	
Côte d'Ivoire[4, 6, 11]			/																/	
Djibouti[6]			/																	
Egypt[3, 6]	/		/																	
El Salvador[3, 4, 6]	/		/																/	
Georgia[4, 6, 7, 10, 11]	/		/																/	

Country	Reimbursement and pricing policies													Alternative funding models for high-cost drugs				Flexibility of patent law	Assistance programs	
	National reimbursement decision	Local reimbursement scheme	List of essential medicines	Health Technology Assessment	Price negotiation	External reference pricing	Internal reference pricing	Value-based pricing	Price regulation	Copayment reduction	Insurance scheme for the poor	Centralized purchasing	Collective negotiation and procurement	Managed entry agreements	Adjusted cost-effectiveness threshold	Orphan drugs	Dedicated funds for anticancer drugs	Compulsory licensing	Patient Assistance Programs	Assistance foundations
Ghana[3, 4, 6, 10, 11]	/		/																/	
Honduras[4, 6]			/																/	
India[1, 4-7, 9, 25]			/		/						/							/	/	
Indonesia[1, 3, 4, 6, 9]	/		/	/															/	
Kenya[3, 4, 6, 10, 11, 75]	/		/																/	
Kyrgyzstan[4, 7, 10, 11]	/																		/	
Kiribati[6]			/																	
Kosovo[7, 13, 17]	/																			
Lao[4]																			/	
Lesotho[4, 6]			/																/	
Mauritania[3, 4, 6]	/		/																/	

Country	Reimbursement and pricing policies													Alternative funding models for high-cost drugs				Flexibility of patent law	Assistance programs	
	National reimbursement decision	Local reimbursement scheme	List of essential medicines	Health Technology Assessment	Price negotiation	External reference pricing	Internal reference pricing	Value-based pricing	Price regulation	Copayment reduction	Insurance scheme for the poor	Centralized purchasing	Collective negotiation and procurement	Managed entry agreements	Adjusted cost-effectiveness threshold	Orphan drugs	Dedicated funds for anticancer drugs	Compulsory licensing	Patient Assistance Programs	Assistance foundations
Moldova[4, 10, 11, 13, 14]	/																		/	
Mongolia[4, 10, 11]																			/	
Morocco[3, 4, 6]	/		/																/	
Myanmar[3, 6]			/																	
Nicaragua[4, 6]			/																/	
Nigeria[4, 6, 10, 11]			/																/	
Pakistan[4, 6]			/																/	
Palestine[3]																				
Papua New Guinea[6, 10, 11]			/																/	
Philippines[3, 4, 6, 9]	/		/																/	
Solomon Islands[6]			/																	

Country	Reimbursement and pricing policies													Alternative funding models for high-cost drugs				Flexibility of patent law	Assistance programs	
	National reimbursement decision	Local reimbursement scheme	List of essential medicines	Health Technology Assessment	Price negotiation	External reference pricing	Internal reference pricing	Value-based pricing	Price regulation	Copayment reduction	Insurance scheme for the poor	Centralized purchasing	Collective negotiation and procurement	Managed entry agreements	Adjusted cost-effectiveness threshold	Orphan drugs	Dedicated funds for anticancer drugs	Compulsory licensing	Patient Assistance Programs	Assistance foundations
Sri Lanka[4, 6]			/																/	
Swaziland[4]																			/	
Sudan[3, 4, 6, 10, 11]	/		/																/	
Timor-Leste[6]			/																	
Tunisia[3, 6]	/		/																	
Ukraine[7, 14]	/																			
Uzbekistan[4, 10, 11]																			/	
Vanuatu[99]			/																	
Vietnam[1, 3, 4, 9]	/			/															/	
Zambia[3, 4, 6, 10, 11]	/		/																/	

Country	Reimbursement and pricing policies													Alternative funding models for high-cost drugs				Flexibility of patent law	Assistance programs	
	National reimbursement decision	Local reimbursement scheme	List of essential medicines	Health Technology Assessment	Price negotiation	External reference pricing	Internal reference pricing	Value-based pricing	Price regulation	Copayment reduction	Insurance scheme for the poor	Centralized purchasing	Collective negotiation and procurement	Managed entry agreements	Adjusted cost-effectiveness threshold	Orphan drugs	Dedicated funds for anticancer drugs	Compulsory licensing	Patient Assistance Programs	Assistance foundations
Low-income countries																				
Afghanistan[6]			/																	
Benin[4, 10, 11]																			/	
Burkina Faso[3, 4, 6, 10, 11]	/		/																/	
Burundi[6]			/																	
Central Africa[4, 6]			/																/	
Chad[6]			/																	
Democratic Republic of the Congo[4, 6, 10, 11]			/																/	
Eritrea[6]			/																	
Ethiopia[4, 10, 11]			/																/	

Country	Reimbursement and pricing policies													Alternative funding models for high-cost drugs				Flexibility of patent law	Assistance programs	
	National reimbursement decision	Local reimbursement scheme	List of essential medicines	Health Technology Assessment	Price negotiation	External reference pricing	Internal reference pricing	Value-based pricing	Price regulation	Copayment reduction	Insurance scheme for the poor	Centralized purchasing	Collective negotiation and procurement	Managed entry agreements	Adjusted cost-effectiveness threshold	Orphan drugs	Dedicated funds for anticancer drugs	Compulsory licensing	Patient Assistance Programs	Assistance foundations
Guinea[4, 6]			/																/	
Haiti[10, 11]			/																/	
Madagascar[4, 10, 11]			/																/	
Malawi[3, 10, 27]	/																		/	
Mali[6]			/																/	
Mozambique[4, 11]																			/	
Nepal[4, 6, 10, 11]			/																/	
Niger[11]																			/	
North Korea[6]			/																	
Rwanda[4, 6, 10, 11]			/																/	
Senegal[4, 6, 10, 11]			/																/	

Country	Reimbursement and pricing policies													Alternative funding models for high-cost drugs				Flexibility of patent law	Assistance programs	
	National reimbursement decision	Local reimbursement scheme	List of essential medicines	Health Technology Assessment	Price negotiation	External reference pricing	Internal reference pricing	Value-based pricing	Price regulation	Copayment reduction	Insurance scheme for the poor	Centralized purchasing	Collective negotiation and procurement	Managed entry agreements	Adjusted cost-effectiveness threshold	Orphan drugs	Dedicated funds for anticancer drugs	Compulsory licensing	Patient Assistance Programs	Assistance foundations
Sierra Leone[11]																			/	
Somalia[6]			/																	
Syria[6]			/																	
Tajikistan[4, 11]																			/	
Tanzania[4, 6, 10, 11]			/																/	
Togo[4, 6, 10, 11]			/																/	
Uganda[4, 6, 7, 10, 11]	/		/																/	
Yemen[6]			/																	
Zimbabwe[3, 4, 6, 11]	/		/																/	

Health policies and programs were categorized by countries' income classifications and by themes in **Table 6** and by countries' income classifications and by sub-themes in **Table 7**. Out of 55 high-income countries, reimbursement and pricing policies were implemented in 96.36% of countries, followed by alternative funding models for high-cost drugs (45.45%) and assistance programs (18.18%). Flexibility of patent law was not found to be implemented in any high-income countries. Out of 49 upper middle-income countries, reimbursement and pricing policies were implemented in 91.84% of countries, followed by assistance programs (57.14%), alternative funding models for high-cost drugs (14.29%) and flexibility of patent law (2.04%). Out of 45 lower middle-income countries, reimbursement and pricing policies were implemented in 91.11% of countries, followed by assistance programs (71.11%) and flexibility of patent law (2.22%). Alternative funding models for high-cost drugs were not found to be implemented in lower middle-income countries. Out of 29 low-income countries, reimbursement and pricing policies were found in 79.31% of countries, followed by assistance programs (72.41%). Alternative funding models for high-cost drugs and flexibility of patent law were not found to be implemented in low-income countries. Out of 178 countries, reimbursement and pricing policies were implemented in 91.01% of countries, followed by assistance programs (51.12%), alternative funding models for high-cost drugs (17.98%) and flexibility of patent law (1.12%). Themes and sub-themes were summarized below along with quantitative data from **Table 7.**

***Table 6** Health policies and programs by countries' income classifications and by themes*

Income classification	Countries	Reimbursement and pricing policies		Alternative funding models for high-cost drugs		Flexibility of patent law		Assistance programs	
	n	n	%	n	%	n	%	n	%
High-income countries	55	53	96.36%	25	45.45%	0	0.00%	10	18.18%
Upper middle-income countries	49	45	91.84%	7	14.29%	1	2.04%	28	57.14%
Lower middle-income countries	45	41	91.11%	0	0.00%	1	2.22%	32	71.11%
Low-income countries	29	23	79.31%	0	0.00%	0	0.00%	21	72.41%
All countries	178	162	91.01%	32	17.98%	2	1.12%	91	51.12%

Table 7 Health policies and programs by countries' income classifications and by sub-themes

Income classification	Reimbursement and pricing policies n (%)													Alternative funding models for high-cost drugs n (%)				Flexibility of patent law n (%)	Assistance programs n (%)	
	National reimbursement decision	Local reimbursement scheme	List of essential medicines	Health Technology Assessment	Price negotiation	External reference pricing	Internal reference pricing	Value-based pricing	Price regulation	Copayment reduction	Insurance scheme for the poor	Centralized purchasing	Collective negotiation and procurement	Managed entry agreements	Adjusted cost-effectiveness threshold	Orphan drugs	Dedicated funds for anticancer drugs	Compulsory licensing	Patient Assistance Programs	Assistance foundations
High-income countries (55 countries)	48 (87%)	4 (7%)	10 (18%)	32 (58%)	12 (22%)	8 (15%)	7 (13%)	2 (4%)	2 (4%)	2 (4%)	1 (2%)	0 (0%)	3 (5%)	23 (42%)	5 (9%)	5 (9%)	13 (24%)	0 (0%	9 (16%)	2 (4%)
Upper middle-income countries (49 countries)	32 (65%)	1 (2%)	33 (67%)	8 (16%)	4 (8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)	3 (6%)	1 (2%)	8 (16%)	6 (12%)	0 (0%)	0 (0%	1 (2%)	1 (2%)	28 (57%)	0 (0%)
Lower middle-income countries (45 countries)	19 (42%)	1 (2%)	35 (78%)	2 (4%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)	32 (71%)	0 (0%)
Low-income countries (29 countries)	4 (14%)	0 (0%)	23 (79%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	21 (72%)	0 (0%)
All countries (178 countries)	103 (58%)	6 (3%)	101 (57%)	42 (23%)	17 (10%)	8 (4%)	7 (4%)	2 (1%)	2 (1%)	3 (2%)	5 (3%)	1 (0.5%)	12 (7%)	29 (16%)	5 (3%)	5 (3%)	14 (8%)	2 (1%)	90 (51%)	2 (1%)

Reimbursement and pricing policies

Reimbursement and pricing policies of this review covered from reimbursement decision, pricing strategies, copayment reduction, insurance scheme for the poor to procurement strategies.

National reimbursement decision.

National reimbursement decision was found to be implemented in 103/178 countries (57.87%) and comprised of 48/55 high-income countries (87.27%), 32/49 upper middle-income countries (65.31%), 19/45 lower middle-income countries (42.22%), and 4/29 low-income countries (13.79%). In all countries, patient access to high-cost anticancer drugs mainly depends on their countries' coverage and reimbursement decision since the costs of therapy are beyond most patients' willingness to pay.[3, 7] Thus, payers need careful consideration, because decision to not reimburse means denial of access. The decisions can be made with the use of World Health Organization (WHO) Model List of Essential Medicines[151] or Health Technology Assessment (HTA) which were summarized separately.

Local reimbursement scheme.

Local reimbursement scheme was found to be implemented in 6/178 countries (3.37%) and comprised of 4/55 high-income countries (7.27%), 1/49 upper middle-income countries (2.04%), and 1/45 lower middle-income countries (2.22%). Local reimbursement scheme was not found to be implemented in any low-income countries. Local reimbursement scheme is utilized in countries where local, provincial or regional governments exist to determine their own reimbursement decisions or drug reimbursement formularies. Provincial governments were found in Canada and China.[8]

In China, after the National Essential Drug List has been issued by central government, the local governments then adjust their provincial Reimbursement Drug List. The list determines drug reimbursement by public medical insurance plan. Access to high-cost anticancer drugs was limited in China, as many drugs were not listed into neither national or provincial list.[8]

In Canada, patient access to high-cost anticancer drugs depends on where they live because each province independently determines its own health benefit scheme including

reimbursement drugs.[41] Menon, et al., found significant interprovincial variations in patient access to anticancer drugs across 10 provinces of Canada, with only 7 out of 115 anticancer drugs which were available in all provinces [41]. Common Drug Review (CDR) was established in 2003 to make central national listing recommendation for provincial governments.[41, 100] Also, the Joint Oncology Drug review was established in 2007, which was later succeeded by the pan-Canadian Oncology Drug Review (pCODR) 2011, to specifically evaluate anticancer drugs and make national listing recommendations with the aim to better coordinate the review of anticancer drugs across Canada. However, the decisions to accept the recommendations still depend on the provincial governments.[35, 100]

Regional governments were found in Italy[120], Spain[69, 95] and Sweden.[120] In Spain, the reimbursement decisions are made both centrally at the Ministry of Health and regionally in the regional governments.[95] HTA is performed both centrally by Bot PLUS [69] and regionally by the Regional Health Care Governments.[95] In Sweden, positive reimbursement decisions are made at national level and then need to be adopted at regional. Regional county councils can reimburse anticancer drugs not recommended at the national level. Thus, variations in reimbursed anticancer drugs were found across the country.[120] In contrast to the previous countries, pricing and reimbursement decisions in Italy are made nationally, but the regional governments can still charge copayments to patients differently. Regional drug lists were the same, but price variations were found across the country.[120]

One common characteristic of local reimbursement schemes in these countries is the independent decision made by local health authorities and not surprisingly this will lead to "post-code prescribing" in which a patient's access to high-cost anticancer drugs depends on where they live.

Lists of essential medicines

List of essential medicines was found to be implemented in 101/178 countries (56.74%) and comprised of 10/55 high-income countries (18.18%), 33/49 upper middle-income countries (67.35%), 35/45 lower middle-income countries (77.78%), and 23/29 low-income countries (79.31%).

Since 1977, WHO has been establishing a WHO Model List of Essential Medicines which provides guidance for countries in prioritizing patient access to essential medicines. Essential medicines are selected by the WHO based on disease prevalence, efficacy, safety, and comparative effectiveness. In 2015, the WHO model list selected 48 anticancer drugs which included 3 high-cost anticancer drugs; imatinib, rituximab and trastuzumab.[151]

Many countries, especially LMICs used this model list as a negotiating tool to enlist these high-cost drugs to their national drug formularies.[6, 8, 25, 77, 119] However, LMICs were found to be struggling to comply with the model list. Anticancer drugs in the national formularies in LMICs were concordant with WHO Model List with the median concordance of 42.71%. Even WHO considered these anticancer drugs as essential, it was impossible for LMICs to list every drug due to the high-cost of these drugs.[6]

Health Technology Assessment.

As resources are limited, it is impossible for any health system to provide full access to every anticancer drug launched into the market. Health Technology Assessment (HTA) is a multidisciplinary process that summarizes and evaluates information regarding, but not limited to, efficacy, safety, cost-effectiveness and ethical and societal preferences of medical therapies and technologies to inform reimbursement decision for payers. Cost-effectiveness analyses shows value for money in specific context of individual health system. Two key measures used for value for money are Quality-Adjusted Life Years (QALYs) and Incremental Cost Effectiveness Ratio (ICER). HTA was found to be implemented in 42/178 countries (23.60%) and mainly comprised of 32/55 high-income countries (58.18%), followed by 8/49 upper middle-income countries (16.33%), and 2/45 lower middle-income countries (4.44%). HTA was not found to be implemented in any low-income countries.

Some countries may explicitly define cost-effectiveness threshold. For example, an ICER threshold of £20,000 to £30,000 per QALYs in the United Kingdom (UK) [5] and 45,000 Australian Dollar (AUD) to 75,000 AUD in Australia.[36] Some countries, especially LMICs, comply with WHO recommendation of ICER threshold at 3 times the country's GDP per capita.[5] Each country has their own HTA organization and process.

However, HTA could delay drug reimbursement due to its complexity and time-consuming processes. One study found that trastuzumab took 10 years to gain reimbursement status in certain Central and Eastern European (CEE) countries.[7] Moreover, patients may not be able to access to affordable high-cost anticancer drugs if the company decided not to submit their drug for reimbursement decision in the first place.

Even the HTA and review process are strict, Canada and Denmark have created special HTA path for anticancer drugs.[35] In Canada, as previously described, the pCODR was established to specifically review all anticancer drugs used in Canadian provinces, except Quebec. The pCODR does not publicly define explicit cost-effectiveness threshold, resulting the decision to reimburse high-cost anticancer drugs with relatively poor cost-effectiveness.[35] In Denmark, the National Board of Health was established in 2008 to separately review cancer drugs for national reimbursement. Also, it was found that the Danish Center for Health Technology Assessment rapidly reviewed anticancer drugs within 3 months, compared with normal process of 1 to 2 years in noncancer drugs.[35] These special HTA paths facilitate patient access to high-cost anticancer drugs through prioritization of oncology before other therapeutic areas.

Price negotiations.

Price negotiations were found to be implemented in 17/178 countries (9.55%) and comprised of 12/55 high-income countries (21.82%), 4/49 upper middle-income countries (8.16%) and 1/45 lower middle-income countries (2.22%). Price negotiations were not found to be implemented in low-income countries.

Price negotiations were done between payers and companies after the evaluation for reimbursement or between purchasers and companies at procurement process. HTA results, especially cost-effectiveness analyses and budget impacts facilitated price negotiations [5, 31, 37, 63, 119]. Pharmaceutical companies need to cut down drug prices to comply with country's cost-effectiveness threshold to be rendered as acceptable for payers. For example, in South Korea, there is a two-stage process for price negotiations, first HTA-price negotiation process to lower price according to the cost-effectiveness analysis and sequential obligatory price negotiation process with South Korean payer.[37] In Canada, the pan-Canadian Pharmaceutical Alliance negotiates drug price for the whole country with the aim to achieve lower drug prices and

consistent price across the country.[100] Price negotiations could lower price substantially. However, details in pricing negotiations in most countries were not disclosed.

External reference pricing.

External reference pricing was found to be implemented in 8/178 countries (4.49%) and comprised of 8/55 high-income countries only (14.55%). There are two types of reference pricing system including external reference pricing and internal reference pricing.[19]

External reference pricing sets price based on price of one price, or average price, or median price, or specific equations using prices from several reference countries. Some countries utilized external reference pricing (international reference pricing) to set price of high-cost anticancer drugs, especially in European countries which maximum prices were set based on the average price in other European countries.[64, 73, 120] Multinational pharmaceutical companies would try their best to hinder revealing their real prices by several strategies as the used of Managed Entry Agreements to make net price remain confidential[39] or simply delay or avoid product launches in countries with rigorous external reference pricing.[37]

Internal reference pricing.

Internal reference pricing was found to be implemented in 7/178 countries (3.93%) and comprised of 7/55 high-income countries only (12.73%). Internal reference pricing, on the other hand, sets single reimbursement price for a group of drugs clustered by mechanism of action, molecular similarity or sometimes therapeutic effect.[19] This system was utilized in many European countries.[19, 47, 120] For example, in Germany and Netherlands, anticancer drugs with limited added benefits compared to existing therapy were grouped and priced within similar drugs in a therapeutic class.[47, 137] This system allowed patient access to several anticancer drugs within the same therapeutic class.

Value-based pricing.

Value-based pricing was found to be implemented in 2/178 countries (1.12%) including Italy and United Kingdom. Value-based pricing is to set price according to the added therapeutic value of a new product compared to existing treatments. Values of drug included, but not limited to, QALYs gained, innovation, unmet need, lack of alternative treatment and burden of disease. This system not only limits spending on drugs with low values but also incentivizes further research and development of drugs with more added values.[15] Value-based pricing was introduced in Sweden and United Kingdom and the systems relied on cost-effectiveness analysis and cost-effectiveness threshold. Prices of anticancer drugs with low additional benefits were set against country's cost-effectiveness threshold. The threshold could be higher for drugs with more added values especially those treating rare or life-threatening diseases.[24, 73]

Price regulation.

Price regulation was found in Japan[27] and United Kingdom[73, 120] to set a reasonable drug price in balance with return on investment for pharmaceutical companies. In United Kingdom, price of branded drug was regulated the rate-of-return by the Pharmaceutical Pricing Regulation Scheme using a spending cap.[73, 120] The detail of price regulation in Japan was not described.[27] Thus, the high-cost anticancer drugs were priced more reasonably with control over return on investment in research and development process.

Copayment reduction.

In countries where patients have to copay medicinal services or drugs, if the high-cost anticancer drugs are not fully covered by health system, patients have to face with substantially high copayments. Copay reduction was found to be implemented in 3/178 countries (1.69%) and comprised of 2/55 high-income countries (3.64%) and 1 upper middle-income countries (2.04%).

In France, Affection Longue Durée or ALD30, which is a special regulation for chronic diseases which require more than 6 months of continuous care, provides patients an exemption from copayment for drugs in ALD30's list. In 2005, 20% of total expenditures of ALD30 covered 244,139 oncology cases.[120] In 2013, China's Ministry of Health reduced copayments for 20 specific

priority disease including 8 cancers which covered 70% of out-of-pocket inpatient medical expenses.[8]

In the United States, Medicare beneficiaries received high-cost anticancer drugs through a prescription drug benefit under Medicare Part D. However, Medicare Part D provided incomplete coverage for high-cost anticancer drugs, because of substantially high copayments. In 2010, there were 310 USD deductibles then coinsurance of 25% of drug costs up to 2,960 USD. After that patients fell into the "Donut hole", a coverage gap in which patients paid 100% of drug costs until a total of 4,700 USD out-of-pocket was reached. From that point on, patients were covered by catastrophic coverage with coinsurance of 5% drug costs, which was still high since anticancer drugs normally cost 10,000 USD per month. These copayments were reset every calendar year. It was found that some patients fell into the donut hole after just only two months of therapy.[86, 89, 152] Therefore, the Affordable Care Act was introduced with the aim to close the donut hole by 2020 by gradually reducing coinsurance rate in the donut hole from 100% to 25% with 50% contribution from pharmaceutical companies.[90, 152] Studies found beneficiaries would spend 1,114 USD [90] to 2,550 USD less.[152]

Insurance scheme for the poor.

In some countries, governments established separate insurance schemes specifically for the poor or uninsured. Insurance coverage for the poor was found to be implemented in 5/178 countries (2.81%) and comprised of 1/55 high-income countries (1.82%), 3/49 upper middle-income countries (6.12%) and 1/45 low-income countries (2.22%).

In the United States, Medicaid and low-income subsidies provide coverage for poor patients, but services are varied by states.[152] China also established the Urban and Rural Social Medical Aid system to help patients with difficulty dealing with high-cost anticancer drugs. Eligibility criteria included low-income patients who are severely ill or belong to families with financial difficulties.[8] In Russia, the Dopolnitelnoe Lekarstvennoe Obespechenie (Additional Medicines Supply) program covers poor population. This program allows patients to receive prescription drugs for outpatient care free of charge or at discounted price.[8] Mexico also provided health coverage for the uninsured and the poor to access breast cancer diagnosis and treatment through the Seguro Popular.[98] Government-funded insurance scheme for the poor has been established in India. Each state established its own insurance scheme for the poor and

reimbursement formulary, although reimbursed drugs of these schemes still lacked essential anticancer drugs and had insufficient coverage of total costs of therapy.[25]

Centralized purchasing.

Centralized purchasing is when one responsible organization procures anticancer drugs for the whole country. Centralized purchasing for high-cost anticancer drugs was found in Thailand. In Thailand, high-cost anticancer drugs are listed under E2 access program, a subcategory under National List of Essential Medicines. The Government Pharmaceutical Organization (GPO) was assigned by payers to centrally purchase high-cost anticancer drugs and supply to each hospital under its Vendor Managed Inventory system to ensure continuous drug supply. Central purchaser increases purchasing power thus lower drug prices are achieved.[119]

Collective negotiation and procurement.

Collective negotiation and procurement were formed among countries in Latin America including Argentina, Bolivia, Brazil, Colombia, Chile, Ecuador, Guyana, Paraguay, Peru, Suriname, Uruguay, and Venezuela in September 2015. The joint committee bargained for and purchased high-cost drugs with successful collective cost savings of around USD 20 million for member countries from antiretroviral drugs. The committee also plan to purchase anticancer drugs using this joint bargaining to increase purchasing power.[5]

Alternative funding models for high-cost drugs

Some countries, especially high-income countries, have since created alternative funding models to facilitate patient access to high-cost drugs. These strategies are mostly used in situations when the innovative anticancer drugs are not cost-effective.

Managed Entry Agreements.

Managed Entry Agreements (MEAs) are contractual agreements between payers and pharmaceutical companies to share the risk of uncertainties of drug submitted for pricing and reimbursement. MEAs were found to be implemented in 29/178 countries (16.29%) and comprised of 23/55 high-income countries (41.82%) and 6/49 upper middle-income countries (12.24%). MEAs were not found to be implemented in lower middle- and low-income countries.

MEAs were called differently in different countries. For example, patient access schemes in the United Kingdom,[18] managed access programs in Australia,[38] and coverage with evidence development in the Netherlands.[137] MEAs are utilized when the reimbursement decisions of "yes" or "no" cannot be made due to uncertainties of drug about clinical evidences, financial impacts or cost-effectiveness.[39] There are two main types of MEAs: performance-based MEAs and financial-based MEAs in which the former mainly address clinical uncertainties and the latter address financial uncertainties. Performance-based MEAs linked drug performances or patient's outcomes to drug reimbursement. Financial-based MEAs offered financial security for payers by indirectly lowering drug price such as, simple discount, price-volume agreements and rebates. Some MEAs are considered mixed type as they utilized both performance-based and the financial-based agreements in their design.[18, 39]

MEAs were utilized in many high-income countries in Europe,[18, 39, 118] Australia,[2] Canada,[2] Israel,[7] South Korea,[37] New Zealand[37] and the United States.[31] Upper middle-income countries in Europe including Bosnia and Herzegovina, Bulgaria, Romania, and Serbia established their own MEAs.[18] MEAs were also found in Brazil and China.[7] The types and designs of MEAs varied from country to country. For example, most MEAs in Italy were performance-based with refund for non-responders at individual patient level. The majority of MEAs in the United Kingdom were financial-based with simple discounts as the most utilized design.[39]

MEAs facilitate access to high-cost anticancer drugs which would be otherwise not reimbursed by health system payers. Performance-based MEAs allows data collection of real-world clinical effectiveness to address clinical uncertainties at the time of reimbursement decision which will be used to re-evaluate the decision after several years. Evidences are normally collected through registries. However, burdens of data collection limit quality and validity of collected data. Thus, it was found that even after the period of data collection, uncertainties were not resolved.[137] On the other hand, financial-based MEAs offered relatively simple agreement such as simple discount and complex schemes such as utilization, rebates, and price-volume agreements. MEAs were found to be increasing overtime in high-income countries. One of the attractive attributes of MEAs is that the pharmaceutical companies can negotiate price with health system payers while the real net price remains confidential. This hinders the effectiveness of external reference pricing as listed prices are not the real price used in one particular country.[39]

Adjusted cost-effectiveness threshold.

Innovative anticancer drugs are high-cost which mostly rendered them as not cost-effective under many countries' willingness to pay. However, sometimes payers cannot turn down the decision to cover for cost-ineffective anticancer drugs because of public pressures. The alternative way to fund these drugs is to adjust the cost-effectiveness threshold to be higher for certain circumstances. The higher cost-effectiveness threshold straightforwardly increases acceptance of high-cost anticancer drugs given the higher chances of these drugs being cost-effective. Adjusted cost-effectiveness threshold was found in 5/178 countries (2.81%) which are high-income countries (5/55, 9.09%).

In Australia, the Pharmaceutical Benefits Advisory Committee could recommend reimbursement of high-cost anticancer drugs by employing the "rule of rescue". The criteria include severe and progressive diseases, small number of patients and no alternative treatment options available.[35] In Korea, a higher cost-effectiveness threshold can be applied for the reimbursement of high-cost anticancer drugs considering disease severity and societal values and impacts of the innovative drugs.[37] In the Netherlands, cost-effectiveness threshold was ranged between €20,000 and €80, 000 depending on disease severity and medical need. Thus, anticancer drugs could be reimbursed when higher cost-effectiveness threshold was used.[120]

Lastly, Sweden adjusts cost-effectiveness threshold according to disease severity which therefore adjusts for anticancer drugs.[120]

In the United Kingdom, End-of-life criteria were created specifically to fund life-prolonging drugs to treat diseases with short life expectancy. In 2009, NICE in England introduced End-of-life criteria which allowed ICER of drugs beyond cost-effectiveness threshold of £30,000. The criteria included 1) drug indicated in diseases with life expectancy less than 24 months, 2) drug with benefits of extend life additionally by at least 3 months, and 3) drug used in small population not exceeding a cumulative total of 7,000 for all licensed indications in England. Later, in April 2016, the third criterion was removed. Therefore, End-of-life criteria is now not exclusive to a small number of populations. In Scotland, the Scottish Medicines Consortium also created End-of-life criteria for drugs treating diseases which normally lead to death within 3 years along with Rarity criteria for orphan drugs. The End-of-life criteria in both England and Scotland leads to higher proportion of anticancer drugs approved for reimbursement.[153]

Adjusted cost-effectiveness threshold is relatively specific to anticancer drugs given that many countries consider disease severity and societal values when making reimbursement decisions which mostly adjust for cancers. However, most countries did not explicitly state the extent of cost-effectiveness threshold adjustments.

Orphan drugs.

Orphan drugs defined as drugs treating rare diseases affecting small number of populations with definite numbers varied from country to country. Many countries adjusted cost-effectiveness threshold for drugs treating rare disease which often applied to cancers. This was one of the mechanisms to incentivize research and development of drugs treating rare diseases. In order to increase access to orphan drugs for cancers, some countries adjust cost-effectiveness threshold to facilitate reimbursement decision or provide full coverage without copayments.[30, 153] Policies and programs related to orphan drugs were found in 5/178 countries (2.81%) which are high-income countries (5/55, 9.09%).

In France, orphan drugs in life-threatening diseases without alternative treatment options are 100% funded under the List of Long-term Afflictions.[30] In the Netherlands,100% reimbursement is provided for drugs receiving orphan status.[111] In Scotland, the Scottish

Medicines Consortium created Rarity criteria which accepted higher cost-effectiveness threshold for orphan drugs (affecting fewer than 2,500 patients per 5 million population) and ultra-orphan drugs (prevalence of 1 in 50,000 or less).[153] In South Korea, orphan drugs are exempted from conducting cost-effectiveness analyses.[37] In Australia, Life Saving Drugs Program was established to reconsider reimbursement of cost-ineffective drugs treating rare and life-threatening diseases. Under this program, drugs are fully covered for eligible patients.[30] However, these criteria were not specifically established for cancers, but most of the time, anticancer drugs would be eligible.

Dedicated funds for anticancer drugs.

Dedicated funds are established for anticancer drugs given the societal priority of cancers over other diseases. Dedicated funds include special national funding for anticancer drugs, additional payments for high-cost drugs, or special programs providing access to drugs awaiting reimbursement decision. Dedicated funds for anticancer drugs were found to be implemented in 14/178 countries (7.87%) and comprised of 13/55 high-income countries (23.64%) and 1/49 upper middle-income countries (2.04%).

In Australia, under public pressure, the government decided to cover trastuzumab for late-stage metastatic breast cancer in spite of three rejections from the Pharmaceutical Benefit Advisory Committee (PBAC) after that the Highly Specialized Drugs Program was established to provide funds for several anticancer drugs.[15, 33] Dedicated funds for anticancer drugs also exist in Hongkong, Canada, Denmark, France, and Poland.[15, 113]

In Belgium, France, the Netherlands, and Sweden dedicated funds exist to provide additional payments for high-cost drugs to hospitals to facilitate access in practice.[111, 120] In Thailand, an prior authorization program, called E2 access program was established under Thai National List of Essential Medicines, to provide retrospective reimbursement as drug products to the hospitals.[119] In New Zealand, the Managed Access Programs provide patient access to drugs awaiting reimbursement approval.[92] Lastly, In England, the government established the Cancer Drugs Fund (CDF) with £200 million budget in April 2011 to provide coverage for anticancer drugs for patients who otherwise will not be able to access to these drugs. Anticancer drugs under CDF are those receiving negative recommendation from NICE or in-process of reimbursement approval.[15] The CDF was estimated to cover more than 5,000 patients with 45 cancer indications.[71] However, due to uncontrolled increased budgets of the CDF, the CDF was

integrated to NICE appraisal program in April 2016. Drugs under CDF will be provided coverage for two years while further evidences are collected. Thus, CDF changed to coverage with evidence development program with the chances of being delisted if further evidences show no additional benefits or unresolved uncertainties.[53]

Flexibility of patent law

Compulsory licensing.

The World Trade Organization (WTO) Trade-Related Aspects of Intellectual Rights agreement (TRIPs) allows any country with public urgent need to issue a compulsory license without consent from patent holder to produce a generic drug. Also, the Doha Declaration allows countries without competency of producing its own generic drug to import from other countries. Before issuing a compulsory licensing, government may request a voluntary licensing from pharmaceutical manufacturer.[1] Compulsory licenses for anticancer drugs were issued in India and Thailand.[20, 119] In Thailand, government issued compulsory licenses for three anticancer drugs (docetaxel, letrozole and erlotinib) in 2008 to purchase generic drugs from India which resulted in cost saving of more than USD 140 million over 5 years.[20, 119] Also, the Indian government issued compulsory license to locally manufacture sorafenib.[5] Compulsory licensing significantly increases patient access to high-cost drugs. Even if it is not issued, compulsory licensing can be used as negotiating tool to lower drug price, as seen in Colombia.[5]

Assistance program

Patient Assistance Programs.

Pharmaceutical companies have developed Patient Assistance Programs to increase patient access to companies' drugs including anticancer drugs. The programs donate drugs to eligible patients free of charge.[140] The most successful patient assistance program is the Glivec International Patient Assistance Program (GIPAP). GIPAP is the international patient assistance program supported by Novartis to provide imatinib (Glivec) for chronic myelogenous leukemia and gastrointestinal stromal tumors in developing countries. Physicians had to be qualified to join the program. Also, patients had to meet eligibility criteria including income screening. In 2005, GIPAP had provided access to 14,500 patients in 81 countries who were otherwise unable to access to imatinib.[4] Another form of patient assistance program was found in Thailand. Pharmaceutical companies provided special marketing arrangements to lower drug costs by offering promotional indirect discounts, for example, "buy 3 and get 1 free", for self-paying patients. These arrangements reduced out-of-pocket payments for self-paying patients along with masking the real net price within the country.[119]

Assistance foundations.

Apart from all the policies and programs mentioned above, patients may be provided access to affordable high-cost anticancer drugs through assistance foundations or charities. A charity called the Hong Kong Anti-Cancer Society is established to assist patients who need financial support by giving cash subsidies and obtaining free drugs from pharmaceutical companies.[16] In the United States, patient foundations, such as the Patient Access Network Foundation, the Chronic Disease Fund, and the Leukemia & Lymphoma Society provide financial support to Medicare patients. However, not every patient got financial support, as each foundation has its own eligibility criteria, eligible drugs, diseases and limited budget.[89, 92]

4.2 RESULTS FROM QUALITATIVE IN-DEPTH INTERVIEW (STUDY OBJECTIVE II)

Interviews were conducted between July 2018 and November 2018 with 9 informants in Thailand, including 5 health care professionals, 3 representatives from pharmaceutical companies, and 1 representative from patient advocacy group. There were 6 key themes which emerged from the analysis. These themes were synthesized by patient access to high-cost anticancer drugs under different programs and drug formularies as shown in **Table 8.** Access to high-cost anticancer drugs is summarized below with translated quotes from interviewees.

Table 8 Access to high-cost anticancer drugs across three health benefit schemes in Thailand

High-cost anticancer drugs	Universal Coverage Scheme	Social Security Scheme	Civil Servant Medical Benefit Scheme
National List of Essential Medicines drugs (NLEM)			
E2 access program	Full coverage (Prior authorization)	Full coverage (Prior authorization)	Full coverage
Non-National List of Essential Medicines drugs (Non-NLEM)			
Oncology Prior Authorization (OCPA)	X	X	Prior authorization
Comptroller General's Department's (CGD) List of high-cost oncology and hematology drugs	X	X	Advanced payments
Anticancer drugs neither listed on OCPA nor CGD's List of high-cost oncology and hematology drugs *approved by Thai FDA before January 1, 2018*	X	X	Prescribing criteria for Non-NLEM
Anticancer drugs neither listed on OCPA nor CGD's List of high-cost oncology and hematology drugs *approved by Thai FDA after January 1, 2018*	X	X	X
Patient Access Programs (PAP)	Only self-paying patients	Only self-paying patients	Only self-paying patients

National List of Essential Medicines

E2 access program

Patients under Universal Coverage Scheme (UC), Social Security Scheme (SSS), and Civil Servant Medical Benefit Scheme (CSMBS) can indifferently access to high-cost anticancer drugs in E2 access program under Thai NLEM. E2 access program provides full coverage for high-cost drugs prescribed by qualified physicians for patients who meet prior authorization requirements. One interviewee pointed out:

"More patients can access (to high-cost anticancer drugs) since the NHSO listed them (high-cost anticancer drugs) to the E2 access program. However, in the past, these drugs could not be prescribed at all."

This program has a special feature that the procurement of these high-cost anticancer drugs is under responsibility of the Government Pharmaceutical Organization (GPO), a state enterprise which manufactures generic drugs for public hospitals. GPO centrally procures high-cost anticancer drugs for the National Health Security Office (NHSO), payer of UC patients and the Social Security Office (SSI), payer of SSS patients and distributes to hospitals using its Vendor Managed Inventory (VMI) system. Drugs are separately distributed for UC patients and SSI patients through GPO, given the fact that each payer has different timeline for healthcare financing. For CSMBS patients, hospitals can directly purchase E2 access program drugs from pharmaceutical companies and get financial reimbursement from the CSMBS payer, the Comptroller General's Department (CGD). Also, if anticancer drug indications are both covered by E2 access program and OCPA, OCPA will be used for CSMBS patients.

In practice, hospitals with few cases have to wait for prior authorization process which takes just several days. In contrast, tertiary hospitals are allowed to stock high-cost drugs in E2 access program for their patients in case of drug shortage. Hospitals record the number of drugs used and send data to payers for reimbursement. After that, payers will reimburse high-cost anticancer drugs as return drug products to the hospitals through distribution by GPO. As a result, the process is not prior authorization as the name suggests. Pharmacists can dispense high-cost anticancer drugs to patients as soon as the criteria are met. Auditors from payers will audit the documents retrospectively and if some criteria are not met, hospitals have to return drug products to the payers. One interviewee explained:

"No, no, it is not prior authorization. They (payers) will audit retrospectively. When the data are sent into the database, they consider that as approved. However, if they audit and find that some criteria are not met, hospitals have to return drug products to the payers because payers reimbursed hospitals as drug products."

In case of targeted cancer therapies which require special tests, some pharmaceutical companies might offer coverage of test costs in exchange for no further drug price discounts. The pharmaceutical companies might use third-party laboratories or set in-house laboratory for university hospitals which would have a lot of cases.

For anticancer drugs in E2 access program with generic brands in the market, patients will get generic brands instead of original brand, because the procurement regulations in Thailand only allow hospitals to procure drugs with price under the Median Price – a price calculated from procurement prices in many hospitals. As a result, anticancer drugs with generic brands in E2 access program are no longer expensive.

Patients can indifferently access to high-cost anticancer drugs in NLEM, although the reimbursement decision process is long. The NLEM will open for submission every three years. Therefore, access to innovative high-cost anticancer drugs will be delayed for years or a decade. Also, innovative anticancer drugs are less likely to be listed to the NLEM. One interviewee pointed out:

"If we talk about the NLEM, we usually think about drugs which are sold for more than 5 years or drugs with incoming generic version or existing generic versions. These drugs are those with the higher chance of listing to the NLEM. Compared to the innovative drugs, launched this year. It is very hard for these to get into the NLEM, because they need to be in the market for a while and their prices are still high"

Non-National List of Essential Medicines

Patients who need high-cost anticancer drugs which are not listed to the NLEM may not be provided access. For UC and SSS patients, most of the time, they are covered only for the use of NLEM drugs. It was ensured by many interviewees that UC and SSS patients have indifferent access to high-cost anticancer drugs. If drugs are NLEM, they can access; if not, they have to pay out-of-pocket. The following are summaries of alternative pathways for patients to access to high-cost anticancer drugs which are not NLEM drugs.

Oncology Prior Authorization (OCPA)

CSMBS patients can access to high-cost anticancer drugs provided in the Oncology prior authorization (OCPA) which mostly includes indications not listed in the NLEM. Because most of OCPA drugs are non-NLEM, UC and SSS patients are not covered and have to pay out-of-pocket.

Patients have to be registered to online database. In the program, physicians have to complete prescribing criteria for OCPA drugs and wait for approval from the CGD. CGD guarantees approval time within 5 working days. The approval has to be renewed every 3 months. Therefore, physicians have to strictly monitor patients as required by the prescribing criteria.

OCPA has been inactive for more than a decade until 2018, when CGD started to modify the list of anticancer drugs in OCPA. The CGD will further list more anticancer drugs into OCPA. At first, the drug selection process was mainly based on price. For example, there are three targeted therapies for lung cancer that the CGD considered as interchangeable, so the CGD asked the pharmaceutical companies to lower drug price then choose only one drug with the lowest price into OCPA. This price negotiation strategy cut down not only the price of the winning drug, but also the competing drugs as well. The prices were lowered substantially by 70%. The lowered prices also benefit self-paying patients.

However, the "choose one drug only" strategy not only limits patient access to the competing drugs which are not chosen, also there will be problems especially in the occurrence of adverse events when using the chosen drug. One interviewee said:

"There might be patients who experienced adverse event of this (chosen) drug. They have to change (to use another drug). Therefore, if they (payers) mainly decide only on prices. They will be only one choice, which limits access .... and practice. This is all or none"

Comptroller General's Department's (CGD) List of high-cost oncology and hematology drugs

In 2018, the CGD announced a list of high-cost oncology and hematology drugs which comprised of 41 drugs. All of these drugs are non-NLEM. Therefore, UC and SSS patients cannot access to these drugs unless they pay out-of-pocket. While CSMBS patients can access to these drugs on one condition that they have to pay the drug costs in advance and later get reimbursement from their original affiliations. However, the reimbursement is not guaranteed and physicians are more likely not to recommend and prescribe these drugs even if they might benefit the patients. One interviewee pointed out:

"The physicians dare not prescribe (these drugs), because they don't know whether patients who pay in advance will get reimbursement. The problem is, is like we push the (financial) burden to them (patients). If we let them pay in advance, maybe they will not get their money back. Therefore, the physicians are like, no no, we should not offer these drugs (to patients) even many of these drugs have good (clinical) evidences"

These drugs will gradually be included into OCPA from time to time with faster timelines, and more flexibility to include high-cost drugs compared to the NLEM process. In addition, not only price negotiations, but CGD starts to accept the idea of using Managed Entry Agreements as part of OCPA. One interviewee explained:

"Previously, the CGD do not, do not (use other pricing strategies). They just only consider the prices. For example, new drugs, we will look for the use of PAP (patient access program) to help calculate the average. However, the CGD do not only look for PAP, they also look for other things apart from free drugs, like capping. Which means that, okay, when patients achieved progression free survival (of one particular anticancer drugs) maybe 10 months. After that, it will be about sharing risk between the CGD and the pharmaceutical companies. If patients survived the PFS, the companies will pay for everything (after that)."

Anticancer drugs neither listed on OCPA nor CGD's List of high-cost oncology and hematology drugs approved by Thai FDA before January 1, 2018

Apart from the NLEM, OCPA and CGD's list, there are still high-cost anticancer drugs which are not part of any drug formularies. For UC and SSS, these drugs are Non-NLEM, so access depends on patient out-of-pocket payments. However, for CSMBS patients, physicians can prescribe non-NLEM drugs under any criterion in the Prescribing criteria for non-NLEM drugs, A-E. The criteria include A) Adverse events or hypersensitivity reaction from NLEM drugs, B) Treatment failure from NLEM drugs, C) Lack of NLEM drugs for patients, but drug indications have to be approved by Thai Food and Drug Administration (FDA), D) Contraindication or Drug interactions to NLEM drugs and, E) NLEM drugs are more expensive. CSMBS patients can access to high-cost anticancer drugs under criteria A to E, which will be covered under fee-for-service payments from the CGD. One interviewee explained:

"This drug is not listed in the list (NLEM) yet, so they (physicians) cannot use. However, this drug is non-NLEM. The requirements for them to use (prescribe) are that they have to look at the requirements … only for CSMBS patients, about which is the approved indication, does it follow the guideline?"

CSMBS patients cannot access to every non-NLEM drug previously mentioned because the CGD has announced that the prescribing criteria for non-NLEM drugs applied only to those approved before January 1, 2018.

Anticancer drugs neither listed on OCPA nor CGD's List of high-cost oncology and hematology drugs approved by Thai FDA after January 1, 2018

Non-NLEM drugs not listed in OCPA or CGD's list approved by Thai FDA after January 1, 2018 will be absolutely not covered under fee-for-service payments for CSMBS patients. These drugs will gradually be incorporated into CGD's list or OCPA list later but process and criteria for listing are not publicly available. Also, as these drugs are non-NLEM, they are certainly not covered for UC and SSS patients.

Patient Access Programs (PAP)

Patient Access Programs (PAP) are established by the pharmaceutical companies to support self-paying cancer patients. PAP vary in design by drug indication and sometimes by patients' incomes. One drug may have many PAPs separately for each indication with further different pricing and design for different patients. Most PAP are designed with the use of "Buy X boxes get Y boxes free", as the pharmaceutical companies consider this as supporting the patients without lowering their drug prices. These PAP support self-paying patients who need non-NLEM drugs. One interviewee pointed out:

"In the point of view that, if the system, the government does not cover. It is good, in some parts, for the affordable self-paying patients. There are benefits for those who can afford to pay, instead of paying it all, there is one (pharmaceutical company) that helps them support the (financial) burden"

If the physicians consider using high-cost anticancer drugs with existing PAP, they will inform the patients about the design and drug costs. Once patients accept the recommendations and signed consent form, physician will register them into PAP. After that, third-party companies, hired by pharmaceutical companies, will contact patients because the pharmaceutical companies are prohibited to directly contact with patients. Third-party will distribute free drugs to the hospitals. After that pharmacists will also be responsible to check every visit whether this visit, patients receive free drugs or they pay out-of-pocket. The free drugs distributed to the hospital will be labeled as "Patient Access Program Drug" and sometimes labeled with patient name and these drugs will not be entered the hospital stock and inventory system. These PAPs place burden on health care providers. One interviewee explained:

"It is a burden to the hospital. If it, if it is possible. (pharmaceutical companies should) discount them all (high-cost drugs with PAP) and after that they can enter the hospital (stock and inventory) system."

The pharmaceutical companies are trying to make PAP simpler. For example, one PAP for one drug. This will reduce burden to the healthcare professionals as they will not have to deal with various designs of PAP.

CHAPTER V
DISCUSSION

5.1 DISCUSSION OF SYSTEMATIC REVIEW OF LITERATURE (STUDY OBJECTIVE I)

This review reports the systematic literature review of health policies and programs implemented in 178 countries to facilitate access to high-cost anticancer drugs in the last two decades. Most studies were done in high-income countries.

In low-income countries, access to high-cost anticancer drugs was mainly facilitated by list of essential medicines and pharmaceutical companies-sponsored PAPs. These low-income countries still relatively lack proper healthcare infrastructure and reimbursement decision process. The governments or payers decide to reimburse anticancer drugs based on the WHO model list. However, low-income countries can afford less than half of essential anticancer drugs. One of the strategies for patient to access to high-cost anticancer drugs is pharmaceutical companies-sponsored PAPs. The GIPAP allowed thousands of patients in LMICs to access to high-cost anticancer drugs, namely imatinib, which would otherwise be impossible for patients to afford.[4] PAPs for anticancer drugs are increasing. The Max foundation, a non-profit global health organization in collaboration with multinational pharmaceutical companies, major cancer institutions, and patient associations in LMICs, is established to deliver life-saving anticancer drugs with no costs to patients in LMICs. From January 2017 to December 2018, the Max foundation has delivered more than 4 million doses of anticancer drugs for 15,074 patients in 72 countries.[154] The collaboration of Max foundation with local healthcare provider and patient association makes PAPs more sustainable within each country health system. In middle-income countries with proper healthcare infrastructure and reimbursement decision process, the national reimbursement decision made by responsible organizations are more structured and evidence-based. In some upper middle-income countries, alternative funding models for high-cost anticancer drugs especially MEAs, are being implemented to deal with uncertainties and the risk among payers and industries. In high-income countries, various strategies are being implemented especially alternative funding models for high-cost drugs, however, these strategies might prioritize cancer among other diseases given the societal values.

Payers from all over the world face challenges in making reimbursement decision especially for high-cost anticancer drugs given they are not able to cover every single anticancer

drug launched into the market. These drugs have changed treatment paradigm from a well-defined number of cycles of therapy to lifelong which resulted in increased budgetary constraint.[61] National reimbursement decision is the fundamental step to enable patient access to high-cost anticancer drugs as these drugs are far beyond patients' affordability. Data limitations are common for innovative oncology drugs as registration trials are designed to show evidences of efficacy, mostly surrogate endpoints, which normally are not informative to decision-makers.[63] HTA is used in many countries to assess for value for money using various factors determining reimbursement including cost-effectiveness. Cost-effectiveness analyses facilitate access to drugs that prove value for money under country's willingness to pay threshold or the cost-effectiveness threshold. However, the threshold also limits patient access to anticancer drugs at the same time if they are not cost-effective. To deal with uncertainties and cost-ineffectiveness from anticancer drugs, various alternative funding models were utilized including Managed Entry Agreements, adjusted cost-effectiveness threshold, End-of-life criteria, orphan drug reimbursement, and dedicated funds for anticancer drugs. However, most of these strategies were not established specifically for anticancer drugs, but the nature of anticancer drugs such as rarity, progressiveness, lack of alternative treatment options and societal values eventually made them applicable for alternative funding models.

This review has some limitations. First, the systematic literature review included only covered studies published in peer-reviewed journals in English language and grey literature search was not performed. Publications might be published in other languages and sources. Incomplete data was expected to exist. However, this review process was to ensure the academic level of evidences through peer review process. A global survey with key informants in each country is needed to capture the complete set of policies and programs, both publicly available and unavailable, which are being implemented to facilitate access to high-cost anticancer drugs. Second, review was limited to anticancer drugs only, although in many circumstances policies and programs were not specifically designed and implemented for anticancer drugs. Therefore, the broader scope of review in high-cost drugs of every therapeutic area could be done in the future. Also, this review was unable to summarize impacts of utilized policies and programs on access to anticancer drugs as the studies were varied and specific to the context of individual country health systems. A systematic review of literature with narrow scope to specific policies or programs is needed to synthesize the impacts, both desirable and undesirable.

5.2 DISCUSSION OF QUALITATIVE IN-DEPTH INTERVIEW (STUDY OBJECTIVE II)

The in-depth interview reports the implementation of health policies and programs facilitating access to high-cost anticancer drugs in practice. This study did not seek to describe interviewees' perceptions of patient access to high-cost drugs.

Patients under different health benefit schemes access to anticancer drugs differently. For UC and SSS patients, they can access to these drugs under the NLEM, especially E2 access program, which was established specifically for high-cost drugs. Only eligible patients receive treatment under internal prior authorization process of each hospital. Drugs in E2 access program are centrally procured by the GPO which could further lower the price given their purchasing power. However, patients may not timely access to high-cost anticancer drugs. These innovative anticancer drugs are less likely to be listed to the NLEM, given their high-cost. This is not surprising because budget constraints are a problem in every country. Payers cannot afford to pay for every high-cost anticancer drug. They have to consider the reimbursement decisions thoroughly while balancing the patient access to high-cost anticancer drugs and sustainability of the health system. For CSMBS patients, alternative pathways exist to access some high-cost anticancer drugs. These include OCPA and CGD's list of high-cost oncology and hematology drugs. Access to OCPA drugs are more reassuring with clear criteria and process while access to drugs in the CGD's list are not certain as patients have to pay drug costs in advance and may or may not get reimbursement from their original affiliations.

Patient Access Programs play important role in providing support to the self-paying patients. However, various designs of PAP especially many PAPs for one drug place burden to the healthcare providers. Thus, the pharmaceutical companies are trying to simplify PAP by offering one PAP for one drug. In the future, the use of MEA will be incorporated into the OCPA listing process. MEA is more likely to be applicable for OCPA, because of strict prior authorization and monitoring program given that the approval lasts only 3 months. The OCPA program can set the prior authorization process and monitoring program according to the agreements between the pharmaceutical companies and the CGD. Thus, uncertainties and risks are shared among them. Finally, if MEA are successful for OCPA in the future, this might be applied for the NLEM as well.

The study results comply with the findings from quantitative study by Hirunrassamee, et al., which found that the percentage of patients receiving new drugs for lung cancer was significantly different among three health benefit schemes during 2003 to 2005. CSMBS patients

(67%) were more likely to receive new drugs compared with UC scheme (19%) and SSS patients (10%).[122] Also, this study was consistent with results from Sruamsiri, et al.,[119] that the implementation of multiple interventions, including E2 access program, compulsory licensing, price negotiation and PAP, increased the number of patients treated with letrozole, imatinib and trastuzumab, which are high-cost anticancer drugs.

This study has 2 major limitations. First, the payers from three funds (NHSO, SSO and CGD) were not interviewed. The aspects of access to high-cost anticancer drugs in the payers' perspective were not captured, for example, the rationale behind reimbursement decisions and reimbursement processes. However, the aim of this study was to investigate how the current situation of patient access to high-cost anticancer drugs, interview with health care professionals, pharmaceutical companies and patient advocacy groups could show the patient access to these drugs under the implementation of health policies and programs across 3 health benefit schemes. Second, healthcare providers were limited only to those who work in the tertiary hospitals. The patient access to high-cost anticancer drugs in the primary and secondary hospitals were not fully captured. However, most cancer patients who need access to high-cost anticancer drugs are treated in the tertiary hospitals, given the fact that the medical oncologists and other related specialists are working there.

CHAPTER VI

CONCLUSION AND RECOMMENDATION

6.1 CONCLUSION

Access to high-cost anticancer drugs mainly depends on each individual country's pricing and reimbursement policies as the costs of these drugs are beyond patients' affordability. Low- and middle-income countries mainly facilitate patient access through the list of essential medicines and pharmaceutical industry-initiated patient assistance programs, but still they struggle to make all the essential anticancer drugs available for their population. In contrast, high-income countries utilized alternative funding models for high-cost anticancer drugs to overcome uncertainties and relatively poor cost-effectiveness of these drugs. Finally, all of these policies and programs need to be complimentarily implemented by various stakeholders with the aim to increase patient access to high-cost anticancer drugs.

In Thailand, access to high-cost anticancer drugs across three health benefit schemes are different. Patients under 3 health benefit schemes can indifferently access with full coverage for high-cost anticancer drugs in the NLEM, specifically under the E2 access program. Apart from that, UC and SSS patients have to pay out-of-pocket. While CSMBS patients still have alternative pathways to obtain these drugs, like OCPA. However, OCPA is limited by the number of reimbursed drugs in the list as well as strict prior authorization process. PAP also plays a major role in supporting self-paying patients, but they have to be simpler in order to reduce burdens to the healthcare professionals. The use of MEA was found to be introduced to Thailand.

6.2 RECOMMENDATION – LESSONS LEARNED FOR THAILAND

From the results of the 2 objectives combined, there are several lessons learned for Thailand. Health system in Thailand, as a universal coverage health system, provides patients access to high-cost anticancer drugs mainly through the reimbursement decision to list drug into the National List of Essential Medicines, with the use of Health Technology Assessment to inform the decision makers. From the results of systematic review of literature, it was found that we are lacking the alternative funding models for high-cost anticancer drugs especially the use of Managed Entry Agreements (MEA). Because of the delay from the NLEM selection process, innovative anticancer drugs are less likely to be listed. If MEA are officially introduced into the

system, these drugs might be more likely to be adopted. MEA have 2 major types, the performance-based agreements and the financial-based agreements or mixed typed utilizing both designs. MEAs have different pros and cons which will be discussed below, in context of the Thai health system.

The performance-based agreements mainly share the risks of uncertainties from clinical evidences through data collection in individual patient level or population level. The individual patient level data collection might be better for Thai health system because population data collection level requires good IT facilities with good data collection to ensure the quality and validity of collected data. Performance-based agreements could be outcome guarantees (if treatment responses are not met, the pharmaceutical companies will pay for the drug costs), or conditional treatment continuation (only respondent patients continue to receive drugs). These agreements can be applied to Thailand. Healthcare professionals have to carefully monitor for patient responses and send information into the database for reimbursement. These agreements can limit the costs for the public payers, as they do not have to pay for non-responders. However, healthcare financing systems must be in place to support the implementation of MEA.

On the other hand, financial agreements mainly share uncertainties from financial impacts of drugs especially the budget impact to the public payers. Financial agreements can be as simple as simple discount (pharmaceutical companies offer simple discount to the payers), price-volume agreements (drug costs will be lowered if some specific volumes are exceeded), or utilization capping (number of patients are pre-specified, if there are more patients than in the agreements, pharmaceutical companies pay the rest) or budget capping (budget for an anticancer drug is pre-specified, money exceeding this budget are paid by the pharmaceutical companies). The financial agreements tend to look more applicable for Thailand, as some designs require less management. Simple discount might not be the best choice for financial-based agreements in Thailand. Normally pharmaceutical companies will accept this design on one condition that the discounts remain confidential. Therefore, Thailand needs some system to mask the price to promote the use of this design, which might not be applicable. Therefore, utilization capping and budget capping are more applicable as these designs help public payers control their budgets. However, Thailand needs good IT facilities to monitor the utilization and budget and financial channel when pharmaceutical companies have to pay for drug costs.

In conclusion, the results suggest that MEA will be the most applicable choice for Thai health system to adopt in the future to further facilitate patients in need to access to high-cost anticancer drugs while some uncertainties and risks are shared with the pharmaceutical companies. To achieve this, data collection systems are needed.

APPENDIX

FULL SEARCH STRATEGY WITH RESULTS

PubMed: October 8, 2018

	Search terms	Hits
#1	Search (Policy[Mesh]) OR (Program OR Programs OR Programme OR Programmes)	1,245,017
#2	Search (Access OR Accessibility)	355,439
#3	Search Antineoplastic Agents[Mesh]	381,734
#4	Search (Neoplasm[Mesh]) AND Molecular Targeted Therapy[Mesh]	15,218
#5	Search (Antineoplastic Agents[Mesh]) OR ((Neoplasm[Mesh]) AND Molecular Targeted Therapy[Mesh])	389,349
#6	Search ((((Policy[Mesh]) OR (Program OR Programs OR Programme OR Programmes))) AND ((Access OR Accessibility))) AND ((Antineoplastic Agents[Mesh]) OR ((Neoplasm[Mesh]) AND Molecular Targeted Therapy[Mesh]))	415
#7	Search (((((Policy[Mesh]) OR (Program OR Programs OR Programme OR Programmes))) AND ((Access OR Accessibility))) AND ((Antineoplastic Agents[Mesh]) OR ((Neoplasm[Mesh]) AND Molecular Targeted Therapy[Mesh]))) Filters: Publication date from 2000/01/01; Humans; English	368

EMBASE: October 11, 2018

	Search terms	Hits
#1	policy OR policies OR program OR programs OR programme OR programmes	1,245,017
#2	access OR accessibility	355,439
#3	'antineoplastic agent' OR 'molecularly targeted therapy'	381,734
#4	#1 AND #2 AND #3	15,218
#5	#4 AND (2000:py OR 2001:py OR 2002:py OR 2003:py OR 2004:py OR 2005:py OR 2006:py OR 2007:py OR 2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py OR 2016:py OR 2017:py OR 2018:py)	389,349

Web of Science: October 8, 2018

	Search terms	Hits
#1	TS=(Polic* OR Program*)	1,791,373
#2	TS=(Access OR Accessibility)	551,124
#3	TOPIC: (anticancer drugs)	57,431
#4	TS=(Cancer AND (Drugs OR Medications OR Pharmaceuticals))	233,059
#5	TS=(Antineoplastic agents OR Antineoplastic drugs OR Anticancer drugs OR Anti-cancer drugs)	77,670
#6	#5 OR #4	255,532
#7	TS=((Cancer OR Oncolog*) AND (Drugs OR Medications OR Pharmaceuticals))	237,622
#8	TS=(Drugs OR Medications OR Medicines OR Agents OR Pharmaceuticals)	2,802,693
#9	TS=(Cancer OR Oncolog* OR Hematolog* OR Haematolog* OR Neoplasm)	2,215,431
#10	#9 AND #8	402,693
#11	#10 AND #2 AND #1	1,119
#12	(#1 AND #2 AND #10) AND LANGUAGE: (English)	1,076
#13	(#1 AND #2 AND #10) AND LANGUAGE: (English); Timespan=2000-2018	1,031

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