Improving Decision-Making for Drug Reimbursement in Iran

Amir Ansaripour

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Verbeteren van besluitvorming voor vergoeding van geneesmiddelen in Iran

Thesis

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Human beings are members of a whole,

In creation of one essence and soul.

If one member is afflicted with pain,

Other members uneasy will remain.

If you have no sympathy for human pain,

The name of human you cannot retain.

Saadi Shirazi (1193-1291), Gulistan (The Rose Garden)
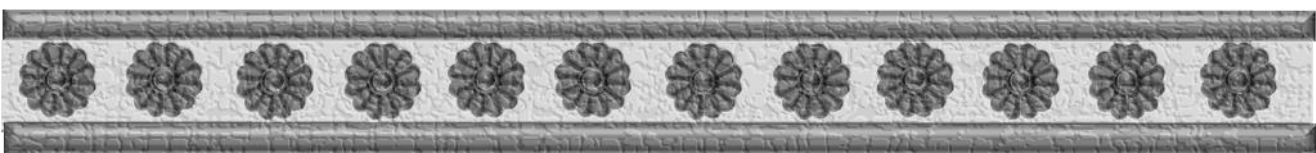*(Book-1258), Chapter 1, story 10*
Translator: Arianpour

To:

Insurees of the Social Security Organization in Iran
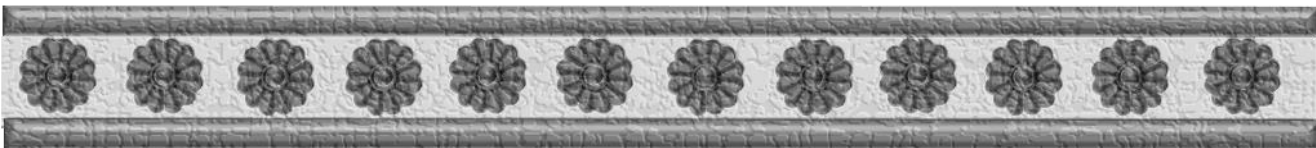
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Chapter 1

Introduction

1

Decision making in a healthcare system

Decision making in any healthcare system potentially has both immediate and long-term impacts on public health outcomes, patient quality of life, and healthcare budgets. It is an important process that helps policymakers choose appropriate new healthcare programs, interventions, or services by guiding them to consider the available resources in order to achieve the objectives of good healthcare governance. Reimbursement decision making is an outstanding example of governance in a healthcare system as it plays an essential role in the efficient allocation of resources.

Reimbursement decision making

The main objective of decisions regarding reimbursement (insurance coverage) of new health technologies is to provide patient access to various healthcare services in an affordable manner. There are a wide variety of policies throughout the world for reimbursement of services in a healthcare system. It would not be a far-fetched assumption to say that in all of these policy frameworks, the decision makers inherently would like to provide the best patient access along with affordable healthcare services. However, the final outcomes of different decisions cannot always be exactly what the policymakers had expected to achieve due to uncertainties about the decisions that were made.[1] Positive or negative consequences of reimbursement decision making are derived from the level of uncertainties that policymakers are facing in decision making based on their initial knowledge.

Health technology assessment (HTA) techniques are widely used in high-income countries (HICs) in order to improve predictability and reduce the uncertainties in reimbursement decision making. HTA helps policymakers make a more reliable decision by providing different types of studies such as:

- **Cost-effectiveness** studies to assess health gains relative to the costs of different health interventions.[2]
- **Budget impact** studies to estimate the financial consequences of approving a new intervention.[3]
- **Health equity** studies to investigate the unfair and preventable or remediable disparities in health services and outcomes among groups of people.[4]
- **Burden of disease** studies to measure population morbidity and mortality.[5]
- **Evidence-based medicine** studies to improve decisions by individual doctors about individual patients.[6]

One important aspect of the knowledge based decision making is the cost-effectiveness of a new technology compared to the current routine practice [2]. In fact, a cost-effectiveness analysis (CEA) is the core of an HTA study. In one outer layer of this core,

different types of knowledge such as budget impact, burden of disease, and equity analyses are included. These all help policymakers estimate the necessary financial resources and set priorities for new interventions. Subsequently, in an ideal situation, this knowledge should be applied in a framework called a multiple criteria decision analysis (MCDA) to make a reimbursement decision considering the relative importance of criteria obtained from the previously defined knowledge.[7] Conducting systematic approach for reimbursement decision making is expected to mostly result in better consequences corresponding with the goals of decision making.

Overall goals of a reimbursement decision-making system

The goals of a reimbursement decision-making system can be variously defined, depending on the differing perspectives of patients, healthcare professionals, and policymakers. What is clear is that the ultimate goals should include the rational expectations of all involved parties. However, there are always issues such as limited financial resources that cause decision making to be more complex. Actually, the art of decision making is a constant balancing act between various expectations and available resources. This means that proper reimbursement decision making happens when it can concurrently pursue these three main goals: [8]

1- **Quality of care**, focusing on patient centralization, reliability, accessibility, and safety.
2- **Population health**, applying proven interventions to address behavioral, social, and environmental determinants of health in addition to delivering higher quality care.
3- **Affordability of healthcare services**, reducing the cost of quality healthcare for patients, families, employers, and governments.

Therefore, the best decision is reached when decision making focuses on reaching all these three goals (Figure 1.1), and this is what is referred to as the art of decision making. In this case, changes made in the healthcare system are sustainable and all stakeholders will benefit from its advantages. In other cases, the outcomes of decision-making cannot cover all of the expectations of the different parties and, therefore, the sustainability of the decision would be under question. The fact is that goal setting is always easy, but achieving the goals requires information. In other words, policymakers need to have enough knowledge regarding the possible consequences of their decisions.
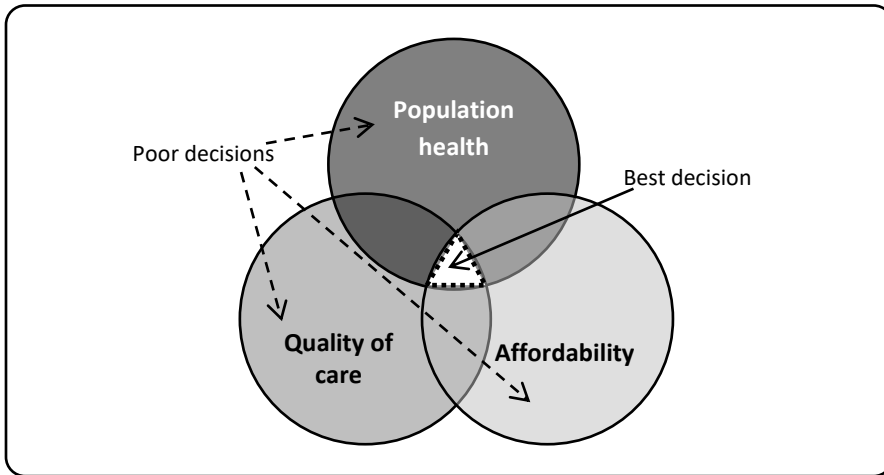
Figure 1.1: The main goals from a reimbursement decision-making system. Adapted from a report to the USA congress entitled "*The national strategy for quality improvement in healthcare*". [8]

Knowledge production for reimbursement decision making in middle-income countries

Various studies have shown that HTA-based decision-making systems are not coherently implemented in many middle-income countries (MICs), although HTA studies are increasing in these countries [9,10]. For example, a published study showed that despite the establishment of specific pharmacoeconomic agencies, the drug reimbursement decision-making procedures in Thailand, China, and South Korea face issues such as a low number of pharmacoeconomic researchers, lack of reliable information.[11] In fact, policymakers cannot make effective decisions due to limited evidence or poor quality research. For example, a review that assessed the quality of 24 economic evaluations of breast cancer control originating from low and middle-income countries reported that the majority of the studies were of poor quality, particularly in terms of examining costs. [12]

Reimbursement decision making in Iran

There is a very complex process in Iran to decide whether a technology should be reimbursed or not. The rationale behind this process is partly based on a healthcare law entitled *Iran Universal Health Insurance Coverage* adopted by the Iranian Parliament in 1994.[13] According to this regulation, the Iran Supreme Council of Health Insurance is responsible to assess new technologies that have been registered for reimbursement

decision making. The Iran Supreme Council of Health Insurance encourages applicants for reimbursement of a new technology to submit their application along with a CEA.

Drug reimbursement decision making in Iran

The drug reimbursement process in Iran can be described as a shared responsibility process, since the decision-making process is distributed between two ministries with different interests: the Ministry of Health and Medical Education and the Ministry of Welfare and Social Security. Ultimately, it is the Iranian Cabinet that approves a drug and recommends its use to all health insurance organizations. The details of the decision process will be explained in the second chapter; however, it is worth noting here that this structure causes some problems that affect the process of decision making. For example, new drugs are officially launched on the market before that the Iranian Cabinet make reimbursement decision. Patients have to pay the whole public price of non-reimbursement medications. The Ministry of Health, which is responsible for drug pricing, use the external reference pricing method for imported drugs that are mostly expensive [14]. None of performance-based and finance-based risk sharing agreements are not implemented and also price negotiation has not efficiently affected drug prices in Iran.

A case study on drug reimbursement decision making in Iran

This thesis is focused on the drug reimbursement decision-making system in Iran as an MIC. It also examines the use of trastuzumab in the treatment of breast cancer as a case study to investigate possible solutions for improving the current reimbursement decision-making process in Iran and other MICs with the same healthcare system.

Breast cancer

Breast cancer is the most frequent cancer in women worldwide with an estimated 1.67 million new cancer cases diagnosed in 2012 (25% of all cancers).[15,16] Breast cancer is increasing, particularly in MICs, where most cases are diagnosed in the late stages.[16] In MICs like Iran, this increased frequency will lead to greater dilemmas because of their more limited financial resources and the subsequent impact of breast cancer on the healthcare budget due to existence of effective but costly treatments. An additional reason to expect increasing numbers of breast cancer patients is the increased use of better diagnostic strategies.[17]

-   **An epidemiological perspective on breast cancer in Iran**

The most recent study showed that the age-standardized incidence rate of breast cancer per 100,000 people increased from 16 in 2003 to 28 in 2009 in Iran.[18] The

increasing breast cancer incidence rate has made it one of the most frequent malignancies among Iranian women.[19] Two other studies have shown that the mortality rate due to breast cancer is increasing among Iranian females. The age-standardized mortality rate of breast cancer per 100,000 people increased from 3.69 in 2003 to 4.92 in 2010 (Figure 1.2).[20,21]
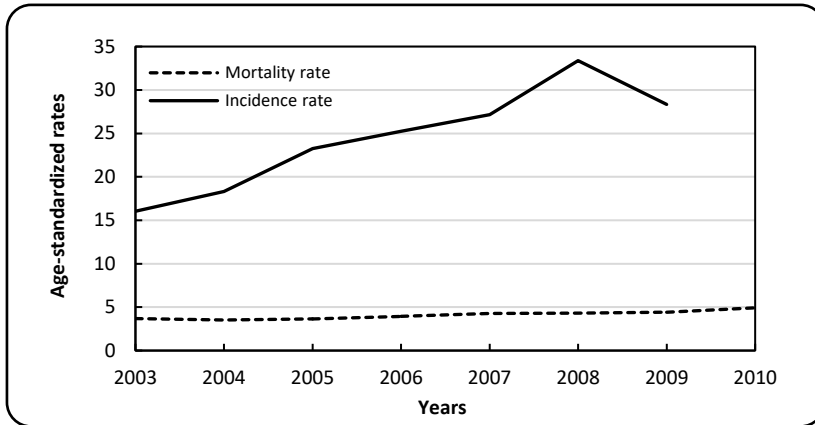
Figure 1.2: Age-standardized breast cancer mortality [18,19] and incidence [17] rates per 100,000 persons

- **An economic perspective on breast cancer in Iran**

To date, two studies have investigated the direct medical costs and economic burden of breast cancer in Iran. The first study studied the direct medical costs of breast cancer patients in one hospital in Isfahan and found that the costs of different therapies in 2010 per patient varied from $1,670 ($=USD) at stage I to $22,133 at stage IV.[22] In the second study, researchers reported the total economic burden of breast cancer in Iran as $947,374,468 in 2010.[23] According to the results of this study, a significant proportion of the cost of breast cancer (77%) was productivity loss due to the breast cancer mortality rate. The direct medical costs accounted for 19% of the total estimated costs.[23] Treatment of breast cancer is the most expensive therapy among the different types of cancer in Iran, due to the use of monoclonal antibodies. Based on the annual reports of Iran's Social Security Organization (SSO), a health insurer which covers approximately 50% of all Iranians (~40 million), trastuzumab (a monoclonal antibody) alone accounted for almost 20% of all chemotherapy costs in 2015.[24]

- Using monoclonal antibodies in breast cancer

Monoclonal antibodies have been established as one of the most successful therapeutic strategies for both hematologic malignancies and solid tumors in the last 25 years.[25] To date, 14 monoclonal antibodies have been approved by the U.S. Food and Drug

Administration and there are several more monoclonal antibodies in the late stages of clinical trials.[26] Trastuzumab (Herceptin®) is used widely in the treatment of overexpressed human epidermal growth factor receptor 2 (HER2-positive) breast cancer.[27] It is estimated that 25%–30% of patients suffering from breast cancer have HER2-positive breast cancer.[27] Various studies have investigated the safety and efficacy of trastuzumab.[28] As a consequence, trastuzumab is widely use in different stages of breast cancer in many countries. Different durations of trastuzumab use in the early stages of breast cancer were tested to address its safety and efficacy. These durations varied from 9 weeks [29] to 2 years [30]. However, the most common duration of trastuzumab use, which is also recommended in many clinical guidelines, is one year (52 weeks).[30] Subsequently, various studies were conducted to investigate the cost-effectiveness of trastuzumab. The results of these CEAs showed that this duration of trastuzumab is cost-effective in many HICs due to their high threshold of willingness to pay. [31,32]

Current recommendations of one-year trastuzumab use for HICs have a huge impact on the healthcare budgets in MICs. Therefore, as an expensive drug, trastuzumab has continued to be a topic of conversation in many healthcare systems since its launch into the pharmaceutical markets. Trastuzumab's huge share of total drug expenditure, particularly in MICs, has raised policymakers' concerns regarding efficient resource allocation in their countries.

The overall goals of a reimbursement decision-making system and current system in Iran

An overview of the consequences of the current reimbursement decision-making system in Iran shows that the process of decision making could not provide a pervasive improvement on the overall goals of a reimbursement decision-making system. In general, to understand the consequences of the current reimbursement decision making in Iran, it would be appropriate to look at the amounts of patient out-of-pocket payments, life expectancy, and disease-caused mortality rate as the indicators for affordability of healthcare services, population health, and quality of care respectively. According to data from the World Health Organization (WHO), the share of total health expenditure of Iran's GDP increased during past two decades.[33] Figure 1.3A shows that this rate of increase (184%) over 19 years (1995–2014) was much greater than the average growth rate of two groups of countries at the same socio-economic level, the
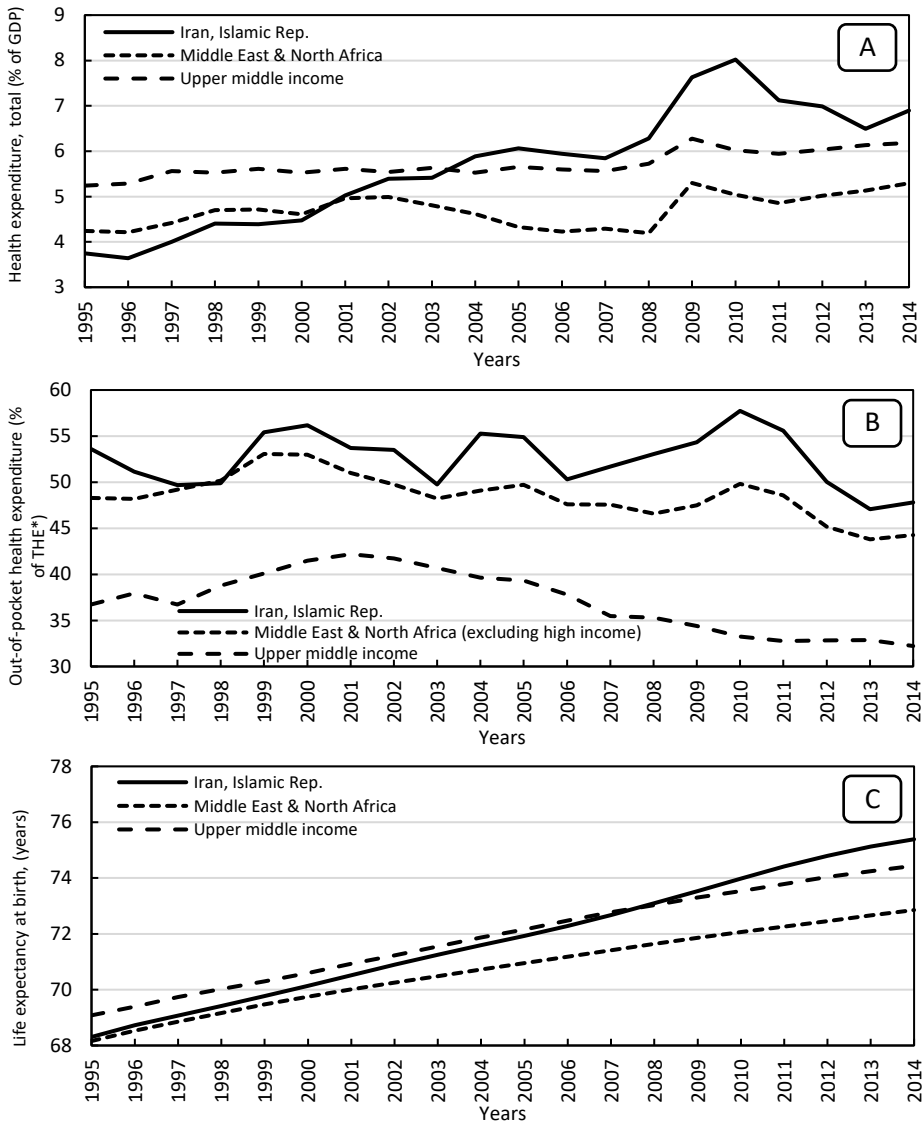
Figure 1.3: Iran's total health expenditure (% of GDP) **(A),** out-of-pocket health expenditure (% of total expenditure on health (THE) **(B),** and life expectancy at birth **(C)** compared with two groups of countries (Middle-East & North Africa and upper middle-income countries) 1995-2014.

(**Source**: The World Health Organization Global Health Expenditure database)

*Total health expenditure

Middle East and North Africa (125%), and upper middle-income countries (118%). This means that Iran spent a larger share of its GDP in the healthcare sector than other countries. This is, however, were not desirable. For example, it is expected that out-of-

pocket payments decline when total health expenditure growths. As Figure 1.3B shows, despite Iran's allocation of greater financial resources, their amount of out-of-pocket payment did not significantly change (R^2 = 0.024), while in upper middle-income countries, a slight increase in total health expenditure meant that out-of-pocket payment significantly declined (R^2 = 0.521).

On the other hand, as Figure 1.3C shows, more investment in the healthcare sector may causes an improvement in life expectancy at birth in Iran over the same time period. Iranian life expectancy at birth has significantly grown compared to the average life expectancy at birth in Middle East and North Africa (p=0.525). However, as Figure 1.2 shows, the mortality rate of breast cancer is increasing while the total health expenditure is also growing. Therefore, from the perspective of the overall goals, the current process has not successfully improved the affordability of healthcare services and quality of breast cancer care even though the overall population health has improved in Iran. This interpretation is compatible with a report from the World Bank that provides an explanation regarding Iranian healthcare sector [34]. It describes that Iran achieved a significant improvement in total population health and implemented a basic but strong primary health care system while some necessary restructuring across some key strategic interventions was necessary to improve efficiency and equity such as governance, patients access to healthcare services, and financing [34].

Consequently, a realization of the principle of concurrently improving the overall goals is likely unattainable within this current framework. As a matter of fact, the weakness in the knowledge production infrastructure may be one of the most important causes for this shortcoming of the current process.

Thesis aims and research questions

The overall aim of this thesis is to investigate how an MIC (in this case, focusing on Iran) can improve its drug reimbursement decision-making system. This thesis, therefore, tries to answer the following research questions for Iran considering the above mentioned content:

- What is the current structure of the drug reimbursement decision-making system, who are the key stakeholders, and what are the main issues regarding the current drug reimbursement decision-making system?
- How consistent are the national guidelines with the medical literature? And what do Iranian doctors do in daily practice with the recommendations found in the current national guideline for treating HER2-positive breast cancer?
- What are the possible solutions to overcoming the lack of patient registry data?

- What are the main real-world cost components of the treatment of HER2-positive breast cancer?
- What is the cost-effectiveness of trastuzumab in the treatment of early HER2-positive breast cancer? What is the optimal trastuzumab therapy in terms of duration of trastuzumab use?
- Can the transfer of economic evaluation results from HICs help policymakers in MICs to make better reimbursement decisions?
- Is external reference pricing a threat to internationally equal affordability and does it help MICs in terms of pharmaceutical pricing?
- What are the prerequisites for improving pharmaceutical pricing and reimbursement decision making to enhance the capacity of performance-based and finance-based risk-sharing arrangements?

Thesis outline

This thesis includes three parts and each of these provides an answer to one or more research questions.

In the first part (chapters 2 and 3), the current situation and subsequent consequences of the drug reimbursement decision-making system in Iran are discussed.

- Chapter 2 explains the current process of drug reimbursement decision making, introduces the key stakeholders, and investigates the strengths and weaknesses of this process. It also describes how the process is split between two ministries and why the process is time-consuming.

- Chapter 3 explains that the national guideline published by the Iranian Ministry of Health recommends a 9-week regimen for trastuzumab to treat HER2-positive breast cancer instead of the 52-week regimen currently recommended in many other countries. It investigates the degree of clinician adherence to this national guideline in Iran.

The second part focuses on knowledge production in MICs. As already mentioned, obtaining information is not an easy task in MICs and researchers have to find solutions to overcome this shortage of information. Therefore, this part provides some solutions for this problem. In addition, it describes some economic evaluations and a scenario analysis for efficient and affordable treatment. This part has three chapters (4–6).

- Chapter 4 provides a solution for MICs dealing with issues of obtaining real-world evidence of the cost-effectiveness of treatments. It is obvious that patient registries play an important role in this; however, implementation is costly and sometimes infeasible in many MICs. This chapter discusses how

patients can be classified into different stages of HER2-positive breast cancer in the absence of a comprehensive patient registry. Then, it would be possible to estimate the direct medical costs of HER2-positive breast cancer treatment in Iran. This study uses validated data-mining algorithms applied to a huge claims database from the Iran SSO.

- Chapter 5 provides a cost-effectiveness analysis from the Iranian healthcare perspective and investigates an optimal duration of trastuzumab use in Iran. It also explains why the implementation of clinical guidelines around the world, which have recommended a one-year trastuzumab regimen as standard care for early HER2-positive breast cancer, could have a remarkable impact on total drug expenditures in MICs if trastuzumab were to be reimbursed.

- Chapter 6 investigates the compatibility between the results of a model-based cost-effectiveness analysis in Iran with the transferred results of studies performed in some HICs. It provides some recommendations about how policymakers can use the results of these two methods for reimbursement decision making.

The third part provides recommendations to improve the system. It describes how MICs can benefit from HTA studies and knowledge production in order to achieve the overall goals of a reimbursement decision-making system. This part has two chapters, which are chapter 7 and 8.

- Chapter 7 investigates feasibility of internationally drug affordability and the importance of price differentiation in enhancing drug affordability and accessibility in MICs. Using prices of 10mg trastuzumab across 14 HICs and 5 MICs. The inability to purchase across countries were estimated in two different scenarios. This chapter also provides some recommendations to improve pricing systems in MICs.

- Chapter 8 examines the prerequisites for improving pharmaceutical pricing and reimbursement in Iran. Using an analysis of strengths, weaknesses, opportunities, and threats (SWOT), the current pharmaceutical pricing and reimbursement decision-making system in Iran is compared with the pharmaceutical governance and infrastructures in six reference countries (England, Germany, Hungary, Italy, Poland, and Turkey) that have implemented performance-based and finance-based risk-sharing policies. Subsequently, it provides recommendations for policymakers in Iran and other MICs who are considering the implementation of innovative pricing and reimbursement policies.

Finally, Chapter 9 presents a general discussion of the main findings of this thesis and provides policy recommendations for improvement of the current process of decision making in Iran. This chapter also explains the limitations faced while doing the research for this thesis.

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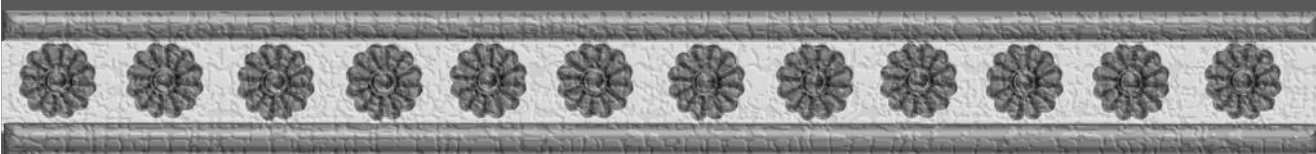
Part I

The current drug reimbursement decision-making system in Iran
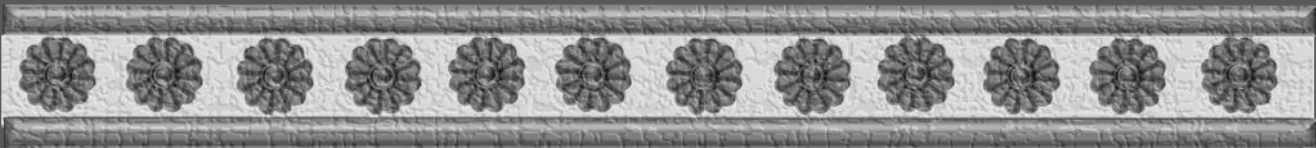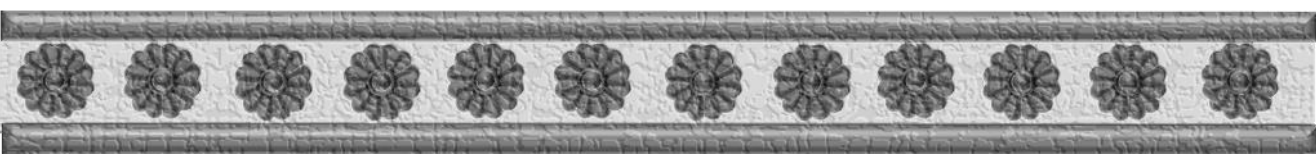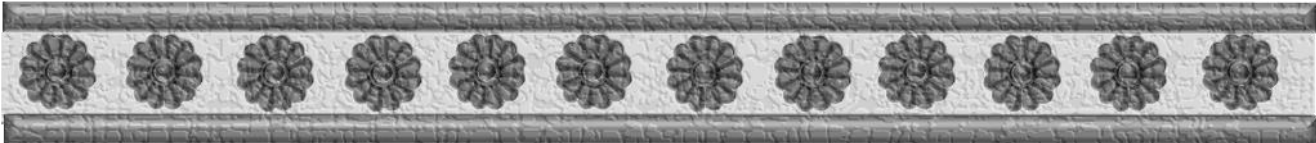
Chapter 2

The Drug Reimbursement Decision-Making System in Iran

Amir Ansaripour, Carin A. Uyl-de Groot, Adri Steenhoek, W. Ken Redekop

Abstract

Objective: Previous studies of health policies in Iran have not focused exclusively on the drug reimbursement process. The aim of this study is to describe the entire drug reimbursement process and the stakeholders, and discuss issues faced by policy makers.

Methods: Review of documents describing the administrative rules and directives of stakeholders, supplemented by published statistics and interviews with experts and policymakers.

Results: Iran has a systematic process for the assessment, appraisal and judgment of drug reimbursements. The two most important organizations in this process are the Food and Drug Organization, which considers clinical effectiveness, safety and economic issues, and the Supreme Council of Health Insurance, which considers various criteria, including budget impact and cost-effectiveness. Ultimately, the Iranian Cabinet approves a drug and recommends its use to all health insurance organizations. Reimbursed drugs account for about 53.5% of all available drugs and 77.3% of drug expenditures. Despite its strengths, the system faces various issues, including conflicting stakeholder aims, lengthy decision-making duration, limited access to decision-making details and rigidity in the assessment process.

Conclusion: The Iranian drug reimbursement system uses decision-making criteria and a structured approach similar to those in other countries. Important shortcomings in the system include out-of-pocket contributions due to lengthy decision-making, lack of transparency, and conflicting interests amongst stakeholders. Iranian policymakers should consider a number of ways to remedy these problems, such as case studies of individual drugs and closer examination of experiences in other countries.

2

Introduction

Expenditures in Iran on pharmaceuticals (inpatient and outpatient) accounted for more than 23% of all health care costs incurred by the Social Security Organization in 2011 (Social Security Organization, internal annual reports). Previous studies have shown that the Iranian pharmaceutical sector is complex and that the process of decision-making about drug reimbursement is complicated [35]. Beyhaghi and Basmenji concluded that the current system suffers from a lack of integration and clarity, and emphasized the need to implement a more transparent and consistent system [36]. Delgoshaei et al attempted to describe major problems in the drug reimbursement process in Iran and pointed to undefined and unreliable mechanisms, a reliance on traditional price setting methods, and a disregard for insurer capacity to actively negotiate prices with suppliers. Other weaknesses mentioned by them included insufficient support for the vulnerable classes (e.g. the retired) and indigent groups, and inadequate measures to promote rational prescribing and dispensing of low-price alternatives at the pharmacy level [37].

A study of the drug reimbursement process in Iran is an important step to ensuring that the budget is used optimally. However, studies to date have not performed a detailed examination of the drug reimbursement process. The aim of this study was to describe the decision-making process regarding drug reimbursement in Iran. This paper covers the current reimbursement process relating to drugs in Iran up to the end of July 2012, and we describe the role of the two main stakeholders (the Ministry of Health and Medical Education (MoHME) and Ministry of Welfare and Social Security (MoWSS)) and other important actors and stakeholders in this process.

Methods

Three different methods were used in this study. To investigate and describe the administrative rules and the directives of stakeholders involved in the drug reimbursement process, we examined formal government documents, including the latest laws enacted by the Iranian parliament, legislative documents and published internal regulations of various stakeholders [13,38-44]. Interviews were conducted with three policymakers and experts in Ministry of Welfare and Social Security (MoWSS), Food and Drug Organization (FDO) and the Medical Services Insurance Organization (MSIO) enabled us to add some details about the reimbursement process. Finally, we used periodically released and publicly available statistics, especially drug sale statistics published by the Food and Drug Organization (FDO). The numbers and costs of drugs sold by drug distribution companies to pharmacies are available in these publications [38], which enabled us to generate an overview of the current situation in Iran.

Results

Health Insurance Systems

Major changes in the Iranian national health insurance system began in 1994 with the introduction of universal health insurance [13]. This policy contained a description of the role of each stakeholder in the health care sector, the financing of health insurance organizations (HIOs), the health services tariff policy, and the minimum health service package to be adopted by all HIOs. Since the introduction of this policy, Iran has had four major health insurers: the Social Security Organization (SSO), the Medical Services Insurance Organization (MSIO), the Armed Forces Health Insurance Organization (AFHIO) and the Imam Khomeini Relief Foundation (IKRF) [13].

The SSO, established in 1953, is a non-governmental organization which covers about 43% of the population. The insurees comprise wage-earners and salaried workers, many self-employed personnel in different businesses, and many civil servants [39]. SSO provides two kinds of health care schemes: direct and indirect health care. Direct health care is provided to SSO beneficiaries through 69 hospitals (8550 hospital beds) and 275 clinics [40]. Beneficiaries can also receive indirect health care from other providers, including health centers (privately, government-owned, army) and charity organizations. SSO beneficiaries who referred to direct health care do not have to make any payments or copayments (unless they receive indirect health care) [40]. Besides health care services, the SSO provides other social services relating to pension payments, disability compensation, and unemployment insurance services. These long-term services account for two-thirds of annual SSO expenditures.

The MSIO is a governmental organization established in 1994 which insures about 41% of the population, comprising mainly civil servants, the self-employed and rural populations. The MSIO provides only health insurance services and has variable financing. The activities of MSIO are similar to the indirect health care provided through the SSO.

The two other health insurance organizations, the Armed Forces Health Insurance Organization (AFHIO) and the Imam Khomeini Relief Foundation (IKRF) respectively cover almost 6% and 2.5% of the population. AFHIO beneficiaries include armed forces personnel and their families while IKRF beneficiaries include people with physical disabilities and people with economic or social crises that are so severe that they are not self-sufficient [41].

In addition, there are an additional 30 or so smaller health financing schemes for privileged members of society or large organizations (e.g., government ministries,

municipalities, banks and cooperatives), which provide coverage to their employees and their families [45,45].

Key points about the Iranian health insurance organizations are as follows:

1- Governmental organizations involved in the health care system are supervised by different ministries in the government. The SSO and the MSIO are supervised by the Minister of Welfare and Social Security, the AFHIO is supervised by the Minister of Defense, while the IKRF falls under the direct supervision of the Iranian president.

2- The occupation held by the head of household is the most important factor that determines HIO enrollment, insurance premiums and level of commitment of HIO to reimburse healthcare services. In fact, most people cannot select their health insurer and insurance premiums are paid monthly by their employers. Only self-employed people can choose between the SSO and the MSIO.

3- According to some experts, some people may benefit through coverage by multiple health insurers while others may have no health insurance coverage at all. The number of people without any coverage is estimated to be up to 10 percent of the population. Although the socioeconomic proportions of non-insured people have not been investigated, the experts argue they are mostly young and poor people, who are not eligible to register by the SSO, MSIO and AFHIO and do not need health care services (because of being young). Moreover, some rich people would not be insured since they can easily afford to pay for health care services in the private sector.

4- The contents of the minimum benefit package of the four main health insurers are determined by the Supreme Council of Health Insurance (SCoHI) and all insurers are obliged to provide whatever is included in the package. By law, patients must make copayments of 10% and 30% of the costs of inpatient and outpatient services, respectively. Insurers make direct payments to pharmacies on a monthly basis and patients have to pay both copayments and a dispensing fee. The dispensing fee (about 0.70 Euro in 2011) is a fixed-rate fee for labeling and repackaging that is generally paid out of pocket for every prescription received. In addition to the minimum benefit package and copayment rules, organizations can provide excess services to prevent catastrophic household health expenditures. They may cover some non-reimbursed drugs or decrease the patient's share of financial contribution. The ratios of cost-sharing in drug services provided by HIOs for diseases are shown in Table 2.1. Cancer patients treated with non-reimbursed drugs receive financial support from HIOs using different approaches. For example,

Table 2.1: The financial contribution of drug reimbursement services by main Iran health insurance organizations.

Diseases or indications	DBC[1]	Outpatients					Inpatients				
		SSO		MISO	AFHIO[2]	IKRF	SSO		MISO	AFHIO[2]	IKRF
		DHC	IHC				DHC	IHC			
Cancers	14.8	100	85	90	100	100	100	90	90	100	100
Dialysis (All drugs)		100	100	100	100	100	100	100	90	100	100
Hemophilia (All drugs)	3.4	100	100	100	100	100	100	100	90	100	100
Thalassemia (All drugs)		100	100	100	100	100	100	100	90	100	100
Kidney transplant	1.3	100	100	100	100	100	100	100	90	100	100
Other organ transplants (Immunosuppressives)	0.9	100	100[3]	70	100	100	100	100	90	100	100
Multiple sclerosis (Interferon drugs)	9.4	100	90	90	100	100	100	100	90	100	100
Other diseases	70.2	100	70	70	70	70	100	90	90	100	100

1- Drug budget contribution percentage based on IHC of SSO annual reports for outpatients in 2.10.2011-2.10.2012.
2 AFHIO, provide the basic and supplementary health insurance together.
3 In addition to immunosuppressives, other necessary drugs based on kind of transplantation also covered by the SSO.
Abbreviations: AFHIO: *Armed Forces Health Insurance Organization,* ***DBC:*** *Drug Budget Contribution,* ***DHC:*** *Direct Health Care scheme at SSO,* ***IHC:*** *Indirect Health Care scheme at SSO,* ***IKRF:*** *Imam Khomeini Relief Foundation,* ***MISO:*** *Medical Insurance Services Organization,* ***SSO:*** *Social Security Organization*

the SSO pays a limited yearly grant directly to patients. The MSIO compensates patients for the costs of the drug, the maximum amount being equal to the costs of pharmacologically similar drugs that are reimbursed. The AFHIO covers all drug costs through obligatory supplementary insurance. Lastly, the IKRF covers 50% of the costs of all non-reimbursed drugs.

Drug registration process in Iran

All new drugs (except orphan drugs, with a disease prevalence of 1 in 200.000 people or less) [46] must be registered by the Council to Consider and Compile Drugs (CCCD) before they can become available in Iran. This council is part of the FDO that is responsible for drug policy, which in turn is supervised by the minister of Health and Medical Education. All CCCD members are MoHME employees and most of them are clinicians or pharmacists. The first step in the registration of any new drug that is produced or imported is the completion of 3-4 drug registry forms (Figure 2.1). The applicant (e.g., pharmaceutical firm, group of physicians, specialist society) must prepare documents that address the following items: efficacy, safety and adverse events, comparative efficacy with similar drugs, approval history, contraindications –
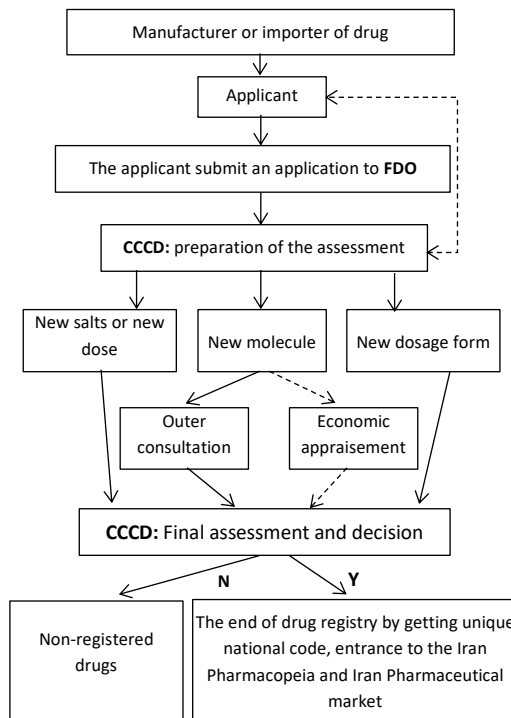
Figure 2.1: Overview of drug registration process in Iran.
Abbreviations: CCCD: Council to Consider and Compilation Drugs, FDO: Food and Drug Organization, Y: Yes, N: NO
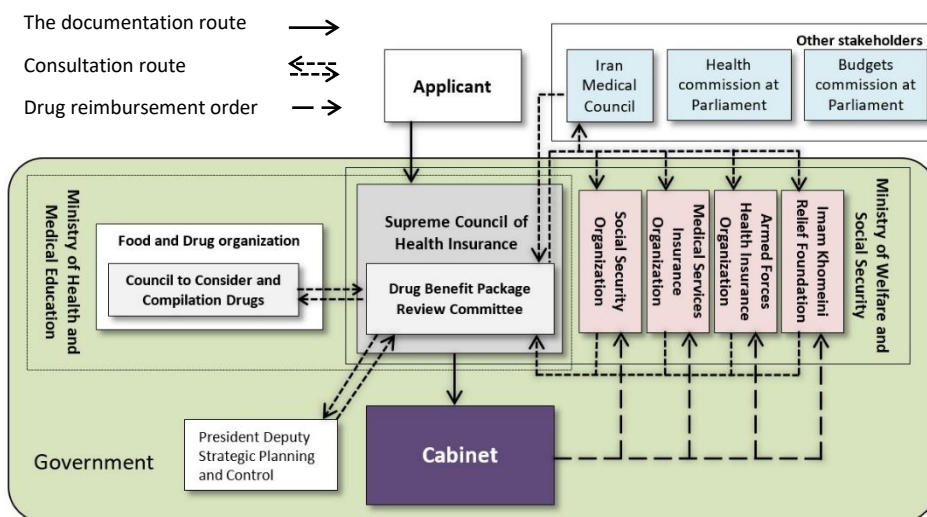
Figure 2.2: Overview of drug reimbursement system in Iran (Stakeholders roles map)

warnings – precautions – monitoring parameters, pharmacokinetics, patient compliance and pharmacoeconomic studies [42]. However, the CCCD may exclude one or more of these items based on the kind of drug and the availability of data.

Applications fall into three categories: 1) new molecules; 2) new dosage forms; and 3) new salts or new doses of any drug if the base has already been approved by CCCD. Suppose the drug erythromycin, with stearate as a salt in its formulation, are available on the market and approved by CCCD. If a new application of erythromycin contains a different salt (e.g., ethyl succinate), it will fall in the third category.

If the application involves a new molecule, consultation will be sought from the heads of medical and pharmaceutical societies, national research centers and medical universities. Approval of the drug by other organizations (such as the FDA, EMA, and TGA) and its use in at least five countries (including the USA, EU countries or other countries with a GDP similar to Iran's) have an important role in the evaluation. Once a drug is approved, it is given a unique national code and can be distributed, prescribed and used throughout the entire country. However, patients using the drug will have to pay 100% of the drug costs until the drug is added to the reimbursement list.
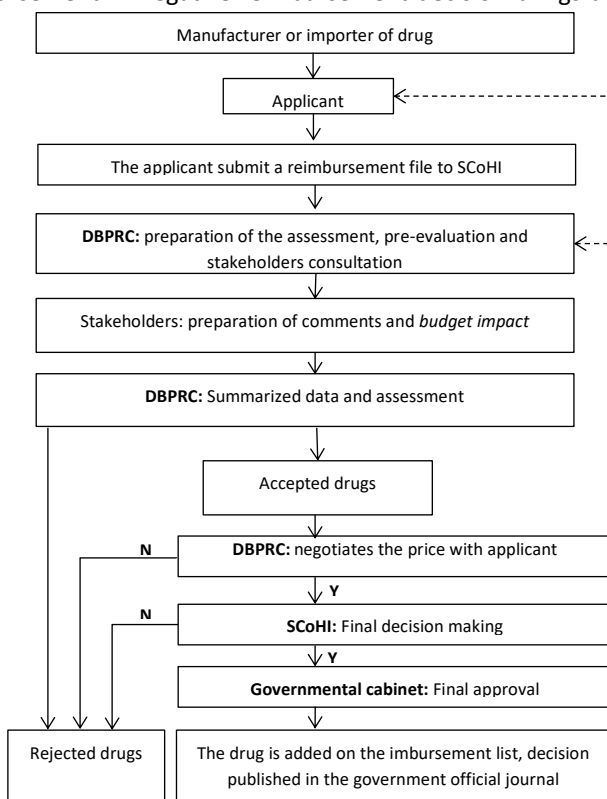
Drug reimbursement process in Iran

The SCoHI is the organization that deals with drug reimbursement decisions in Iran. The Drug Benefit Package Review Committee (DBPRC) is part of the SCoHI and is responsible for drug assessment. All members and stakeholders of SCoHI have a representative in

this committee. Based on Iran's rules, all of the health services covered by health insurance organizations should complete the reimbursement process. The main rule, as previously mentioned, is universal health insurance and one of the most important parts of this law is the appointment of the Supreme Council of Health Insurance as an important health insurance policy center. The members of this council are the minister of MoWSS (who is also the chairman of the council), minister of MoHME, minister of Economic Affairs and Finance, vice president on Strategic Planning and Control, CEO of SSO, CEO of MSIO, CEO of AFHIO, president of the Islamic Republic of Iran Medical Council chief of IKRF and two members of the Iranian Islamic Parliament (Health Commission and Budget Commission). The process of reimbursement of health services is described in section 10 of the Iran universal health insurance for health care law. Figure 2.2 shows the roles of the stakeholders in the assessment of a drug's eligibility for reimbursement. Only drugs that have completed the registration process at FDO and received a national code can enter the SCoHI process (Figure 2.3); otherwise the application is rejected. Applicants (drug companies, physicians, physician specialist societies, etc.) must complete a formal application and submit all of the necessary documents. These documents contain information about the drug and its characteristics, the proposed price, the cost in each treatment period, a list of alternative drug therapies with an analysis of their advantages and disadvantages, and documentation of the clinical and economic aspects of the drug. This information is categorized into items, each of which contributes a certain number of points towards the application. The maximum possible score is 100 points. If the total score based on an initial evaluation performed by SCoHI's experts is less than 50 points, the application is rejected. However, if the total score is 50 points or more, the application will be sent to all DBPRC members, who will be asked to provide comments on the new drug, including the probable effect that it will have on their budget. Once these comments are received, the DBPRC will start the assessment process. If a drug application receives more than 80 points and no significant objections from the council, it will be sent to the SCoHI with a positive vote. The final DBPRC decision will also consider the budget impact for the country as well as cost-effectiveness results from other countries. If they find that rich countries have concluded that a drug is not cost-effective, then this new drug will be considered unlikely to be cost-effective in Iran.All documents are then sent to all stakeholders two weeks before a general meeting is held where all stakeholders gather to discuss the application. The documents contain the following information:

- Comparison of effectiveness with other drugs in the Iranian pharmacopeia that have the similar therapeutic effects.
- Estimated impact on the use of other drugs, which can help to estimate the overall impact of a drug on a health insurer's budget.

- Cost modelling for one therapeutic course in outpatient care and comparison with other drugs with the same therapeutic effects.
- Average monthly increase in sales in the 6-month period prior to the reimbursement application.
- Drug price in other countries with a GDP similar to that of Iran's.
- Opinions and comments of certain departments of major medical universities (the choice of department is based on the kind of drug).

All stakeholders will have two weeks to examine the information, after which a general meeting will be held. The first goal in the meeting is to reach consensus about whether or not to reimburse the drug. If consensus is not achieved, the members will vote for or against reimbursement. A negative reimbursement decision brings the process to an

Figure 2.3: Overview of drug reimbursement process in Iran.
Abbreviations: DBPRC: Drug Benefit Package Review Committee, SCoHI: Supreme Council of Health Insurance, Y: Yes, N: NO

end since there is no opportunity to reapply for reimbursement. However, if the reimbursement decision is positive, a meeting is arranged with the drug company to negotiate the drug price. If the drug company is able to agree with the DBPRC about the price, the application for reimbursement will be accepted, otherwise it will be rejected.

Once the price has been set, the DBPRC will release a document containing the following information:

1- Conditions of reimbursement (e.g., which specialists can prescribe the drug, which indication(s) the drug can be used for and location of production (Iran or other country)). For example, rituximab is only reimbursed if it is prescribed by an oncologist to treat non-Hodgkin's lymphoma and will not be reimbursed for other purposes (e.g., rheumatic disorders).

2- Dosage forms under reimbursement.

3- Whether or not health insurance organizations need to set up a patient registry for the specific drug.

4- Assessment of reimbursement eligibility by a health insurance organization before a patient purchases the drug.

The DBPRC will then send the positive results of their decision with the agreed prices to the chairman of the SCoHI (Minister of Welfare and Social Security), who will then provide a final summary of comments made during a meeting with the SCoHI. After this process of deliberation is completed, a report with SCoHI conclusions is sent to the Iranian Cabinet, which makes the final official decision. According to experts, the Cabinet has never rejected a drug approved by SCoHI. Following Cabinet approval, the drug is added to the reimbursement list and the decision is published in the Government's official journal.

Patients can receive the drug with different copayments based on disease category (Table 2.1). Once an international nonproprietary name (INN) in a specific dosage form is added to the reimbursement list, all brand names with a similar dosage form are also added. However, HIOs will be required to reimburse only the lowest price of all available brands. For instance, assume that three brands of ranitidine 300 mg were available on the market with three different prices (95, 100, and 110 Rials). If ranitidine is covered, all three brands are covered but the health insurer will only reimburse 95 Rials (the price of the cheapest brand) and patients wanting a more expensive brand will have to pay the extra costs themselves.

Overview of the current situation

Currently, there are 3530 INN national codes in Iran's drug pharmacopeia [43] and 1800 INN national codes and 90 raw materials for some drugs produced by pharmacies are reimbursed [44]. Most vitamins, nutritional supplements, infertility drugs and herbal extracts are not on the reimbursement list. Based on statistics provided by the FDO [38],

Table 2.2: The top twenty non-reimbursement drugs based on sales in the period between 2.10.2011 and 2.9.2012 (1 Euro ≈ 16000 Rials in 2011)

Drug	Major indication	Drug sales of total non-reimbursement sales		FDO approval date[2]	What is clear decision from SCoHI?
		%	€		
Trastuzumab 440mg vial	Certain breast cancers	3.0	18,269,992	Before 2008	No (4/2010)
Follitropin 75iu amp	Infertility	2.5	15,233,374	Before 2008	No Application
Orlistat 120mg cap	Obesity	2.4	14,492,096	Before 20·٨	No Application
Ibuprofen 400mg pearl[1]	Moderate pain	2.3	13,498,195	Before 2011	No Application
Pantoprazole 40mg tab[1]	Gastroesophageal reflux	2.2	13,050,840	Before 2008	No (4/2009)
Tamsulosin 0.4mg cap	Benign prostatic hyperplasia	2.2	12,907,345	Before 2008	No (6/2010)
Sildenafil citrate 100mg tab	Erectile dysfunction	1.9	11,239,538	Before 20·٨	No Application
Menotropins 75 iu fsh+75iu lh amp	Fertility disturbances	1.8	10,809,738	Before 2011	No Application
Vaccine-influenza virus killed	Protect against influenza virus	1.7	10,437,869	Before 2008	No Application
Drospirenone/Estradiol 3/0.03mg tab	Hormonal contraceptive	1.5	8,928,217	Before 2011	No Application
Bevastizumab 400mg/16ml vial	Various cancers, colorectal, lung, breast, glioblastoma kidney and ovarian.	1.4	8,303,165	Before 2011	No Application
Salbutamol 100mcg/dose 200dose inhaler[1]	Relief of bronchospasm	1.3	7,900,956	20/11/2009	No Application
Buprenorphine 2mg sl tab[1]	Moderate to severe chronic pain	1.3	7,624,896	Before 2005	Under study
Celecoxib 100mg cap	Osteoarthritis, rheumatoid arthritis, acute pain	1.2	7,245,080	Before 2000	No (4/2002)
Zoledronic acid 4mg vial	Osteoporosis	1.1	6,707,129	Before 2008	Yes (Wait for Government Cabinet)
Pantoprazole 20mg tab[1]	Gastroesophageal reflux	1.1	6,565,955	Before 2008	No (4/2009)
Celecoxib 200mg cap	Osteoarthritis, rheumatoid arthritis,	1.0	5,891,905	Before 2000	No (4/2002)
Prospan® [1] syrup	Expectorant	0.9	5,678,314	Before 2011	No Application[3]
Acetaminophen/ Caffeine/ Ibuprofen 325/40/200mg cap[1]	Moderate pain	0.9	5,566,815	26/09/2011	No Application
Tramadol 100mg tab	Moderate to severe pain	0.9	5,431,981	Before 2002	No Application
Sum		**32.6**	**195,783,400**		
Total		**100**	**600,562,577**		

1- There are some others dosage forms in Iran reimbursement list. Background color is changed to gray in this group of drugs.

2- When the exact dates were not accessible, we looked at the Iran pharmaceutical market and if drug was been accessible in each year, we used "Before that year" to describe the FDO approval date.

3- Other internal products are reimbursed.

Abbreviations: FDO: Food and Drug Organization, SCoHI: Supreme Council of Health Insurance

over a one-year period (2.10.2011-2.9.2012), the expenditures of the drugs found on the reimbursement list is approximately 77.3% of the total expenditures of all drugs sold to pharmacies by distribution companies. The rest is paid by patients or supplemental insurance. Since no reliable report about expenditures of non-reimbursed drugs is available, we used sale reports to describe the results of the reimbursement process. The top twenty non-reimbursed drugs (based on the results of the previous report) are shown in Table 2.2. This list of drugs includes both essential and non-essential drugs, where drugs are considered non-essential if therapeutically equivalent drugs are already available on the market.

Although sales statistics cannot accurately describe overall drug use over long periods of time, it can at least help to estimate the costs of non-reimbursed patient expenses in various groups of diseases and changes in the use of non-reimbursed drugs. As seen in Table 2.2, since the exact date of presentation of application to SCoHI is unknown, it is not possible to estimate the mean duration of the application process. However, it is known that some applicants received a decision a couple of years after submitting their reimbursement application. This delay appears to be due to the SCoHI screening of drugs. Many controversial drugs seem to have been held back by bureaucratic barriers while less controversial ones easily passed this bureaucratic filter. On the other hand, there are twelve drugs with a "No Application" status, which usually reflects a situation where the applicant is not entirely confident about gaining approval from SCoHI because of incompatibility properties of their drugs and SCoHI expectations. However, in other cases, it is likely that some companies choose not to apply for reimbursement since they are sure their drugs will sell well in Iran without it.

Discussion

Drug reimbursement decision-making is an important process in the health care sector and has an essential role in the efficient allocation of resources. Moreover, the expansion of health insurance schemes with affordable and comprehensive packages of basic services is a great aid in achieving health equity. While Iran is a developing country with an economy that is transforming into a market-based economy, the Iranian state still plays a key role in the economy, since it owns large public and quasi-public enterprises which partially dominate the manufacturing and commercial sectors. The Iranian pharmaceutical market has undergone great growth in comparison with developing countries and the market is expanding quickly while a major share goes for biotechnology drugs during 1977-2010 [47]. Therfore, as a middle-income country with a total health expenditure in 2011 of 6.0% of the GDP [48], evidence-based decision-making and the appropriate use of available resources are of paramount importance. While there is a process now in place to assess whether or not a new drug is eligible for reimbursement in Iran, previous studies have found that this process lacks efficiency in

making quick and sound reimbursement decisions. This paper's approach was to go one step further by providing a more comprehensive view of the current situation, which enabled us to identify both the strengths and the shortcomings of the review process.

Our study revealed some strengths of the current process. The drug registration and reimbursement system in Iran basically uses the same decision-making criteria that are applied in many other countries, which include efficacy, safety, and economic considerations. SCoHI has managed to eliminate some of the problems arising from a lack of therapeutic guidelines by drawing up restriction rules on the consumption of some reimbursed drugs based on their indications (see rituximab example above). HIOs can not only provide an appropriate financial contribution, especially for high risk patients, but they can also provide extended universal coverage in Iran. Improved planning in the area of reimbursement would help to improve this strength even further. Price negotiation, budget impact and priority for drug coverage are important activities in the process of drug reimbursement.

The drug reimbursement process in Iran can be described as a shared responsibility process, since decision-making process is distributed between two ministries with different interests. The Ministry of Health and Medical Education is expected to ensure patient access to useful drugs, while the Ministry of Welfare and Social Security must try to maximize health insurance coverage with a limited budget. The two ministries therefore have goals which can conflict with each other. In addition, the SCoHI must consider the recommendations of many stakeholders when making reimbursement decisions. These two factors of conflicting aims and many decision-makers may complicate the goal of independent decision-making. This not only might challenge the societal goals of drug reimbursement but also cause other problems like prolonged decisions. One consequence of a prolonged reimbursement process is an increase in out-of-pocket payments by patients, who will have to pay for a drug until it is deemed reimbursable. Some HIOs may therefore use supplemental insurance or decrease other services to help patients needing expensive non-reimbursed drugs.

One issue in the current system is that periodical reports by SCoHI and FDO are not publicly available. The reasons for approving or disapproving drug registration and reimbursements, and the average durations of the registry and reimbursement processes are therefore unknown. This can be viewed as evidence of lack of transparency in the process, which could easily be resolved if information from the SCoHI and FDO were published. In addition, the repetition of some activities during the evaluation process likely means redundancy, inefficiency and delays in decision-making. A good example of this is the requirement by the applicant to supply various economic documents to both the CCCD and the DBPRC.

The drug reimbursement process uses the same approach in dealing with different applications regarding required documents, evaluation and decision-making process, regardless of the budget impact and whether or not the drug is essential. On the other hand, modern HTA methods are not evident in this process. One consequence of these issues is reduction in process dynamicity and accumulation of different applications with different degrees of importance in patient safety. Although standardization of the required documents and assessment protocol of the applications is a strength of the reimbursement system in Iran, it does have its limitations. That is, process dynamicity could be improved by developing different approaches to assess drugs in different categories based on their medical and economic characteristics. Policymakers could then apply a set of criteria to prioritize drug reimbursement reviews. For example, a drug with great budget-saving potential might receive a higher priority. In contrast, a drug could be given a lower priority if another drug (with a similar safety and effectiveness profile) is already available on the market.

Improvements in the drug reimbursement system may not resolve all of the problems that patients have with the if the total drug expenditure in health care would not be matched with the real needs. Moreover, it will be difficult to find a better functioning system which is able to satisfy all stakeholders. If the number of new and expensive drugs continues to be high, this can lead to delays in decision-making and various problems such as distrust between the public and policymakers and an increased numbers and expenditures of non-reimbursed drugs, which can in turn lead to insurance fraud by patients and physicians.

Since sharing of expertise and experience in middle income countries would be helpful for HTA developers and policy makers in these countries [9]. Iran because of its geopolitical properties, market size and the relative superiority in health indicators [34,47,48] is an important country for HTA researchers in the region and the west part of Asia.

Conclusion

The Iranian drug reimbursement system is a shared process between two different ministries and has an important role in the efficient allocation of resources. Some issues that have been discussed cause reduced functionality of this system. Therefore, Iranian policymakers need to make changes and reevaluate the admission process of new drugs to the reimbursement lists under a new set of guidelines and possibly a more efficient regulatory body. In this new set of guidelines, one important step to improving decision-making is greater transparency (e.g., by publishing reimbursement and registry decisions) on details. More transparency will help to improve other key performance indicators of new decision-making process like: independence, timeliness, and

dynamicity. Benchmarking studies on the Iranian drug reimbursement decision making process versus other countries' processes are needed to highlight Iran's procedural difficulties. Other studies, especially case studies, should evaluate the exact drug reimbursement decision-making in Iran. These studies and the experiences of other countries can serve as a framework to find the best solutions to improve the drug reimbursement decision making process.

List of abbreviations

AFHIO	Armed Forces Health Insurance Organization
CCCD	Council to Consider and Compile Drugs
DBC	Drug Budget Contribution
DHC	Direct Health Care scheme (at SSO)
IHC	Indirect Health Care scheme (at SSO)
DBPRC	Drug Benefit Package Review Committee
HIOs	Health Insurance Organizations
FDO	Food and Drug Organization
IKRC	Imam Khomeini Relief Committee
SCoHI	Supreme Council of Health Insurance
MoHME	Ministry of Health and Medical Education
MoWSS	Ministry of Welfare and Social Security
MSIO	Medical Services Insurance Organization
SSO	Social Security Organization
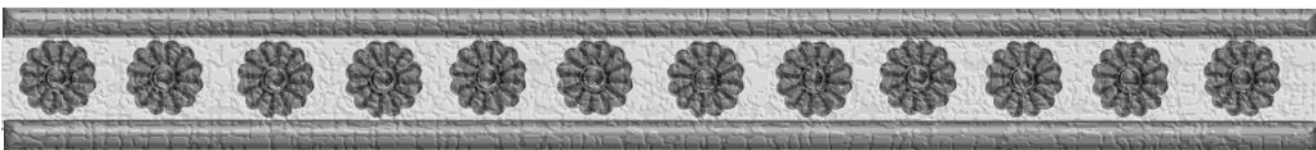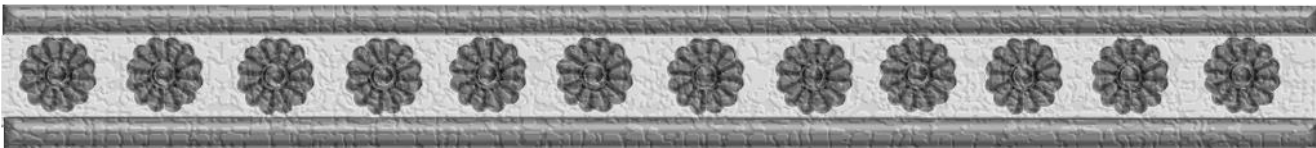
Chapter 3

Which is more important for doctors in a middle-income country, a national guideline or the medical literature?
An adherence survey of trastuzumab use for breast cancer in Iran

Amir Ansaripour, Carin A. Uyl-de Groot, Mohammad Foroozanfar, Salimeh Rahimimoghadam, W. Ken Redekop

Abstract

Introduction: Most national standard therapeutic guidelines in the world recommend a 52-week trastuzumab regimen for breast cancer treatment. In contrast, the national guideline published by the Iranian Ministry of Health recommends a nine-week regimen. Since guidelines are not necessarily followed in daily practice, we assessed the extent to which current routine practice in Iran as a middle-income country matches the recommendations found in these guidelines.

Methods: 128 Iranian oncologists were asked to complete an online anonymous questionnaire. Concurrently, a 3-year retrospective claims database analysis was conducted using data from the Social Security Organization, a health insurer which covers approximately 50% of the Iranian population, to enable comparisons with the questionnaire results.

Results: With a 41% (52/128) response rate, doctors reported a relatively high absolute adherence (86%) to the guideline for HER2 receptor testing but a low rate of absolute adherence (6%) to the guideline for duration of trastuzumab treatment. Doctors indicated that the planned duration was 9 weeks in only 33% of patients; in most cases, the plan was 52-week treatment. Patients with a 9-week treatment plan received trastuzumab for 8.6 weeks on average while patients with 52-week plans received treatment for 29.2 weeks. The general trends found in the survey were confirmed in the claims database analysis of 1295 HER2-positive patients.

Conclusions: Resource-sensitive guidelines may be beneficial in middle-income countries where limited budgets cannot accommodate all innovative technologies. However, Iranian physicians appear to rely more on the medical literature than on national guidelines regarding trastuzumab use. Policymakers, doctors and other stakeholders need to reach some consensus about the optimal way to treat patients. A national guideline needs to be accompanied with country-specific economic evaluations.

Introduction

A standard treatment guideline (STG) is "a systematically developed statement designed to assist doctors and patients in making decisions about appropriate health care for specific clinical circumstances" [49]. STGs are also one of the measures used by policymakers to provide standardized guidance to practitioners and promote efficient use of funds [49], especially when they decide to reimburse a new and expensive intervention.

If the sustainable reimbursement of innovative but expensive medical technologies presents an important challenge to policymakers in high-income countries, it is a near impossibility for policymakers in middle-income countries (MICs). Policymakers in these countries need to take particular care in reimbursement decisions when the total budget impact of reimbursing a drug may be exceptionally high. If the aim of reimbursement is to address the goal of maximizing health given limited available resources, then STGs may help in this endeavor [49]. For example, Iran has attempted to manage the use of monoclonal antibodies like trastuzumab by using national guidelines [50]. Trastuzumab for breast cancer was probably chosen by Iranian policymakers as one of the treatments to be assigned its own guideline because of its high costs per individual and the high probability of a substantial budget impact. In fact, budget concerns probably explain why trastuzumab was not reimbursed when it first entered the Iranian pharmaceutical market in 2007 [51]. The standpoint of the Ministry of Health and Medical Education (MoHME) appears to have changed five years later when it published the first version of the guideline for trastuzumab use in 2012 [52]; trastuzumab was reimbursed one year later [53]. The main recommendation in this STG is a 9-week treatment regimen in women with human epidermal growth factor receptor 2 (HER2) positive breast cancer, which was based mostly on expert opinion and literature reviews. However, since national STGs may represent the culmination of compromises between policymakers and clinicians, they may not reflect how clinicians actually treat their patients. In fact, informal discussions with Iranian clinicians had suggested that trastuzumab use in daily practice deviates substantially from what the guideline recommends.

The aim of this study was to investigate clinician adherence to the Iranian guideline for treating HER2-positive breast cancer. Specifically, we compared what Iranian doctors do in daily practice with the recommendations found in the current guideline for treating HER2-positive breast cancer and explored the degree of association between socioeconomic parameters and trastuzumab consumption.

3

Methods

    General study design

Two different approaches were used to assess clinician adherence. The first approach was to conduct a clinician survey to determine how much clinicians adhere to the guidelines for trastuzumab and the second approach was a claims database analysis. Details regarding these two approaches are provided below.

    Clinician survey

        -    **Study population**

The target population in this survey comprised the specialists working in the areas of oncology, the specialists who are eligible to manage breast cancer in Iran (total number: approximately 264). They can work in the public (e.g., Ministry of Health, Social Security Organization and state hospitals and clinics), private (e.g., private hospitals, clinics, and doctors' offices) or both sectors.

An invitation to participate in the survey, including an internet address link to the questionnaire, was emailed to all specialists in the target population with a known email address (n=128). Specialists who preferred to receive the questionnaire by mail were sent a copy in a sealed envelope.

        -    **Questionnaire**

An online anonymous questionnaire was created on the SurveyMonkey website (https://www.surveymonkey.net). This questionnaire examined treatment preferences in four stages of breast cancer: breast cancer without local or distant recurrence symptoms, contralateral breast cancer or new primary non-breast cancer, ipsilateral loco-regional recurrence and distant recurrence.

Feedback from four oncologists was used to develop and refine the questionnaire. A pilot study of the questionnaire was then performed by sending the questionnaire to 10 respondents, five of whom responded within two weeks. The final version of the questionnaire containing 30 main questions was then sent out to all oncologists.

    Database analysis

A retrospective claims database analysis was conducted using the Social Security Organization (SSO) database. The SSO insures almost 50 percent of the Iranian population (~38 million) [54]. The database, however, does not contain some clinical information such as disease stage or diagnosis coding (e.g., ICD-10). The HER2-positive

patients were therefore identified based on the national health services coding by applying four filters to the database: cancer patient, woman, history of a mammography, and trastuzumab use in the past two years. The combination of these filters yielded a total of 1,298 patients. Data cleaning and exploratory data analysis were then conducted, followed by data extraction. The data analysis was performed at both the national and provincial levels; an additional analysis compared trastuzumab use between the provinces.

Statistical analysis

Microsoft Excel, Access 2013 and R (version 3.1.0) software was used to perform the analyses. Results from the survey and database analysis were compared and the differences between them were tested for statistical significance using Pearson's χ^2 tests for categorical variables and t-tests for interval variables (including variables with a nonnormal distribution given the central limit theorem). Finally, multiple linear regression analysis was used to examine the relationship between the independent variables and trastuzumab use among different provinces. An alpha=0.05 was used to assess statistical significance.

Results

Clinician survey

Of the 128 clinicians invited to participate in the survey, 52 (41%) responded and 48 (38%) completed the entire questionnaire. A description of the respondents is shown in Table 3.1. The respondents were divided into two main groups of university instructors and other specialists.

Table 3.1: The profile of responders

|	Health care sectors	Number of participants (%)	Total (%)
University instructors	Public sector only	10 (19)	**36 (69)**
	Private sector only	2 (4)	
	Both public and private sectors	24 (46)	
Others	Public sector only	6 (12)	**16 (31)**
	Private sector only	4 (8)	
	Both public and private sectors	6 (12)	
	Total	**52**	**52 (100)**

HER2 test

The first part of the questionnaire focused on how doctors determine if a patient has HER-2 positive breast cancer. Most respondents (84%) reported that they first use the immunohistochemistry (IHC) test and then, depending on the IHC test result, order a fluorescence in situ hybridization (FISH) test. The remaining respondents stated that they only examine the IHC results (12%), immediately order a FISH test (4%) or never order a test. Based on the respondents' answers, 91% of all patients underwent at least one type of HER2 test (IHC or FISH). The database analysis yielded somewhat lower percentages, since it showed that 75% of the patients underwent the IHC (74%) and FISH (1%) tests before chemotherapy.

Trastuzumab treatment plan

When clinicians were asked how many of their patients are initially started on a 9-week regimen versus a 52-week regimen, their responses varied widely. At one end of the spectrum, some doctors planned a 9-week regimen for all of their patients while at the other end, some doctors planed a 52-week regimen for all of their patients. The different plans for trastuzumab therapy are shown in Figure 3.1. These results showed that only 6% of respondents stated that they use a 9-week regimen (i.e., the treatment strategy recommended in the national guidelines) with all of their patients, while 39% of respondents had a plan to use a 52-week regimen with all of their patients. When the responses of the clinicians were combined with the frequency of their use of a 52-week vs 9-week plan, the results suggested that two-thirds (67%) of the patients were started on a 52-week regime and one-third (33%) were started on a 9-week plan. There was no significant difference between two specialist groups of university instructors and others (p=0.849) regarding these results.
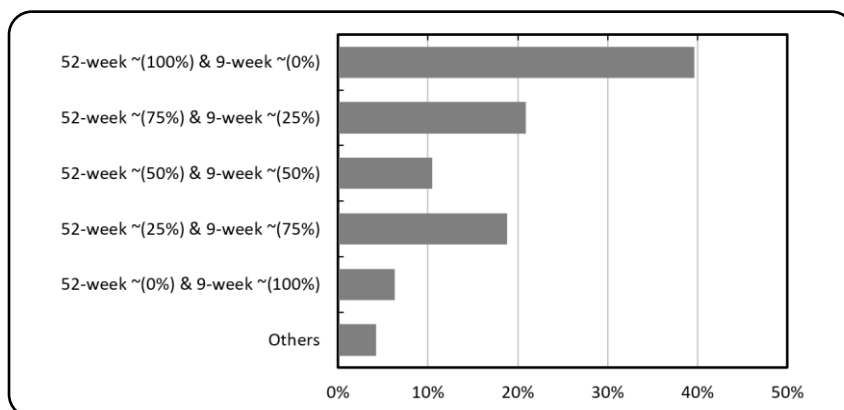
Figure 3.1: Distribution of the proportion of patients receiving the 52-week and 9-week trastuzumab regimens based on the survey results.

The respondents mentioned that patients on average complete only 67% of their trastuzumab regimen. However, the actual percentage depended on the planned treatment duration. Patients who were supposed to undergo a 9-week trastuzumab regimen received trastuzumab for an average of 8.6 weeks while the patients who started their treatment with a 52-week plan received trastuzumab therapy for an average of 29.2 weeks. The database results were slightly lower than the survey results. The average duration of trastuzumab use found in the database was 6 (SD=2, range:1-9) weeks for patients who received trastuzumab for a period of 9 weeks or less (n=196) and 23 (SD=12) (range:9-51) weeks for patients who received trastuzumab for a period longer than 9 weeks (n=303). Overall, patients received trastuzumab for an average duration of 21 weeks regardless of disease stage and completion or continuation of trastuzumab use, which was estimated by assuming that patients who did not use trastuzumab for more than 90 days had stopped using it. There was no significant difference between the survey results and the results from the database analysis (Pearson's chi-squared test, p=0.358) (Figure 3.2).
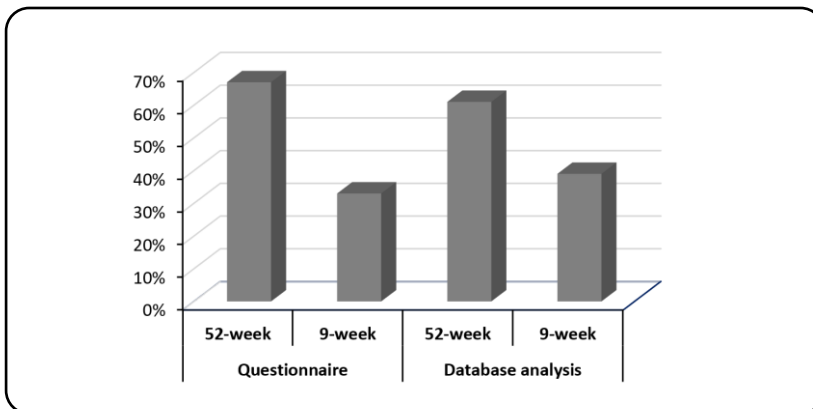
Figure 3.2: The overall average of the proportion of patients receiving the 52-week and 9-week trastuzumab regimens based on the results of the questionnaire and database analysis (difference between questionnaire and database, p = 0.358).

When respondents were asked to provide the reasons to discontinue trastuzumab, they gave not only clinical reasons but also three non-clinical reasons: 1) inability of the patient to pay for trastuzumab and its administration; 2) lack of trastuzumab access in the region where the patient lived; and 3) lack of access to a specialist in the region where the patient lived.

The database analysis revealed wide variation in the duration of trastuzumab treatment among the different Iranian provinces (Figure 3.3). As the map in Figure 3.3 shows, the average treatment duration ranged from 12 weeks in Semnan to 32 weeks in Ilam.

Factors affecting assessment on trastuzumab consumption

We examined the correlation between average duration of trastuzumab treatment per province and several province-level parameters that might affect trastuzumab use, including the number of oncologists and pharmacies, geographical size of the province, average premium per beneficiary (2013), average age of patients in the database and female beneficiaries (n=16,392,192) among different provinces (Figure 3.3). Average premium was used as a proxy for household income, which was not available due to confidentiality reasons. The associations seen between trastuzumab use and the various parameters were small and suggested that these parameters do not adequately explain the variation in trastuzumab use.

	Coefficients	Standard Error	P-value
Number of oncologists*	0.182	0.140	0.207
Number of pharmacies*	-0.230	0.163	0.171
Vastness of province*	-0.023	0.060	0.702
Premium earned by SSO per beneficiaries (2013)*	0.148	0.139	0.295
Patients average age	-0.020	0.015	0.207
Female beneficiaries average age	0.012	0.030	0.689
*Natural Logarithm (LN)	R^2=0.248		
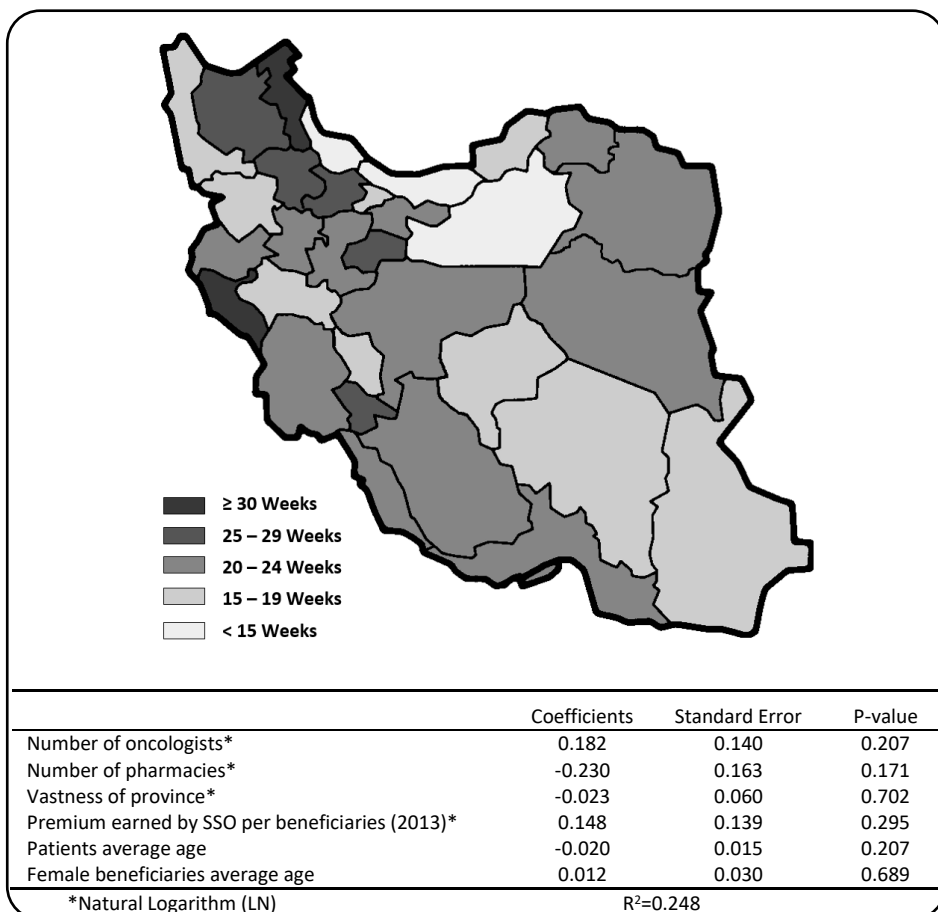
Figure 3.3: The average of trastuzumab continuation (n = 1295) and correlation between the important independent variables and duration of trastuzumab use based on a multiple linear regression analysis among the different provinces in Iran (n = 31).

Discussion

Policymakers with inherently limited healthcare budgets must contemplate the total financial impact of providing an expensive drug when deciding whether to reimburse it. HER2-positive breast cancer is a costly disease due to the use of expensive drugs like trastuzumab and costs will likely continue to increase as new treatment options emerge, such as pertuzumab in combination with trastuzumab. Though indicated for a fairly narrow group of patients (0.07-0.09% of the whole population in Iran), trastuzumab is very expensive compared with many other medications and can therefore have an important impact on healthcare budgets.

If the healthcare budget cannot accommodate the total costs of a specific new drug (including related costs such as administration), policymakers could consider two divergent approaches that will not increase the overall healthcare budget: a benefit package modification (where some services are cut to make room for a new intervention) and a full-payment patient scheme (where patients must pay for all of the costs of the new intervention themselves). These two choices represent the two ends of a reimbursement decision-making spectrum. Policymakers choosing to cut services would face some very tough decisions since many services might have to be omitted from the benefit package to offset the total costs of trastuzumab; these omissions may even lead to more health loss than the health gains from trastuzumab [55]. The other extreme of asking patients to cover all of the costs of trastuzumab could be viewed as ethically inappropriate since trastuzumab is prohibitively expensive for many patients. If these two extremes are excluded as options, the resource-sensitive guideline chosen by Iranian policymakers may be seen as one of the unsatisfying but reasonable solutions for trastuzumab.

Iranian policymakers tried to implement a resource-sensitive guideline with a recommendation of 9 weeks regimen for trastuzumab use [50]. And interestingly enough, the 9-week treatment regimen was recommended despite the explicit admission that it is not as effective as the 52-week regimen [56]. In fact, the only reason to support a 9-week regimen seems to be the high budget impact of trastuzumab, even though the extra budget required to finance a 52-week regimen versus a 9-week regimen might seem limited given a 0.024% annual incidence in women age 30+ years. However, this amounts to a total of almost 9,120 new early breast cancer cases per year [57]. In monetary terms, if we assume an average weight of 70 kg and include administration and cardiac monitoring costs, an extra 40-75 million euros (1 euro=35,500 rials, 2014) would need to be spent to finance an increase in recommended duration from 9 weeks to 52 weeks. Relative to the total annual outpatient health care costs of 1,021 million euros in 2013 [58] for the SSO, this would mean an increase in expenditures of 2-4%.

Guideline adherence is an important indicator of the influence of recommended practices on the behavior of healthcare professionals. Recent studies have shown that there is a wide range in adherence to national guidelines in the treatment of HER2-positive breast cancer. For example, a large observational study on adherence to French prescription guidelines showed fairly low clincan adherence to French post-licensing guidelines, which contrasts with the high level of adherence to the regional clinical guidelines on the treatment of metastatic HER2-positive breast cancer [59]. To our knowledge, no other study has examined physician adherence to guidelines for trastuzumab therapy in early HER2-positive breast cancer. Our results suggest that the use of HER2 authentication methods in daily practice largely reflects what is recommended in the STG. In contrast, the results suggest a poor adherence to the STG regarding trastuzumab use.

Iranian health insurers initially reimbursed a 9-week trastuzumab regimen, in line with the national guideline. Any patients receiving the 52-week regimen therefore had to pay for the remaining costs themselves. Since the cost difference between 9 and 52 weeks is two times the average urban gross annual household income (7,800 euro/year) [60], longer treatment could increase the risk of catastrophic health expenditures, increased inequity and treatment failure. Interestingly, after the first year of reimbursement, insurers decided to reimburse a 52-week regimen due to pressure from physician and patient organizations. Phrases like "Mothers are going to die due to lack of funding" were used to influence the reimbursement policy [61,62]. While this extension of trastuzumab reimbursement satisfied patients and doctors, it also means that money needed to fund trastuzumab treatment will be shunted away from other treatments, which may cause health and efficiency loss elsewhere in the healthcare system [55].

Since STGs in different countries for a particular treatment rely on a common evidence base and local circumstances, it is not surprising to see both similarities and differences between them. Table 3.2 provides an overview of various STGs in different countries for trastuzumab. While the recommendation for the pre-treatment diagnostic assessment is almost the same in many countries, differences between countries can be observed in the duration of trastuzumab therapy. It is worth noting that the 9-week trastuzumab regimen was once recommended in other countries besides Iran. Specifically, PHARMAC (The Pharmaceutical Management Agency) in New Zealand initially funded nine weeks of trastuzumab from 2007 [63], just like the Turkish Ministry of Health before 2010, along with a reimbursement plan [64]. This raises the question of why policymakers in these countries did not recommend the 52-week guideline right from the very start.

Table 3.2: A summary of current trastuzumab guidelines in different countries

Country	Year of publication	Trastuzumab therapy intervals (weeks)	Trastuzumab therapy duration (weeks)	Cardiac monitoring intervals (months)	Ref
Sweden	2014	3	52	-	[65]
USA (NCCN)	2014	1 & 3	52	Every 3	[66]
Belgium	2013	3	52	Every 3	[65]
Finland	2013	3	52	Every 3 or 6	[67]
Scotland	2013	1 & 3	52	Months 4 and 8	[68]
Brazil	2012	-	52	-	[69]
Iran	2012	1	9	Every 3	[50]
Netherlands	2012	3	52	Every 3	[70]
Turkey	2010	1 & 3	52	Every 3	[71]
New Zealand	2009	3	52	Every 3	[72]
Australia	2007	1 & 3	52	Every 3	[73]
UK	2007	3	52	Every 3	[74]

Abbreviations: IHC: *Immunohistochemistry,* **FISH:** *Fluorescence in Situ Hybridization,* **CISH:** *Chromogenic in Situ Hybridization,* **SISH:** *Silver in Situ Hybridization.*

There are two study limitations worth noting. First, the 41% response rate in our physician survey could suggest possible selection bias and it is possible that some physicians provided inaccurate or socially desirable answers in the survey. However, it is unlikely that these factors had a dramatic effect on the overall conclusions of this study since the survey results corresponded reasonably well with the claims database analysis using data on 50% of the Iranian population and almost whole Iranian oncologists. Second, the lack of access to some patient-level information necessitated analyses using province-level data, which are prone to ecological fallacy. This means that even though we found no significant associations between trastuzumab use and various parameters, it is still possible that important associations could be seen if patient-level data were to be used.

Policymakers in MICs must admit that a resource-sensitive guideline can be an ineffective way to constrain costs if guideline adherence is poor. Policymakers in different MICs should share their strategies and experiences like the impact of drug price nego-tiations with manufacturers on the healthcare budget. Within a country, better collaboration between doctors and policymakers is necessary to promote mutual awareness about policymaking criteria and the socioeconomic impact of their decisions. In addition, stakeholders (including policymakers, doctors, patients, health insurers and the general public) need to reach a consensus about the optimal way to treat patients. Efforts to promote cooperation amongst stakeholders could be enhanced by some changes in reimbursement decision-making system [51]. For example, if applicants were required to submit the results of a country-specific cost-effectiveness analysis, knowledge about the cost-effectiveness of an expensive drug like trastuzumab could be

used to facilitate dialogue among the stakeholders, support drug price negotiation with producers, guide rational decision-making and help to improve guideline adherence.

Conclusions

In MICs, budget limitations represent a huge challenge for policymakers when they decide whether or not to reimburse an expensive intervention like trastuzumab. While price negotiations can be effective in containing overall costs, the design and implementation of a suitable resource-sensitive guideline may be another strategy to achieve that goal. However, the functionality of this strategy is totally dependent on physician adherence to STGs. Based on our findings regarding the use of trastuzumab, Iranian doctors appear to rely more on the medical literature than on national guidelines developed by the Ministry of Health. The stark contrast between the STG for trastuzumab and the preferences of doctors can be viewed as a sign that the system is not working as well as it should. It is therefore clear that additional efforts are necessary in the implementation of resource-sensitive guidelines. Policymakers choosing to implement resource-sensitive guidelines must consider ways to improve physician adherence.
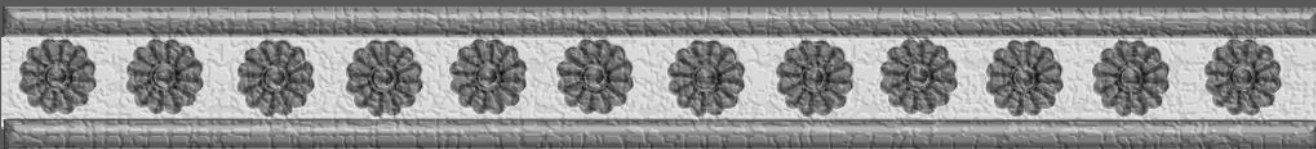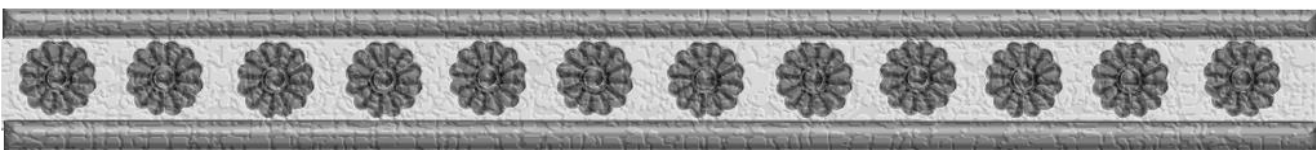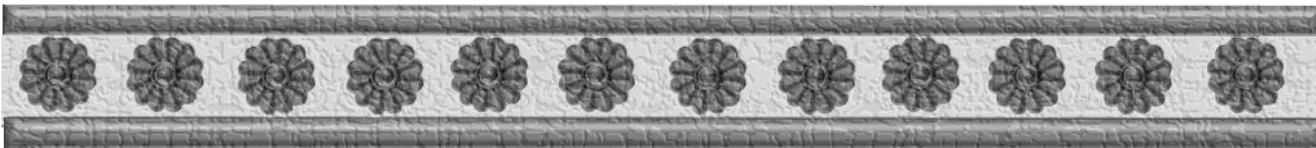
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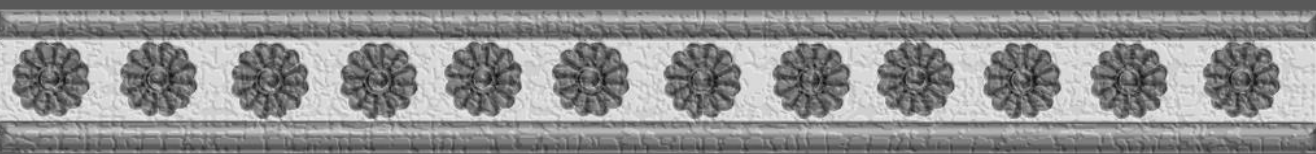
Part II

Production of health economics-related evidence in Iran

Chapter 4

A real-world cost analysis of HER2-positive breast cancer in Iran

Amir Ansaripour, Kazem Zendehdel, Niki Tadayon, Fatemeh Sadeghi,
Carin A. Uyl-de Groot, W. Ken Redekop

Abstract

Introduction: Expensive treatments like trastuzumab for HER2-positive breast cancer (BC) have placed a heavy burden on middle-income countries (MICs), which require a good understanding of real-world healthcare costs to make better reimbursement and implementation decisions. The two aims of this study were to estimate direct medical costs of treatment HER2-positive BC in Iran and to examine the fraction of total costs related to trastuzumab use into three disease stages. Since no patient registries existed, we used claims data and data mining to achieve these aims.

Method: We performed a retrospective analysis of claims data from the Iran Social Security Organization, a health insurer which covers approximately 50% (~40 million) of the Iranian population. A data-mining algorithm using R software, validated using patient dossiers in the Cancer Research Center, identified 1295 patients and divided them into the three main HER2-positive breast cancer stages (early, loco-regional and advanced). Payers perspective was used to calculate the absolute and relative direct costs of medical services associated with the treatment of HER2-positive breast cancer in the public and private healthcare systems.

Results: The number of women totaled 802 (early), 125 loco-regional and 218 (advanced). Mean age was 45, 46 and 48 years, respectively, while mean follow-up in all stages was approximately one year. Average costs of direct medical care in early, loco-regional and advanced stages were €11,796 (95%CI: €9,356-€12,498), €8,253 (95%CI: €6,843-€10,002) and €17,742 (95%CI: €15,720-€19,505), respectively. Trastuzumab accounted for the largest share of total costs in all three stages (range: 53-76%).

Conclusion: Stage-specific cost estimates derived from this study can be used to perform real-world cost-effectiveness analyses of therapies for HER2-positive BC and support healthcare financing decisions. Moreover, wherever comprehensive patient registries are infeasible or costly, real-world costs can be estimated through claims databases and data-mining strategies.

Introduction

Breast cancer (BC) is the most frequent cancer in women worldwide with an estimated 1.67 million new cancer cases diagnosed in 2012 (25% of all cancers) [15,16,75]. BC is also a costly illness throughout the world. For example, the US National Institutes of Health has estimated that medical expenditures for cancer will increase by 27% in 2020 compared to 2010 due to growth and aging of the U.S. population, and estimated that BC will be responsible for a major share of $158 billion in 2020 [17].

BC has become one of the most frequent malignancies among Iranian women [19], which has led to increased efforts to find ways to reduce its burden through prevention or treatment. However, the impact of treating these patients on the overall healthcare budget can be dramatic because of the costs of medications such as targeted therapy with monoclonal antibodies (trastuzumab), even though the proportion of BC patients with HER2-positive is approximately 20-25%, [76]. Consequently, the decisions about financing and reimbursement regarding treatments for HER2-positive BC can be a serious issue for policymakers in Iran and other MICs [76-81].

Cost-effectiveness studies are used to ensure value for money in treatment of BC by any expensive interventions. These studies need stage-specific patient level information both in costs and quality adjusted life years (QALYs) [82]. As far as we know, there is no country-specific cost analysis in Iran that has reported results representing the general Iranian population.

Patient registries play an important role in providing patient level data that can be used to estimate the real-world effectiveness and effectiveness of treatments. However, their implementation is costly and sometimes infeasible in many MICs. Therefore, there is an important knowledge gap for cost estimation in these countries. On the other hand, claims databases are one of the possible sources to investigate resource use and costs in these countries. These sources of data can be used to estimate stage-specific costs, if patients were classified based on their disease stages. In this study, we used a tool to predict some important and necessary information that we normally obtain from patient registries.

The first aim of our study was to estimate a real-world direct medical costs of HER2-positive BC treatment in Iran. The second aim was to examine the fraction of stage-specific total costs related to different stages of HER2-positive BC. These aims were achieved by using data-mining techniques applied to claims databases.

Methods

General study design

In sum, data from a claims database of the largest health insurance database in Iran were processed using data mining, combined with data from other sources, and then analyzed to estimate the direct medical costs of HER2-positive BC in each disease stage from payers perspective. The results of the data-mining process were verified using patient registry data. The following sections describe the main parts of the study. Figure 4.1 shows an overview of the different steps of the study.

Data sources for healthcare resource use

Three sources were used to estimate healthcare resource use. Most data on outpatient services and costs were drawn from a major claims database of the Social Security Organization (SSO), a social and health insurance organization that covers more than 50% (~40 million insurees) of the whole Iranian population [54]. Due to absence of an integrated country level database, data on inpatient services came from two general referral hospitals (Fayazbakhsh and Alborz), which operate under the supervision of the SSO [51]. Outpatient and inpatient data were received anonymously. Lastly, we used the results of a survey of 52 oncologists [76] to estimate some minor outpatient costs in those rare cases where health care services were not covered by the SSO (e.g., services provided by doctors in their private offices). Using all these available data, this study conducted in three steps.

Step 1: Data-mining (Identification and categorization of patients and treatment regimens)

This step comprised several sub-steps which are as follows:

- **Step 1.1: Design of patient classification algorithm**

The results of a survey of oncologists [6] and other sources such as clinical guidelines [1,9,10] were used to design a strategy for patient classification. The strategy was assessed by two academic oncologists and modified based on their feedback. The final patient classification algorithm was based on medication pattern (combination and/or sequence of drug administration) seen between three index dates.
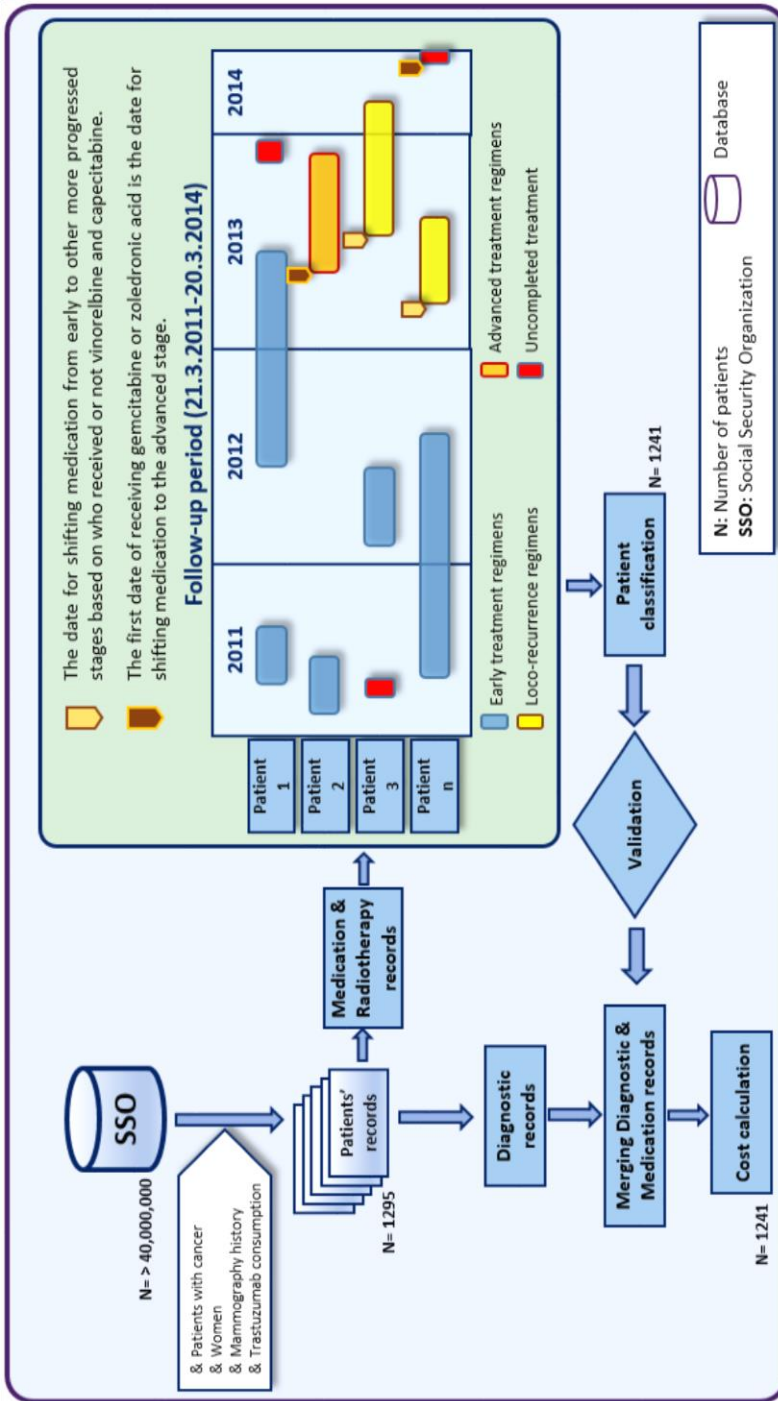
Figure 4.1: An overview of the different steps of the study

- **Step1.2: Data requirements**

Since different types of data were needed to classify patients and estimate stage-specific costs, we prepared a list of necessary data in each category and then defined our data extraction strategy.

- **Step 1.3: Data extraction**

Four filters were used to select patients with HER2-positive BC in the main SSO database: diagnosis of cancer, female, history of a mammography and trastuzumab use in the past two years. The Iranian national health services coding system was used to identify women who underwent a mammography and received trastuzumab. After identifying patients, all cost data associated with BC in various healthcare services (e.g. medication, diagnosis tests, medical imaging, radiotherapy and hospitalization) were then extracted from different databases.

- **Step 1.4: Data cleaning**

This step involved a check for duplications, completeness of data, and consistency of chemotherapy approaches. Any duplicated records were removed from the database. Then, to improve completeness and uniformity of data, two exclusion criteria were applied. Firstly, we excluded patients who did not receive more than five "prescriptions" (or requests for a healthcare service) for a period longer than 2 months since the date of the first prescription containing chemotherapy. Secondly, patients were also excluded if they had a treatment regimen that was different than our previously defined treatment strategies.

- **Step 1.5: Applying classification algorithm**

Classification algorithm was used to categorize patients into three different stages ("early BC", "loco-regional BC" and "advanced BC") based on medication patterns over a 3-year observation period (21.3.2011-20.3.2014). A decision tree induction using a divide-and-conquer approach [83] was used to predict disease stages. We also used distance matrix analysis [84,85] to obtain possible medication combinations (Figure 4.2). In the divide phase, we divided outpatient records into three main groups (radiotherapy, chemotherapy, and other medications). The main groups were continually divided into a number of subgroups of the same (or related) type until these subgroups became simple enough to find possible combination by using distance matrix. Then, in the conquer phase we found possible combinations of medication and radiotherapy over the observation period. Based on the results of the survey and guidelines we combined these different combinations to find the possible medication patterns. Afterwards, we calculated the probability that a particular woman had early

BC, loco-regional BC or advanced BC. The probability that a woman was in a given health state was based on the 'confidence' about the association between our previously defined patterns and discovered patterns. Therefore, the confidence was calculated by the number of discovered medication patterns representing any specific health state divided by the number of all discovered medication patterns in all health states [84]. For example, if data-mining found one medication pattern that represents early BC and there were three discovered medication patterns (regardless of the disease stage), then the value of confidence for early BC would be 33.3%. We also defined a minimum threshold of 70% for stage-specific confidence. If the confidence of one of the three stages was higher than 70%, the patient was categorized into that stage. Otherwise, we examined the possibility of overlap between the groups. In other words, the possibility that patients progressed during the observational period (e.g. from early BC to loco-
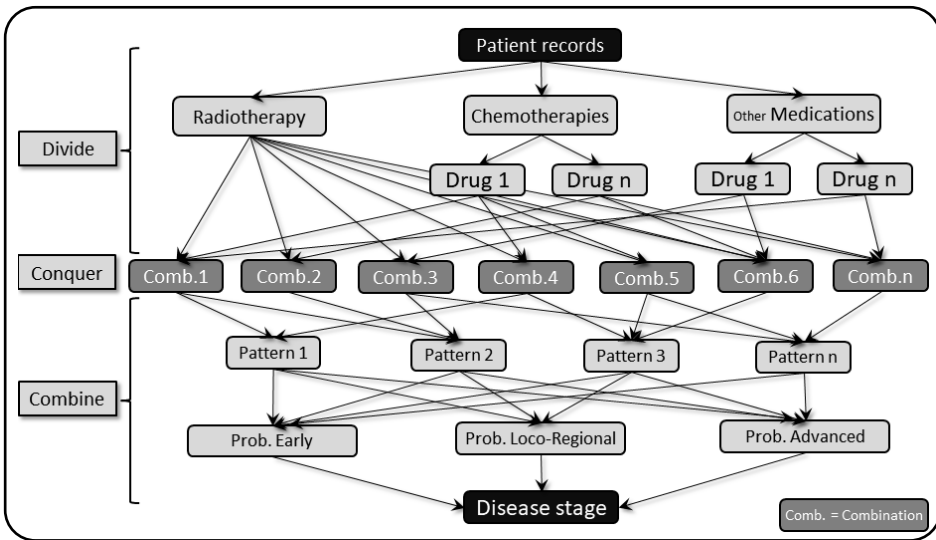
Figure 4.2: The processes of patient classification

regional or advanced BC). In this case, we looked at the difference between index dates of each health state. If the difference between two or three index dates was more than 3 months, patients were categorized into multiple stages with different index dates, otherwise the health state with the highest confidence was selected. For patients with early BC, an index date was set for each patient according to the first date of chemotherapy or radiotherapy (whichever happened earlier) according to possible drug combinations for early BC treatment. The loco-regional BC index date was defined as the first date when the patient received vinorelbine or capecitabine use or single-agent chemotherapy by taxols (docetaxel or paclitaxel). Finally, the index date for advanced BC patients was the first date of gemcitabine, zoledronic acid or temozolomide use. Patients who could not be classified into one of the three stages due to lack of chemotherapy records were categorized as unclassifiable.

In general, data-mining resulted in the classification of patients into three health states, including a patient-specific time interval representing the start and end dates of treatments at any particular health state.

Step 2: Verification of patient classification algorithm

Patient-level data from the Cancer Research Center (CRC) were used to verify the results of the patient classification algorithms. We included all patients at this center who were HER2-positive and SSO beneficiaries (n=51); patients were considered to have HER2-positive BC if their IHC result showed two or more pluses or their FISH test was positive. Verification involved comparing the results of the algorithm results with the clinical results based on the tumor, node, and metastases (TNM) classification system. We examined if patients categorized as having early stage BC by the classification algorithm were in stages I or II of BC, if patients with loco-regional BC had stage III BC and if patients with advanced BC had stage IV BC.

Step 3: Cost calculations

Firstly, 'service-based treatment costs' were estimated using the national coding system for health care services. All outpatient and inpatient services costs are classified based on national coding system for healthcare services. Outpatient care costs were calculated focusing on prevalent healthcare services (e.g. chemotherapy, hormone therapy, radiotherapy, diagnostic tests and medical imaging). Inpatient costs were estimated by extracting data from two hospitals on the surgical procedures used in BC management (e.g., lumpectomy, mastectomy and oophorectomy); this data were extracted from the same period as the outpatient data (21.3.2011-20.3.2014).

Afterwards, we used the results of data-mining to calculate 'stage-specific treatment costs'. As mentioned earlier, data-mining was used to categorize patients into three health states. Moreover, data-mining helped us to determine the duration of time that individual patients spent in each health state (stage-specific time interval). Therefore, stage-specific costs over time were estimated as follows. Various outpatient healthcare services costs (e.g. medications, radiotherapy, diagnostic tests, medical imaging) were calculated based on the individual stage-specific time interval. For those patients whose outpatient and inpatient data were available, inpatient costs were categorized based on their stage-specific time interval obtained from data-mining on outpatient data.

In both service-based and stage-based costs, we also included treatment costs in the private sector, since the unit costs can differ between the public and private sector and patients are free to choose their healthcare provider [51]. Therefore, to estimate the treatment costs of patients in the private sector, the prices of medical services in the public sector were first converted to private prices based on the official private tariffs

in the period of 2011-2014 [86]. Treatment costs in the private sector were then calculated based on amount of resources used and converted prices. In certain rare instances, this conversion was also based on the results of a survey of Iranian oncologists [76]. In all above steps, costs unassociated with BC as well as the costs of uncompleted treatment regimens were excluded from the analysis.

Analysis

The claims data were analyzed to determine the mean and distribution of resource use and costs of different medical treatment regimens, including chemotherapy, hormone therapy, radiotherapy, laboratory tests, medical imaging services and surgery in the different BC stages. 95% confidence intervals (CIs) were calculated using non-parametric bootstrapping. The number of iterations was 2000 times in all cases. All data-mining process and calculations were made using R software (version 3.2.2) for Windows.

Results

Data extraction, cleaning and patient classification

The data extraction process yielded 1,295 patients with an average age of 44 years (Table 4.1). 54 patients were excluded from the study due to small number of prescriptions or inconsistency between their chemotherapy approach and our previously defined drug combinations. Of the 1,241 patients, 802, 125 and 218 patients were categorized into early BC, loco-regional BC and advanced BC, respectively. The mean ages of women in the different health stages ranged from 45-48 years and average follow-up durations per patient was 425 days. Furthermore, on average, the follow-up duration per stage were 397 (early BC), 349 (loco-regional BC) and 357 (advanced BC) days. During the follow-up period, 158 patients with early BC progressed to loco-regional (n=41) or advanced BC (n=106), 19 patients progressed from loco-regional to advanced BC, and 11 patients progressed through all three BC stages. Finally, 284 patients were not classifiable due to lack of chemotherapy records.

Table 4.1: Age characteristics of study patients with HER2-positive BC

Stages	Before analysis	Early BC	Loco-regional BC	Advanced BC
Number of patients	1295	802	125	218
Age	at start date (2011-03-21)	at index date	at index date	at index date
Average [SD]	44 [10]	45 [10]	46 [10]	48 [10]
Age range (%)				
≤34	222 (17)	120 (15)	15 (12)	21 (10)
35-44	447 (35)	261 (33)	46 (37)	54 (25)
45-54	409 (32)	267 (33)	38 (30)	84 (39)
55-64	172 (13)	124 (15)	22 (18)	47 (22)
≥65	45 (3)	30 (4)	4 (3)	12 (6)

Abbreviation: SD: Standard Deviation

Patient classification verification

Patient-level data, obtained from CRC, represents a group of patients who were 65% (n=33) in early BC, 10%(n=5) in loco-regional BC and 25%(n=13) in advanced BC. Verification of the classifications based on data-mining revealed an 84% (n=43) accuracy rate. Specifically, 49% (n=25) of early BC, 12% (n=6) of loco-regional BC and 27% (n=14) of advanced BC patients were correctly categorized. Two (4%) patients had both loco-regional and advanced BC in the observation period. Some patients with loco-regional and advanced BC were incorrectly categorized as having early stage BC (14% (n=7) of patients in the loco-regional stage and 2% (n=1) of patients with advanced BC). In contrast, data-mining was able to categorize patients in loco-regional or advanced BC with 100% accuracy.

Service-based treatment costs - Outpatient costs

The different outpatient costs are shown in Table 4.2. The costs were weighted based on proportion of resource use between public and private sectors; medication costs required no weighting because there are no price differences between the two sectors. The average costs also include the costs of drugs used as concomitant drugs in chemotherapies like antiemetics. The most common chemotherapy regimen among early BC patients consisted of a taxane (docetaxel or paclitaxel) along with doxorubicin and cyclophosphamide (66%). The more expensive medications in early BC comprised different combinations of chemotherapy including docetaxel. Patients with loco-regional BC were almost uniformly distributed among different treatment regimens. Vinorelbine was used in the treatment of almost half (45%) of the advanced BC patients. Tamoxifen and letrozole were the two most common types of hormone therapy.

Table 4.2: A verage costs of outpatient services

Costs as of 20.03.2014 (1€=34,000 rials)	Provided by public sector*	Treated (%)	Mean [SD] €	Range €
		n=1,241		
Medications				
Chemotherapy (Early BC)				
All	NA	802 (65)	11,865 [8,247]	623-45,275
trastuzumab	NA	757 (61)	10,565 [7,668]	332-40,447
doxorubicin + cyclophosphamide + docetaxel	NA	314 (25)	2,480 [1,335]	105-6,925
doxorubicin + cyclophosphamide + paclitaxel	NA	236 (23)	1,164 [433]	249-2,444
epirubicin + cyclophosphamide + docetaxel	NA	100 (8)	2,507 [1,016]	703-5,459
fluorouracil + epirubicin + cyclophosphamide + docetaxel	NA	65 (5)	2,108 [988]	372-4,737
epirubicin + cyclophosphamide + paclitaxel	NA	39 (3)	1,321 [390]	638-2,249
fluorouracil + doxorubicin + cyclophosphamide + docetaxel	NA	19 (2)	1,747 [802]	713-3,474
paclitaxel OR docetaxel + carboplatin	NA	14 (1)	1,953 [1,081]	297-3,721
fluorouracil + epirubicin + cyclophosphamide + paclitaxel	NA	12 (1)	940 [235]	604-1,337
fluorouracil + doxorubicin + cyclophosphamide + paclitaxel	NA	7 (1)	1,293 [560]	402-2,196
Chemotherapy (Loco-regional BC)				
All	*NA*	125 (10)	7,776 [6,768]	75-34,363
trastuzumab	*NA*	90 (9)	8,346 [6,420]	820-29,700
capecitabine	NA	42 (3)	604 [472]	140-2,165
vinorelbine	*NA*	26 (3)	1,129 [1,124]	26-4,929
paclitaxel	NA	19 (2)	750 [612]	188-2,846
paclitaxel OR docetaxel + capecitabine	NA	18 (2)	1,881 [1,415]	151-4,884
docetaxel	NA	18 (2)	1,741 [884]	392-3,697
paclitaxel OR docetaxel + carboplatin	NA	5 (0)	1,597 [1,415]	446-4,047
Chemotherapy (Advanced BC)				
All	NA	218 (18)	14,191 [12,045]	108-49,453
trastuzumab	NA	198 (16)	11,471 [8,793]	756-42,560
vinorelbine	NA	72 (6)	1,967 [1,769]	41-8,845
capecitabine	NA	63 (5)	1,277 [845]	159-3,579
paclitaxel OR docetaxel + capecitabine	NA	29 (2)	1,347 [1,080]	93-2,665
paclitaxel OR docetaxel + carboplatin	NA	15 (1)	1,672 [1,380]	236-5,627
docetaxel	NA	16 (1)	1,039 [830]	265-2,690
paclitaxel	NA	13 (1)	2,021 [1,918]	155-6,217
doxorubicin + cyclophosphamide + docetaxel	NA	3 (0)	1,656 [839]	693-2,227

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Continued	Provided by public sector*	n=1,241		
Costs as of 20.03.2014 (1€=34,000 rials)		Treated (%)	Mean [SD] €	Range €
doxorubicin + cyclophosphamide + paclitaxel	NA	3 (0)	1,207 [685]	542-1,910
fluorouracil + epirubicin + cyclophosphamide + paclitaxel	NA	3 (0)	1,839 [640]	1,223-2,501
epirubicin + cyclophosphamide + docetaxel	NA	1 (0)	713 [NA]	NA
fluorouracil + epirubicin + cyclophosphamide + docetaxel	NA	1 (0)	1,683 [NA]	NA
fluorouracil + doxorubicin + cyclophosphamide + paclitaxel	NA	1 (0)	2,529 [NA]	NA
epirubicin + cyclophosphamide + paclitaxel	NA	0 (0)	0	0-0
fluorouracil + doxorubicin + cyclophosphamide + docetaxel	NA	0 (0)	0	0-0
lapatinib + capecitabine	NA	0 (0)	0	0-0
Hormone therapy				
All	NA	662 (53)	168 [241]	1-1,257
tamoxifen	NA	272 (22)	11 [8]	0-42
tamoxifen + triptorelin	NA	135 (11)	407 [245]	51-1,145
letrozole	NA	115 (9)	67 [48]	8-327
triptorelin	NA	56 (5)	259 [206]	41-812
tamoxifen + letrozole + triptorelin	NA	27 (2)	475 [329]	69-1,257
tamoxifen + letrozole	NA	26 (2)	75 [44]	22-169
exemestan	NA	9 (1)	436 [178]	164-777
letrozole + triptorelin	NA	7 (1)	553 [356]	229-1,187
tamoxifen + exemestan	NA	2 (0)	553 [232]	389-717
goserelin	NA	0 (0)	0	0-0
Visit and administration				
Oncologist visits per session	0.54[#]	1,241 (100)	4[+] [2]	2[Y]-7[Y]
Chemotherapy administration per session	0.61[#]	1,241 (100)	28[#] [23]	4[#]-103[#]
Cardiac monitoring services				
Cardiac drugs	NA	676 (55)	8 [15]	1-156
Internist or Cardiologist visits	0.45	715 (70)	16 [21]	3-206
Cardiology services	0.63	115 (9)	518 [457]	136-1,989
Radiotherapy	0.31	231 (19)	2,426 [1,313]	110-8,530
Laboratory tests				
All	0.21	1,180 (97)	112 [88]	2-1,308
Sampling fees	0.26	1,151 (93)	5 [4]	0-33
Hematology	0.25	1,129 (91)	10 [7]	1-50
Clinical chemistry	0.23	1,060 (85)	24 [24]	1-226
Cytopathology	0.19	786 (63)	6 [8]	2-56
Descriptive pathology	0.19	741 (60)	53 [34]	5-352
Tumor marker	0.16	693 (56)	32 [28]	0-263
Urinalysis	0.22	582 (47)	1 [1]	0-13
Hormones	0.15	549 (44)	13 [12]	3-105

Continued		n=1,241		
Costs as of 20.03.2014 (1€=34,000 rials)	Provided by public sector*	Treated (%)	Mean [SD] €	Range €
Serology and immunology	0.17	403 (32)	10 [15]	1-208
Microbiology	0.27	332 (27)	2 [2]	0-24
pecific clinical chemistry	0.17	320 (26)	8 [6]	1-43
Coagulation	0.17	241 (19)	3 [3]	1-36
Cytogenetics	0.17	24 (2)	162 [114]	2-400
Molecular genetics	0.06	21 (2)	87 [244]	16-1,140
Medical imaging				
All	0.19	1,157(93)	612 [1,158]	3-8,697
Ultrasound	0.14	833 (67)	29 [26]	4-197
X-ray	0.22	787 (63)	25 [18]	3-115
CT Scan	0.24	666 (54)	73 [58]	12-443
Nuclear medicine	0.15	476 (38)	73 [66]	15-1,347
MRI	0.22	313 (25)	80 [67]	30-715
Other services	0.25	26 (2)	83 [27]	21-115

NA Not Applicable

* This column shows the proportions of healthcare utilization in the public sector (Number of services in public sector/Total number of services (private + public)).

# The data obtained from the results of a questionnaire survey. [76]

Y The unit costs obtained from the national health care services tariff 2014 [87]

+ The unit cost obtained from the SSO yearly report (2014) [58]

Abbreviation: SD: *Standard Deviation,* ***CT-Scan:*** *Computed Tomography Scan,* ***MRI:*** *Magnetic Resonance Imaging*

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In all three BC stages, there is a rapid increase in outpatient-related costs during the first year after the index date (Figure 4.3) followed by a gradual increase and a plateau.
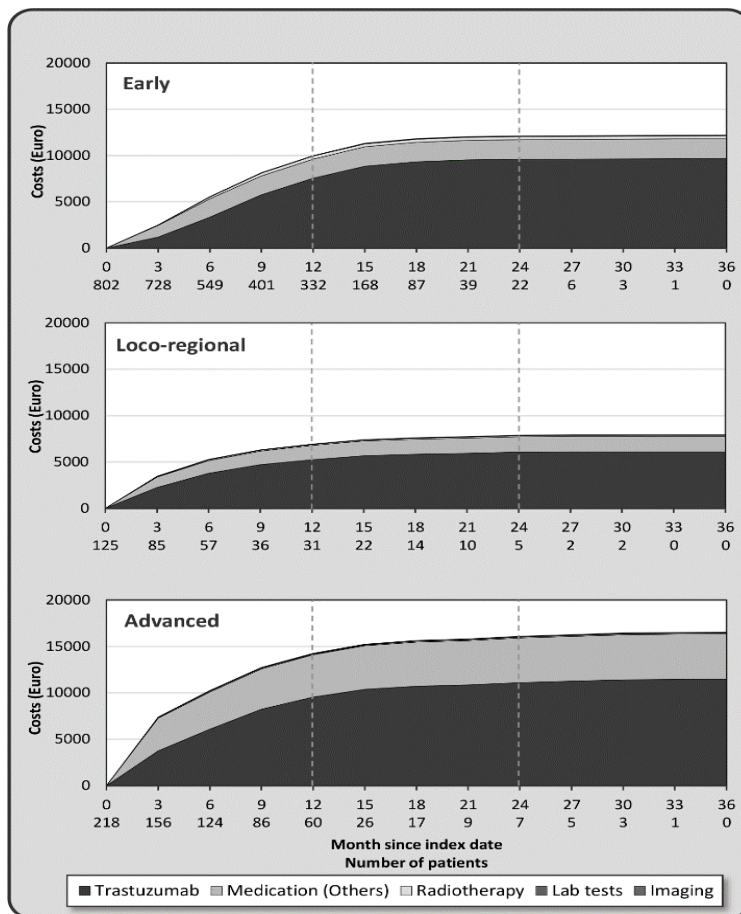
Figure 4.3: Cumulative outpatient costs in different health states of HER2-positive breast cancer in Iran, over a 3-year follow-up period (21.3.2011-20.3.2014).

Service-based treatment costs - Inpatient costs

Table 4.3 shows the inpatient costs based on the two main surgical operations (mastectomy and oophorectomy), which were based on information from two hospitals and 710 patients. The mean costs were calculated using all components of hospitalization costs, including procedure, nursing, accommodation, medication, laboratory tests, medical imaging, pathology, medical equipment and physiotherapy.

The mean costs of mastectomy and oophorectomy were 293 and 261 euros respectively.

Table 4.3: Average costs of mastectomy and oophorectomy.
(Costs as of 20.03.2014; 1€=34,000 rials)

Inpatient services	Number of patients	Mean admission days[SD]	Mean cost[SD] €	Range €
Mastectomy	**141**	**3.57 [3.09]**	**293 [178]**	**31-1,242**
Partial	42	1.93 [1.47]	125 [138]	38-718
Partial with axillary lymphadenectomy	7	3.29 [1.11]	179 [63]	103-254
Simple, complete	20	1.60 [1.43]	103 [65]	53-350
Radical, including pectoral muscles and axillary lymph nodes	7	4.57 [3.26]	190 [90]	68-324
Radical, including internal mammary lymph nodes, unilateral	41	5.49 [3.52]	261 [174]	111-1,144
Modified radical, including axillary lymph nodes but leaving pectoral muscles	24	4.63 [2.90]	309 [247]	31-1,242
Oophorectomy	**569**	**3.38 [4.68]**	**261 [172]**	**62-2,550**
Partial resection of ovary (unilateral or bilateral)	145	3.60 [3.62]	161 [102]	62-756
Wedge resection or bisection of ovary (unilateral or bilateral)	14	6.14 [7.90]	209 [111]	113-547
Ovarian cystectomy (unilateral or bilateral)	374	3.24 [4.83]	200 [196]	66-2,550
Oophorectomy, Unilateral or bilateral, partial or total	36	2.92 [1.42]	166 [104]	83-570

Abbreviation: SD: *Standard Deviation*

Stage-specific direct medical healthcare costs

As Table 4.4 shows, trastuzumab accounted for the largest share of total direct medical costs; its share was almost 76% for early BC, 73% for loco-regional BC and 56% for advanced BC. The relative costs of other medications (including chemotherapy, cardiovascular drugs, analgesics and hormone therapies) were similar in early BC and loco-regional BC but much greater in advanced BC (Figure 4.3). Other cost components comprised a limited share of the total costs.

The average cumulative direct medical costs for early BC were €11,796 (95% CI: €9,356-€12,498) over the follow-up period. The treatment costs for loco-regional BC averaged €8,253 (95%CI: €6,843-€10,002). In contrast, the mean costs for advanced BC (95% CI) was 17,742 (€15,720-€19,505), which was roughly 50% higher than the costs for early stage BC.

Table 4.4: The overall average costs (public and private sectors) in three stages of BC during the follow-up period. Results after applying nonparametric bootstrapping.

Costs as of 20.03.2014 (1€=34,000 rials)

	Provided by public sector*	Early BC	Loco-regional BC	Advanced BC
Number of patients		**802**	**125**	**218**
Average follow up period (Days [SD])		**397 [198]**	**349 [234]**	**318 [204]**
		Mean € (SE) 95%CI	**Mean € (SE)** 95%CI	**Mean € (SE)** 95%CI
Trastuzumab	NA	**9,018** (233) 8,566-9,452	**6,009** (591) 4,975-7,296	**12,985** (648) 11,745-14,340
Medications (Others)	NA	1,838 (44) 1,764-1,944	1,642 (125) 1,422-1,906	**3,547** (127) 3,274-3,858
Specialists visit	0.54	**79** (4) 76-82	**86** (7) 74-98	**119** (11) 107-132
Chemotherapy administration#	0.61	**135** (46) 122-149	**145** (42) 129-161	**220** (16) 201-239
Radiotherapy	0.46	**440** (32) 382-507	**243** (61) 137-385	**121** (48) 57-298
Laboratory tests	0.16	**57** (2) 54-61	**51** (6) 42-65	**54** (5) 46-64
Medical imaging	0.24	**55** (2) 51-60	**77** (7) 64-91	**91** (10) 75-118
Inpatient services	0.83	174 (49) 105-243	-	**335** (102) 215-456
Total (95%CI)		**11,796** 9,356-12,498	**8,253** 6,843-10,002	**17,742** 15,720-19,505

CI Confidence Interval; **NA** Not Applicable; **SE** Standard Error;

* This column shows the proportions of healthcare utilization in the public sector. (Number of services in public sector/Total number of services (private + public).

The data obtained from the questionnaire [76]

Abbreviation: SD: *Standard Deviation,* ***SE:*** *Standard Error*

Discussion

BC is a costly illness throughout the world in general. When monoclonal antibodies like trastuzumab or pertuzumab are used and included for treatment of BC, then it would be a very costly illness with a significant budget impact specifically in MICs. We performed a real-world cost analysis using a large claims database and a validated patient classification algorithm to estimate stage-specific healthcare utilization and costs in associated with HER2-positive BC in Iran.

Our findings show that total direct medical costs per patient averaged €11,796 for early BC, €8,253 for loco-regional BC and €17,742 for advanced BC. The largest share of the total cost is spent on trastuzumab. Other medications like chemotherapy and hormone therapy are the second most important cost drivers in BC. The relative costs of other medications associated with advanced BC were dramatically higher compared with early and loco-regional BC (Figure 4.3). This was due to the use of other expensive medications to manage the effects of cancer metastasis to other organs or other medications to control the side-effects of chemotherapy. In early BC, the most common regimens of chemotherapy were the combination of an anthracycline antibiotic like doxorubicin and cyclophosphamide followed by a taxane like docetaxel. This was also in accordance with the results of a previous study [76]. In contrast to costly outpatient services, inpatient medical cares had only a minor impact on total costs. It should be noted that BC treatment in Iran is mostly provided on an outpatient basis, something that has been emphasized in studies in other countries [88]. For example, Vera-Lionch et al showed that inpatient costs of BC care, even for metastatic BC, accounted for approximately 20% of total BC costs in the United States [88]. These results (Table 4.1) reveal that the average age of BC is lower than the average age seen in other countries. Fifty years has been considered as the average age for early HER2-positive BC based on the majority of trials [30,89,90]. These results also correspond with the findings of previous Iranian epidemiological studies [91,92].

The direct costs of treating patients with BC have been already estimated based on patients referred to one hospital in Iran [22]. Although that study examined the costs in different disease stages, its study population was small, which limited the precision of the results, and only one hospital was included, which limited the generalizability of the findings. In addition, that study did not report the costs of patient subgroups with tumor receptor expression. In contrast, our study provides more details concerning different treatment patterns and cost components on a national level, although it focused only on HER2-positive BC. Another recently published study of the economic burden of BC in Iran estimated the direct medical costs of BC using a societal perspective [23]. However, comparisons between their results and our results are not possible since the authors did not report resource use and unit costs separately [82].

Like any study, our study also has its limitations. The first limitation relates to our study population. That is, one could argue that the claim data covers approximately 50% of the population and therefore may not represent the whole Iranian population. However, our results can be generalizable to the whole population because the four main payers in Iran have the same benefit package and because the SSO covers the insurees from different socio-economic classes in all provinces [6]. Secondly, we focused on BC patients treated with trastuzumab limits the generalizability of the cost

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estimates to other BC patients. While this is certainly true for trastuzumab costs, this selection is likely to have only a limited effect on other costs since trastuzumab use does not affect the choice of drug combinations or decisions about dose adjustment of chemotherapy. Therefore, our findings can cover direct medical costs in both patient populations by including or excluding the costs associated with trastuzumab. Thirdly, since inpatient data from two hospitals was used, our cost estimates of inpatient care might not reflect the average costs across all hospitals in Iran. However, this limitation has no major impact on the overall results since BC management is mainly performed on an outpatient basis in Iran and the outpatient costs were based on data from more than 45,700 (~100%) healthcare providers [58]. Fourthly, while data mining achieved a high accuracy rate of 84% (of classifying patients into the correct stage of BC), it was not perfect, meaning that some patients were incorrectly classified. Cost estimates using the verification results led to an increase in total costs for loco-regional BC (i.e., €10,161, 23% higher than the €8,253 from data mining) and a slight decrease in total costs for advanced BC (i.e., €17,402, 2% lower than the €17,742 from data mining), respectively. Therefore, total costs in loco-regional BC should be used with caution. The accuracy of classification can be improved by adding electronic results of diagnosis tests to the patient classification algorithms. Finally, the cost estimates in our study do not include illegal and informal payments [93] by patients to health care providers. Authorities in the Ministry of Health currently claim that they were able to reduce improper payments significantly over the past three years as a result of president Rouhani's health care reform implementation [94]. However, due to lack of information we are not able to determine its impact on the final results of this study. The importance of excluding these costs may not be significant if the perspective of the health care is taken in estimating costs but could be important if a societal perspective is taken.

This study shows that if relevant data are available, data-mining techniques can provide cost estimates that are invaluable in performing real-world cost-effectiveness analyses in MICs. National level cost-effectiveness analyses can use these cost estimates to determine if these costs are justified from a health economic viewpoint. For example, policymakers can reduce uncertainties about the cost-effectiveness of trastuzumab by performing a cost-effectiveness analysis using the results of our real-world cost analysis.

The quality of reimbursement decision-making can be improved by using information about actual healthcare utilization and costs. One option in high-income countries would be an extensive cost analysis supported by patient registry data and electronic health records. However, implementation of comprehensive patient registries is costly and sometimes logistically infeasible in many MICs. If integrated electronic records are unavailable, researchers may have to rely on small sample sizes or expert opinion (e.g., [22], [23]) to estimate the medical direct costs of an illness. Both of these methods have

their shortcomings, which might affect the internal validity and generalizability of the results. Claims databases would be useful sources for cost analyses in MICs as long as the disease status of patients is known or adequately predicted.

Conclusion

This study estimated the stage-specific direct medical costs associated with HER2-positive BC in Iran using a large claims database and data mining with validated patient classification algorithms using data from a patient registry. The findings show that the largest component in overall costs in all stages of BC is medication and that trastuzumab is the major cost driver. These real-world data can support cost-effectiveness analyses of implementation new technologies for HER2-positive BC management and thereby help to optimize reimbursement decision-making in an MIC.

Acknowledgment:

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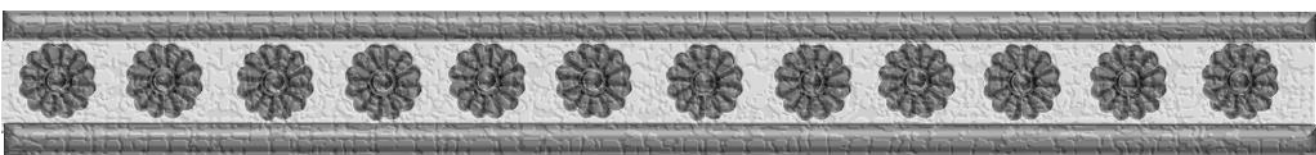
Chapter 5

Adjuvant trastuzumab therapy for early HER2-positive breast cancer in Iran. A cost-effectiveness and scenario analysis for an optimal treatment strategy

Amir Ansaripour, Carin A. Uyl-de Groot, W. Ken Redekop

Abstract

Introduction: Clinical guidelines have recommended a one-year trastuzumab regimen as standard care for early HER2-positive breast cancer. However, this recommendation can have a dramatic impact on total drug expenditures in middle-income countries (MICs). We performed a cost-effectiveness analysis from the Iranian healthcare perspective to find an optimum duration of trastuzumab use in Iran.

Method: We compared four treatment strategies comprising chemotherapy and varying durations of trastuzumab use (no-trastuzumab, 6-month, 9-month, and one-year). A Markov model and probabilistic sensitivity analysis were used to estimate the costs and effects of the strategies. We then examined the cost-effectiveness of the strategies at different willingness-to-pay (WTP) thresholds, and ages at the onset of treatment.

Results: Incremental costs (vs. no-trastuzumab) were €8,826 (6-month), €13,808 (9-month) and €18,588 (12-month) while incremental QALYs were 0.65 (6-month), 0.87 (9-month) and 1.14 (12-month). At a threshold of 3×GDP/capita (€21,000/QALY) and for patients younger than 59 years, the 6-month protocol was most likely to be cost-effective (probability of 42%). At a threshold of 4×GDP/capita (€28,000/QALY), the 6-month and one-year regimens were essentially equal in cost-effectiveness (37% and 35%, respectively). At this WTP threshold, the 6-month and one-year regimens were optimal strategies only for patients up to 66 and 44 years respectively.

Conclusion: In contrast to clinical guidelines, 6 months of trastuzumab may be the most cost-effective option for Iran. The lower absolute WTP threshold and lower life expectancy compared to high-income countries are two crucial parameters in cost-effectiveness of interventions in MICs. It is therefore necessary to strive a balance between maximum population health and maintain affordability in these countries.

Introduction

Trastuzumab is a monoclonal antibody that is used in the management of breast cancer (BC). It has mostly been used as adjuvant treatment for patients in the early stage of BC who overexpress human epidermal growth factor receptor 2 (HER2). Trastuzumab's huge share of total drug expenditure, particularly in middle-income countries (MICs), has raised concerns among policymakers regarding efficient resource allocation in their countries [76]. To date, one year of trastuzumab use is considered as the optimum duration of therapy for the adjuvant treatment of the early stage of HER2-positive BC [28,89,95] based on the results of various randomized controlled trials (RCTs).

Iran, as an MIC, provided a national guideline that recommends a 9-week period of trastuzumab use [50] due to unaffordability of one year trastuzumab therapy [76]. However, clinical evidence suggests that very short durations of trastuzumab therapy cannot provide significant efficacy [28]. Therefore, the main question in this regard is "What is the maximum obtainable level of health in an MIC when we are dealing with an expensive intervention?"

The aim of this study is to provide a model-based cost-effectiveness analysis (CEA) of adjuvant trastuzumab for patients with early HER2-positive BC from the Iranian healthcare perspective. Subsequently, we undertake a scenario analysis to determine the optimum duration of trastuzumab use in Iran.

Methods

In our study, we compared two treatment approaches (chemotherapy with and without trastuzumab) to managing early HER2-positive BC. A Markov model was used to estimate the marginal differences in clinical outcomes and healthcare costs. We designed a cohort for patients with HER2-positive BC and included the necessary information in this model to estimate the incremental cost-effectiveness ratio (ICER) of using trastuzumab for these patients with a lifetime horizon in Iran. Afterward, a scenario analysis was conducted to compare the cost-effectiveness of different strategies of trastuzumab therapy in an MIC.

Model structure

We designed a model structure based on three sources of information (Figure 5.1). Firstly, the routine practice of treating HER2-positive BC in Iran was understood based on a previous study of clinical practice using a claims database and clinician survey [76]. Then, we discussed our interpretations of the results through a number of interviews with two Iranian academic oncologists and based on our final decision on data availability. The model was designed to be able to compare two main arms

(trastuzumab versus no-trastuzumab). It included six main health states: 1) early BC, 2) loco-recurrence BC, 3) advanced BC, 4-5) two progression-free health states after treatment in early BC and loco-recurrence BC, and 6) death. We also included other health-state subgroups for loco-recurrence (loco-regional and second primary BC), and advanced patients (central nervous system (CNS), visceral, bone, and soft tissue metastasis). Moreover, we incorporated long-term cardiotoxicity in all states in which patients use trastuzumab. A three-month cycle length was used in the model [76].

In the model, patients with early HER2-positive BC received chemotherapy with or without trastuzumab. After treatment, patients moved to a follow-up state and could progress to local or advanced BC. Patients stayed in the follow-up state until the occurrence of progression (local or distance recurrence) or second primary BC. We assumed that patients in both arms were equally likely to receive all other medical services. Patients who had progressed to loco-recurrence after receiving the treatment
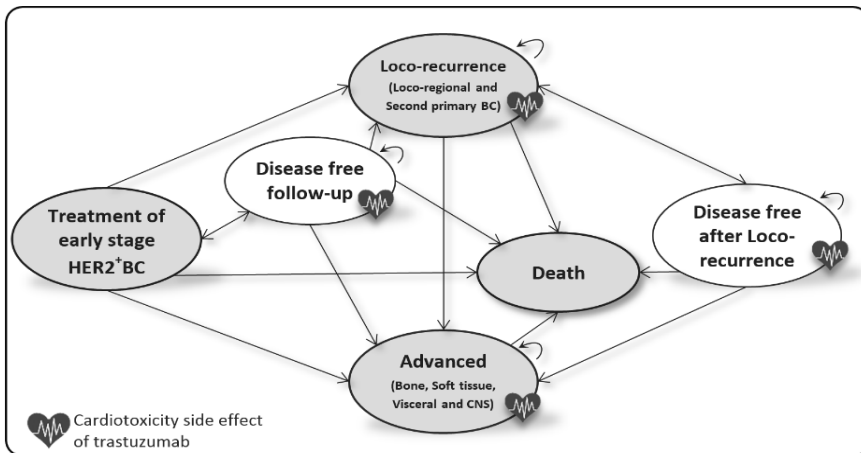
Figure 5.1: The summary model structure

could move to the disease-free state after the local-recurrence state or progress to advanced BC. Patients who progressed to advanced BC stayed there until they died from BC or other causes. Some of the patients who received trastuzumab developed reversible cardiac toxicity. Patients in all health states could die due to background mortality.

Patient characteristics

We set the age at onset of treatment at 45 years in accordance with the results of a variety of current claims database [96] and epidemiological [97-99] studies in Iran.

Transition probabilities

The following items describe the input parameters used in the model as well as their sources. Various transition probabilities used in the model are shown in Table 5.1.

- **Treatment effect**

Effectiveness of trastuzumab was derived from a Cochrane review [28], which was a comprehensive systematic review and meta-analysis of eight RCTs regarding disease-free survival (DFS) of trastuzumab. Due to our study design, we relied on a DFS hazard ratio based on the results of the meta-analysis of those trials (5 of 8) that investigated the effects of more than 6 months of trastuzumab therapy. To include the treatment effect duration in the model, we used an assumption that was used in a CEA of trastuzumab in the United Kingdom (UK) [31], based on discussions with experts.

- **Cancer progression**

For the first 4 years, the recurrence rate in the no-trastuzumab arm was obtained from the latest HERceptin Adjuvant (HERA) trial [30] report after 4-year patient follow-up [100]. For years 5-10, the recurrence rates were taken from the anthracycline-treated HER2-positive subgroup of the national surgical adjuvant breast and bowel project protocol (NSABP) B-15 trial [90]. Since the (NSABP) B-15 trial only focused on lymph node-positive patients, we applied a relative risk of 0.815 based on a study reporting that 63% of Iranian patients have node-positive BC at the time of diagnosis [19] and the assumption that node-positive patients have a recurrence rate that is two times greater than node-negative patients [101]. We also assumed no chance of recurrence after 10 years based on expert opinion. The ratio of loco-recurrences to distant recurrences was obtained from the results of the HERA trial [102]. Two hazard ratios were applied to represent the increased risk of distant metastases after local recurrence. These hazard ratios were 3.22 (95% CI 2.02, 6.55) and 6.14 (95% CI 2.02, 6.55) for years 1-4 and 5-10, respectively [103].

- **Cardiac toxicity**

The results of a systematic review and meta-analysis of the Cochrane review [28] were used to estimate the probabilities of decline in left-ventricular ejection fraction (LVEF) and congestive heart failure (CHF) occurring during one-year of trastuzumab therapy and other chemotherapy drugs. The time of onset and toxicity duration for patients who suffered from reversible cardiac toxicity were taken from the HERA trial [104]. Moreover, patients suffer from CHF based on an age-specific background and these probabilities were obtained from a cohort study of 6,504 individuals in one province of Iran [105].

Table 5.1: Transition probabilities.

Parameter	Base-case estimate	Distribution	Distribution parameters	Source
Trastuzumab effectiveness				
DFS hazard ratio (12 M vs 0 M)	0.62	Log-Normal	μ = -0.49, σ = 0.13	Moja et al. [28]
DFS hazard ratio (6 M vs 12 M)	1.28	Log-Normal	μ = 0.23, σ = 0.16	Pivot et al. [89]
DFS hazard ratio (9 M vs 12 M)	1.14	Log-Normal	μ = 0.13, σ = 0.08	Assumption
Treatment effect duration	48 M	Log-Normal	μ = 3.87, σ = 0.31	Hall et al. [31]
Disease progression				
Recurrence without trastuzumab				
Months 1-48	0.28	Beta	α = 472, β = 1226	Gianni et al. [100]
Months 49-60	0.23	Beta	α = 35, β = 116	Paik et al. [90]
Months 61-120	0.10	Beta	α = 11, β = 94	
Beyond 120	0	Fixed		Expert opinion
Loco vs distant recurrences				
Without trastuzumab	0.355	Beta	α = 100, β = 182	Gianni et al. [100]
With trastuzumab	0.372	Beta	α = 79, β = 133	
Distance recurrence pattern				
Without trastuzumab				
Bone	0.25		α1 = 38	
Soft tissue	0.12	Dirichlet	α2 = 19	Piccart-Gebhart
Visceral	0.53		α3 = 82	et al. [102]
CNS	0.10		α4 = 15	
With trastuzumab				
Bone	0.28		α1 = 24	
Soft tissue	0.07	Dirichlet	α2 = 6	Piccart-Gebhart
Visceral	0.40		α3 = 34	et al. [102]
CNS	0.25		α4 = 21	
Second primary or contralateral breast cancer				
Year 1-4	0.019	Beta	α = 33, β = 1698	Gianni et al. [100]
Year 5-10	0.026	Beta	α = 10, β = 359	Metzger-Filho et al. [106]
Increased risk of distant metastasis after local recurrence (hazard ratio)				
Years 1-4	3.22	Log-normal	μ = 1.16, σ = 0.14	Tanis et al. [103]
Years 5-10	6.14	Log-normal	μ = 1.68, σ = 0.52	
Cardiac toxicity				
Trastuzumab-induced decline in LVEF	0.112	Beta	α = 466, β = 4147	
Trastuzumab-induced CHF	0.025	Beta	α = 135, β = 5471	Moja et al. [28]
CHF due to chemotherapies	0.004	Beta	α = 20, β = 4810	
Duration of reversible cardiac toxicity	3 months	Fixed		Suter et al. [104]
Time of onset during treatment	3-6 months	Dirichlet	αs=8,69,14,27	
Population back ground level of CHF among Iranian females	Age specific	Normal		Talaei et al. [105]
Mortality				
Background mortality for Iranian females	Age specific	Fixed		NOfCR [107]
Breast cancer specific mortality for Iranian females	Age specific	Fixed		Vostakolaei et al. [97]
Mortality from heart failure for Iranian females (one-year - age adjusted)	0.263	Beta	α = 727, β = 2042	Talaei et al. [105]
Mortality due to metastatic BC				
Bone (over 5 years)	0.63	Beta	α = 17, β = 10	
Soft tissue (over 5 years)	0.77	Beta	α = 12, β = 4	Dawood et al. [108]
Visceral (over 5 years)	0.78	Beta	α = 28, β = 8	
Brain (over 9 months)	0.50	Beta	α = 54, β = 54	Niwinska et al. [109]

*Abbreviations: **CHF**: congestive heart failure; **DFS**: disease-free survival; **LVEF**: left ventricular ejection fraction; **M**: months*

- **Mortality**

Age-specific background mortality rates were obtained from online data by the national organization for civil registration (NOCR) [107] which included data on all causes of death in Iran. We used another study of BC mortality rates in three different age ranges [97] to subtract the BC mortality rate from the NOCR data. Data on the age-specific congestive heart failure (CHF) mortality rate in Iran was obtained from an Iranian cohort study [105]. Other parameters regarding BC mortality rates in various metastatic states were extracted from international studies.

Outcomes

Life-years (LYs) and quality adjusted life years (QALYs) were estimated for both arms. Table 5.2 shows the utility values used in this study. We used the results of a study that provided the utility weights for various health states, based on the EQ-5D questionnaire in Sweden [110]. Another study that used the EQ-5D was selected to find the utility weight for patients who suffer from symptomatic heart failure in the UK [111]. Finally, the utility value (EQ-5D) for patients with brain metastases was obtained from a CEA study in the UK [31].

Costs

Direct medical costs were calculated from an Iranian healthcare perspective. We assumed 100% coverage for all healthcare services by payers. It helps policymakers to examine the cost-effectiveness of complete coverage of all services. We used a recent study that investigated healthcare costs and resource use in both the public and private sectors in Iran which covers approximately 50% of all Iranians (~40 million) [96]. Due to the varieties of health insurance coverage in Iran [51], out-of-pocket payments were already included in cost calculations [96]. Therefore, the costs shown in Table 5.2 comprise the total costs of medical services. The average patient weight must be known to calculate the cost of trastuzumab. Therefore, we used data from a 3-year observational period [76] to estimate the average weight based on the average dose of trastuzumab per patient who used trastuzumab. The average dose per patient per prescription was 420mg (95% CI: 415-424) (n=1,295) which corresponds with an average weight of 70kg (69-71). While this may not represent the true average weight of the patients, these real-world data represent the total amounts of trastuzumab used and wasted in reality. Patients received trastuzumab in a 3-week cycle until the end of therapy.

The annual national healthcare tariff [112] was used to inflate or adjust the costs attained from years other than the 2014 to 2017 values.

Table 5.2: Utilities and costs (year 2017).

Parameter	Mean	Standard error	Distribution	Source
Health utilities				
Baseline (Disease free)	0.779	0.017	Beta	Lidgren et al [110]
Treatment of early stage	0.779	0.017	Beta	Assumption
Symptomatic cardiac toxicity	0.600	0.010	Beta	Calvert et al [111]
Loco-recurrence	0.780	0.040	Beta	
Second primary breast cancer (first year)	0.700	0.032	Beta	Lidgren et al [110]
Advanced (Bone, Visceral and Soft tissue)	0.690	0.033	Beta	
Advanced (Brain)	0.600	0.120	Beta	Hall et al. [31]
Costs (€)(1euro=34,000 rilas)				
Treatment				
Trastuzumab (1st cycle)	6,123		Fixed	SSO [113]
Trastuzumab (2nd, 3rd and 4th cycles)	5,623		Fixed	
Early treatment first year	3,689	245	Log-Normal	Ansaripour et al [96]
Trastuzumab administration (6-month)*	188	194	Log-Normal	
Trastuzumab administration (9-month)*	329	359	Log-Normal	
Trastuzumab administration (One-year)*	471	485	Log-Normal	
Follow-up annual cost	370	34	Log-Normal	
Cardiac toxicity				
Symptomatic heart failure annual cost	584	140	Log-Normal	Ansaripour et al [96]
Cancer recurrence costs				
Second primary breast cancer 1st year	6,024	228	Log-Normal	Ansaripour et al [96]
Second primary breast cancer annual cost	As follow-up annual cost		Log-Normal	Assumption
Loco-recurrence 1st year	3,922	177	Log-Normal	
Loco-recurrence annual cost	2,238	357	Log-Normal	Ansaripour et al [96]
Advanced treatment 1st year	18,151	1,394	Log-Normal	
Advanced treatment annual cost	8,324	2,027	Log-Normal	

* The cost of trastuzumab administration in the first 9 weeks is excluded here due to administration of trastuzumab with other chemotherapy drugs in the same sessions. The cost of trastuzumab administration in the first 9 weeks is included in the cost of early treatment in first year.

Analysis

In the absence of a national guideline for economic evaluations in Iran, both costs and effects were discounted by 3.5% per annum as suggested by the World Health Organization's choosing interventions that are cost-effective (WHO-CHOICE) project [114]. A half-cycle correction was also applied.

The influence of specific input parameters on the ICER of CEA was examined using deterministic sensitivity analysis (DSA). The ranges in values were determined based on the literature or expert opinion.

A probabilistic sensitivity analysis (PSA) was performed in order to quantify the overall uncertainty in the expected output measures [115,116]. The log-normal distribution was applied for relative risks, hazard ratios, and costs. The Dirichlet distribution was used for multinomial proportions and the beta distribution was used for binomial proportions and utility weights. The analysis used 10,000 iterations obtained via Markov Chain Monte Carlo simulation.

Based on WHO-CHOICE, the willingness-to-pay (WTP) threshold in Iran would be 3×GDP/capita, which is equal to 21,000 euros per QALY (1€=34,000 rials) [117]. Because widespread international economic sanctions on Iran began in 2012, we used gross domestic product (GDP) per capita in 2011, as reported by the World Bank [118], to avoid the effects of these sanctions on the Iran's GDP.

The building of the model, calculations, and statistical analysis were performed using R software for Microsoft Windows (Version 3.2.2) [119].

Estimation of the optimum duration and the max-age threshold for trastuzumab use

Three scenarios of 6-month, 9-month and one-year of trastuzumab use were designed to compare their cost-effectiveness. We used the results of PHARE (a randomized non-inferiority trial) [89], which compared six months versus one year of adjuvant trastuzumab therapy, and the results of a meta-analysis [28], which compared one year of trastuzumab versus no-trastuzumab therapy. For nine months of trastuzumab use, we assumed that the effectiveness hazard ratio which was half of the non-inferiority hazard ratio in PHARE trial (Table 5.1). The ICERs of the three strategies were calculated, and, eventually, their probability being cost-effectiveness were compared with that of the no-trastuzumab arm. Furthermore, due to the importance of patient age, we investigated how the age threshold for treatment can affect the optimal duration of trastuzumab use. Multiple PSAs were performed with various ages (40-70) as the age at onset of treatment to determine the 'max-age threshold' for the best-case scenario. The 'max-age threshold' represents the maximum age at onset of treatment that still results in the strategy being optimal versus other strategies included in the comparison at a particular WTP threshold.

Model validation

Internal validation was performed to assess how well the model's results for DFS and overall survival (OS) corresponded with the no-trastuzumab and one-year trastuzumab arms from the HERA trial. Similarly, the results of the PHARE trial were used to validate the model's results for the one-year and 6-month trastuzumab strategies.

Results

Over a lifetime horizon, all trastuzumab strategies were cost-effective versus no-trastuzumab at a WTP of 3×GDP (Figure 5.2). The results of CEA, shown in Table 5.3, show that at the WTP threshold of 3×GDP, and a 42% probability, the 6-month protocol was the most cost-effective strategy, while other strategies showed lower rates of being cost-effective. The acceptability curves representing the probabilities that various strategies are cost-effective across various WTP thresholds in the base-case scenario can be found in Figure 5.3. The one-year trastuzumab strategy was cost-effective in only 21% of simulations, and the 9-month and no-trastuzumab strategies were cost-effective in 21% and 17% of cases respectively. When the WTP threshold was increased to 4×GDP, the 6-month and one-year regimens were essentially equal in cost-effectiveness (37% and 35%, respectively). The 9-month regimen had a 20% probability of cost-effectiveness. However, the chance the no-trastuzumab strategy was cost-effective fell to 8% when a WTP threshold of 4×GDP was applied.

Table 5.3: The results of cost-effectiveness analysis

	Cost	QALYs	LYs	ICER (QALY)	ICER (LY)
No-trastuzumab	€14,541	11.1	14.41	NA	NA
6-month trastuzumab	€22,442 Δ = €8,901	11.71 Δ = 0.61	15.18 Δ = 0.76	14,625	11,664
9-month trastuzumab	€28,410 Δ = €13,869	11.95 Δ = 0.85	15.48 Δ = 1.06	16,370	13,037
One-year trastuzumab	€33,160 Δ = €18,619	12.22 Δ = 1.12	15.82 Δ = 1.40	16,695	13,279

Δ = Incremental values for costs and effectiveness of trastuzumab therapy strategists versus no-trastuzumab.
*Abbreviation: **ICER:** Incremental cost-effectiveness ratio, **LY:** Life years, **QALY:** Quality-adjusted life-year*

The base-case and DSA of the model yields ICERs for 6-month, 9-month and one-year were €15,108, €16,800, and €17,086 per QALY versus no-trastuzumab respectively. Subsequently, deterministic one-way sensitivity analysis (summarized in Table 5.4), revealed that the key drivers were the acquisition cost and clinical effectiveness of one-year of trastuzumab use versus no-trastuzumab. Additionally, probabilistic one-way sensitivity analysis showed that when the cost of trastuzumab was changed from -30% to +30% in the base case, the probability of the one-year regimen being cost-effective
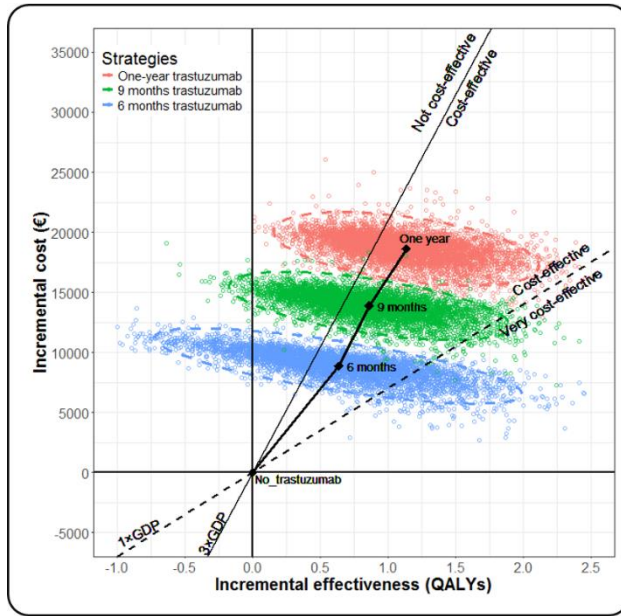
Figure.5.2: Cost-effectiveness plan for trastuzumab use scenarios vs no-trastuzumab (a sample of 7000 results of PSA for every strategy). The ellipses represent 95% confidence intervals.

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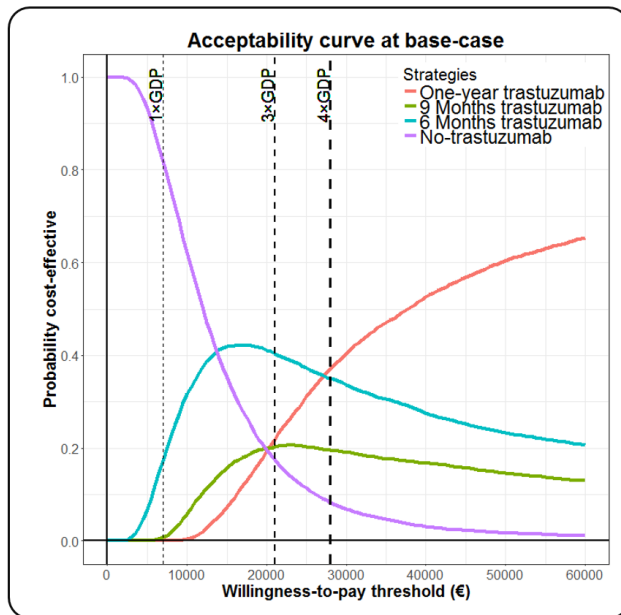
Figure 5.3: Acceptability curves of the base-case scenario.

Table 5.4: The results of one-way deterministic sensitivity analysis; the impact of the top seven key drivers on the incremental cost-effectiveness ratio.

	Limits	Value	Reference No-trastuzumab Cost	Changes	QALYs	Changes	LY	Changes	6-month trastuzumab Cost / QALYs	Changes	Cost /LY	Changes	9-month trastuzumab Cost / QALYs	Changes	Cost /LY	Changes	One-year trastuzumab Cost / QALYs	Changes	Cost /LY	Changes
Base-case	Mean		14,541		11.1		14.4		14,625		11,664		16,370		13,037		16,695		13,279	
Cost of trastuzumab	Lower	-30%							9,135	-38%	7,285	-38%	10,542	-36%	8,395	-36%	10,884	-35%	8,658	-35%
	Upper	+30%							20,116	38%	16,043	38%	22,198	36%	17,678	36%	22,505	35%	17,901	35%
Effectiveness of trastuzumab Disease free survival hazard ratio 12 M vs 0 M	Lower	0.50							7,496	-49%	5,974	-49%	10,338	-37%	8,232	-37%	12,079	-28%	9,610	-28%
	Upper	0.74							62,873	330%	50,398	332%	33,618	105%	26,778	105%	25,740	54%	20,464	54%
Effectiveness of trastuzumab Disease free survival hazard ratio 12 M vs 6 M	Lower	1.20							11,377	-22%	9,070	-22%								
	Upper	1.36							19,924	36%	15,899	36%								
Effectiveness of trastuzumab Disease free survival hazard ratio 12 M vs 9 M	Lower	1.09											14,526	-11%	11,568	-11%				
	Upper	1.18											18,164	11%	14,465	11%				
Age at start	Lower	40	14,688	1%	11.7	6%	15.2	6%	13,352	-9%	10,630	-9%	14,994	-8%	11,921	-9%	15,322	-8%	12,169	-8%
	Upper	50	14,336	-1%	10.4	-7%	13.5	-7%	16,425	12%	13,130	13%	18,307	12%	14,611	12%	18,619	11%	14,840	12%
Discount rate for costs	Lower	0%	17,612	21%					13,497	-8%	10,764	-8%	15,485	-5%	12,332	-5%	15,963	-4%	12,698	-4%
	Upper	7%	12,624	-13%					15,317	5%	12,216	5%	16,932	3%	13,484	3%	17,174	3%	13,660	3%
Discount rate for effectiveness	Lower	0%			18.4	66%	23.9	66%	7,335	-50%	5,791	-50%	8,283	-49%	6,534	-50%	8,499	-49%	6,699	-50%
	Upper	7%			7.8	-30%	10.1	-30%	25,341	73%	20,431	75%	28,088	72%	22,599	73%	28,455	70%	22,854	72%

Abbreviations: LY: life years, M: month; Blank spaces mean that no effects on the results of the base-case scenario
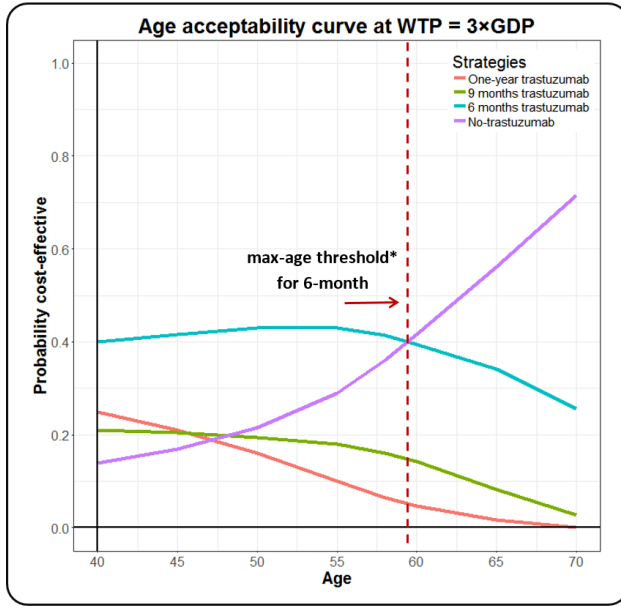
Figure.5.4: The impact of life expectancy on the probabilities being cost-effective among different treatment strategies.

*max-age threshold: represents the maximum patient age at onset of treatment that for those patients strategy remains optimal at a particular WTP threshold.
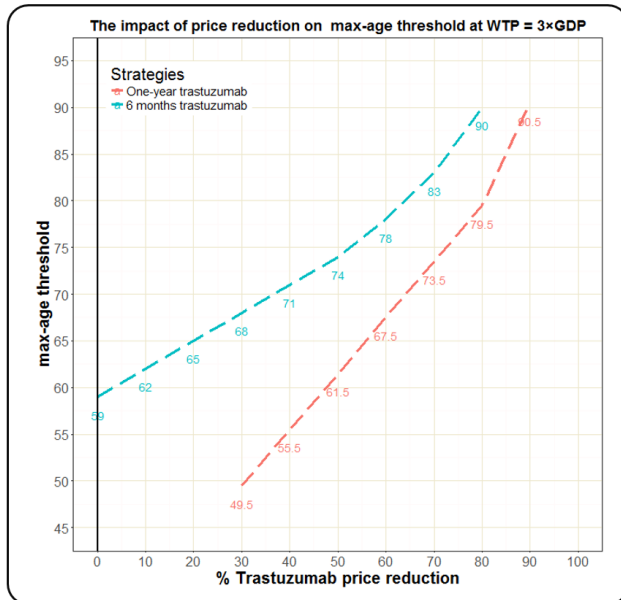
Figure 5.5: The impact of price reduction on max-age threshold at willingness-to-pay 3×GDP in Iran.

decreased from 41% to 8% (Appendix 1). However, 6 months of trastuzumab therapy showed less of a change (9% (34%-43%)) at the threshold of 3×GDP. In contrast, changes in the HR of DFS for 6-month trastuzumab vs no-trastuzumab showed a range of 16% (54%-38%) in the lower (0.50) and upper (0.74) limits (Appendix 2). At a threshold of 3×GDP, the 6-month regimen was the most cost-effective strategy (54%) for the lower limit of HR. The no-trastuzumab strategy was the cost-effective strategy for the upper limit of HR. Finally, our results (Figure 5.4) show that the 6-month strategy is only cost-effective when treated patients are not older than 59 years (the max-age threshold). At this age and a WTP threshold of 3×GDP, the two strategies of 6-month of trastuzumab and no-trastuzumab had almost equal chances of being cost-effective (39.5% vs 40%, respectively). However, this age threshold can change if the WTP is increased or decreased. At the WTP threshold of 4×GDP, one-year of trastuzumab use is cost-effective only for patients who are younger than 44 years, and 6-months of trastuzumab use may be the best strategy for patients between 44 and 66 years old (Appendix 3). Finally, the impact of various ages (40-70) on cost-effectiveness of different strategies are shown in Appendix 4.

Figure 5.5 illustrates the effect of price reductions on max-age threshold. Our analyses revealed that trastuzumab is cost-effective only if the price were to be reduced by 30%. However, this reduction would make one year of trastuzumab the optimal strategy only if it was given to patients younger than 49.5 years. As the Figure 5.5 shows, a 10% reduction in price increases the max-age threshold by three and six years for 6-month and one-year treatment regimen respectively.

The internal validation results for the three strategies including no-trastuzumab, one-year and 6 months trastuzumab use revealed no significant differences between the results of the model and the results of the trials used to perform this study (Table 5.5).

Table 5.5: The results of internal validation

	No-trastuzumab (HERA trial vs Model)	6-month trastuzumab (PHARE trial vs Model)	One-year trastuzumab (HERA trial vs Model)
Overall survival	P-value=0.489	P-value=0.388	P-value=0.424
Disease-free survival	P-value=0.395	P-value=0.319	P-value=0.267

Discussion

The use of monoclonal antibodies such as trastuzumab is a hotly debated topic among policymakers, patients, and healthcare professionals in MICs due to their considerable impact on these nations' healthcare budgets. For example, in Iran, trastuzumab alone

accounts for roughly 93-140 million euros (~4%-6%) of total pharmaceutical expenditure [76]. Trastuzumab is an effective but very expensive drug for patients with HER2-positive BC. Therefore, policymakers in MICs can neither ignore it because of its effectiveness, nor reimburse it with the same duration as clinical guidelines have recommended in high-income countries (HICs) due to its cost. Specifically, more money spent on trastuzumab means less money for other treatments [55]. The questions that healthcare professionals and policymakers in these countries must answer include: "What is the optimum duration of trastuzumab use to provide an efficient and affordable treatment?" and "How can we balance population health and affordability?" In response to these questions, our study provides valuable information regarding the cost-effectiveness of various trastuzumab strategies in Iran, which may also be useful for other MICs. Moreover, to our knowledge, this is the first CEA that examines age heterogeneity of patients and explores the impact of life expectancy on the cost-effectiveness for various trastuzumab strategies in an MIC.

The effectiveness of shorter durations of trastuzumab therapy has been studied in various RCTs. FinHER (Finland Herceptin) trial [120] investigated the clinical outcomes in 9 weeks of trastuzumab use and reported an HR=0.42 (95%CI: 0.21-0.83, p=0.01) for the DFS of trastuzumab use versus no trastuzumab. This study, however, was faced with some limitations such as small sample size and the results of other trials (SOLD [121] and SHORT-HER [122]) that also focused on 9-week trastuzumab use have not yet published. As a result, therefore, we excluded the 9-week strategy as a comparator in this study. The clinical outcomes of 6-month trastuzumab use were the subject of two RCTs (PHARE [89] and PERSEPHONE [123]). Since only the results of PHARE are currently available, we used the PHARE results in this study. Our assumption regarding the DFS HR in the 9-month strategy was not supported by a real RCT. Assumptions were therefore necessary to make to investigate a potentially cost-effective strategy between 6 months and one year of trastuzumab use. Finally, the model was internally validated based on the results of the aforementioned RCTs.

A previously published CEA reported that one year of trastuzumab use is not cost-effective in Iran [124]. However, this study has some methodological inconsistencies when assessed using the Drummond economic evaluation checklist [82] and also used an inappropriate trastuzumab cost. The cost of one-year of trastuzumab use by a 70-kilogram woman was estimated at $48,850, which is inconsistent with the public price of trastuzumab dosage forms (€500 and €1,294 for 150mg and 440mg vials, respectively (€22,992) [125]). Consequently, it was necessary to conduct a new study using appropriate methods and more reliable input parameters. For this purpose, we attempted to design a standard economic evaluation using country-specific information

such as the results of a real-world cost analysis that exclusively investigated HER2-positive direct medical costs in Iran [96].

Our results show that the most cost-effective strategy in the treatment of early HER2-positive BC in Iran is 6 months of trastuzumab as an adjuvant therapy. This strategy remains optimal, even if the price of trastuzumab is reduced by almost 30% (Appendix 1). The one-year strategy is cost-effective only at higher WTP thresholds. Since, the 9-month strategy was dominated by the 6-month and one-year strategies, from an efficiency perspective, the 6-month and one-year strategies are the two best strategies. If the 6-month protocol is considered the standard of care and doctors continue to adhere to this strategy, Iran can save €40 million/year compared to a one-year trastuzumab strategy. It is worth noting that all these results can be vary if the age of patients at onset of treatment is changed and that these various strategies for trastuzumab use would not be cost-effective in patients older than 59 years (Figure 5.4). In other words, in addition to a lower absolute WTP threshold for expensive drugs in MICs, life expectancy in these countries (e.g. 76.6 years for Iranian women) is also generally lower than in HICs. These two issues can affect the results of a CEA in MICs.

We compared our results with the results of model-based CEAs [31,126-129] in other countries that used the same study perspective (healthcare), time horizon (lifetime), and trastuzumab use duration (one-year). Two studies (in China [126] and Belgium [129]) calculated ICER values that were lower than that in our study ($8,041 and €10,315 respectively) while four CEAs (in the USA [127,128], Australia [130], and the UK [31]) estimated higher ICERs ($39,982; $26,417; $A22,793; and £25,803, respectively). Regardless of this variation, in all studies, including our study, ICERs were primarily affected by the cost of trastuzumab. Despite the methodological similarities between this study and other studies, we cannot easily compare our results with other CEAs because of differences in various parameters such as costs of trastuzumab, prices for healthcare services, discount rates, background mortality rates, and sources of estimation of the effectiveness of trastuzumab. On the other hand, a CEA in Colombia using a shorter time horizon (20 years) concluded that trastuzumab is not cost-effective even though trastuzumab was cheaper (US$4,219 vs €22,992) and advanced stage treatment (downstream costs) was more costly (US$52,093 vs €16,926) compared to costs in Iran[131]. However, comparisons between that study and our study are difficult not only because of differences in time horizon and cost components, but also because of differences in the sources of clinical effectiveness and utility values that were used. This means that comparisons between CEAs of trastuzumab between MICs are also prone to the same problems that arise when comparisons between CEAs in HICs are performed.

Our study faced four notable limitations. Firstly, we had to use the results of studies performed in HICs due to the lack of country-specific health-related quality of life (HRQoL). In fact, there are no good-quality publications on HRQoL in Iran. This limitation, however, has no major impact on the overall results since our one-way sensitivity analysis showed ±30% changes on utility values caused less than ±8% on the estimated ICER. Secondly, the HERA trial has recently reported 11 years of median follow-up and data from this could have been used to update the parameter estimates in our model [132]. However, the updated estimate of effectiveness of trastuzumab after 11 years was lower than the effectiveness after two years (i.e., an increase in the hazard ratio for disease-free survival from 0.62 to 0.73). However, the results of one-way sensitivity analysis (Appendix 2) that any reduced effectiveness of trastuzumab would not change the conclusion that the price of trastuzumab must be reduced significantly in order for it to have any chance of being cost-effective for even a subgroup of the patient population (i.e., younger patients). Thirdly, the cost-effectiveness of 9-month strategy was estimated based on an assumption of effectiveness because of lack of data. Despite its low impact on overall results as demonstrated by sensitivity analysis (Table 5.4), our CEA can be updated when the results of SOLD [121] and/or SHORT-HER [122] become available. Finally, while it is known that women with hormone receptor negative tumors have an increased risk of recurrence and death we did not examine the cost-effectiveness of treatment decisions based on hormone receptor status [133]. This is something that should be examined in the future.

New drugs launched in MICs do not necessarily have the same effectiveness or affordability as in HICs. Policymakers and other primary stakeholders, such as healthcare professionals and patient communities, should focus on a strategy that will help to create a balance between the highest attainable level of health and affordability of the new drug. However, if there is a desire to implement widely accepted clinical guidelines in MICs, concessions are unavoidable. There are four approaches that would lead to recommending one-year trastuzumab use in Iran: 1) price reduction, 2) use of a higher WTP threshold, 3) combination of these two methods, and 4) 'watchful waiting' for a generic product. Our results showed that the first two options, either price reduction (by -30%)(Figure 5.3) or the use of a higher WTP threshold (4×GDP), cannot achieve a new balancing point between population health and affordability to switch to a longer course of trastuzumab therapy (Appendix 3). The third option could be a potential solution, however due to changes on price of trastuzumab and WTP threshold, the max-age threshold for one year of trastuzumab use should be re-estimated. Moreover, the use of a higher WTP would set a precedent for other treatments. The 'watchful waiting' approach can indeed enhance affordability in MICs. However, this would mean waiting many years before drugs like trastuzumab would be reimbursed in

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MICs. In many cases, 'watchful waiting' would mean a large amount health loss. Therefore, a more equitable solution would involve revamping pharmaceutical pricing systems to make new drugs more affordable for lower income countries. For example, a 75% price reduction would be needed to make one year of trastuzumab, the strategy recommended in clinical guidelines in HICs, cost-effective for all patients younger than 76.6 years (the average life expectancy) in Iran (Figure 5.5).

Effectiveness and affordability are not the only two factors to consider when policymakers make reimbursement decisions. Other factors, such as budget impact and equity analysis, are also important to consider. In fact, using multi-criteria decision analysis (MCDA) that includes various factors, is likely the best way to help policymakers reach a satisfactory conclusion [7].

Conclusion

Most clinical guidelines prepared in HICs have recommended one-year trastuzumab use due to the efficacy of the drug. However, this treatment strategy would not be an affordable recommendation in MICs due to the lower absolute value of WTP threshold and the lower life expectancy as compared with HICs. Our study showed that 6-month trastuzumab use is the most cost-effective option for the Iranian healthcare setting at a WTP threshold of 3×GDP and a max-age threshold of 59 years. Policymakers and other stakeholders in MICs must find the best way to balance population health and affordability of an expensive intervention.
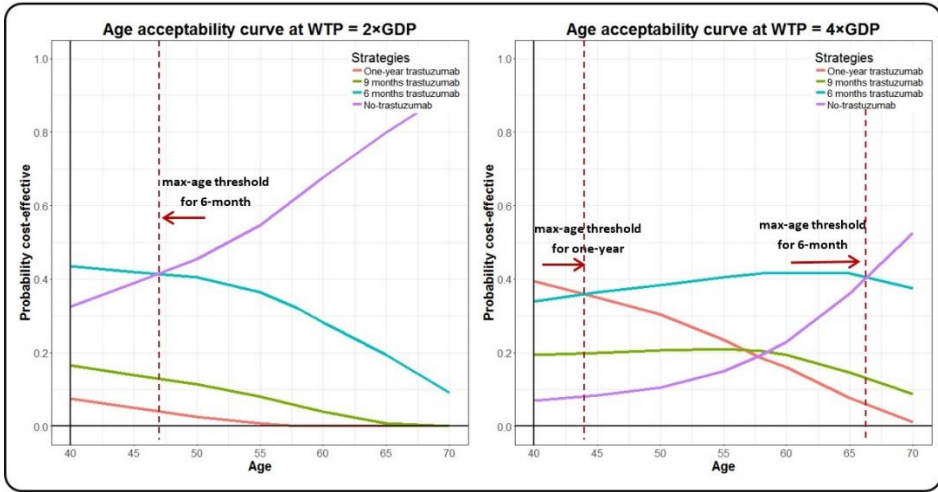
Appendixes
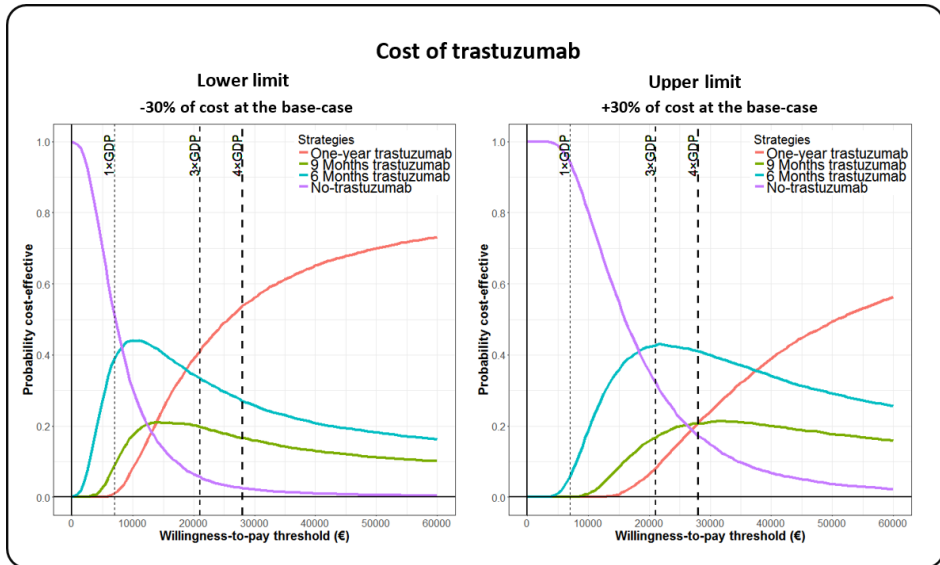
Appendix 5.1: Acceptability curves at the lower and upper limits of cost of trastuzumab as the results of one-way sensitivity analysis.
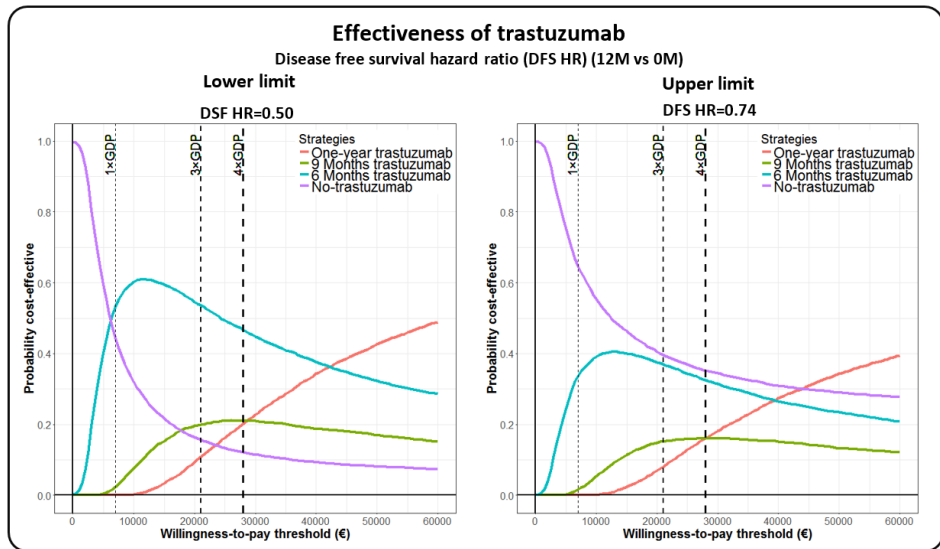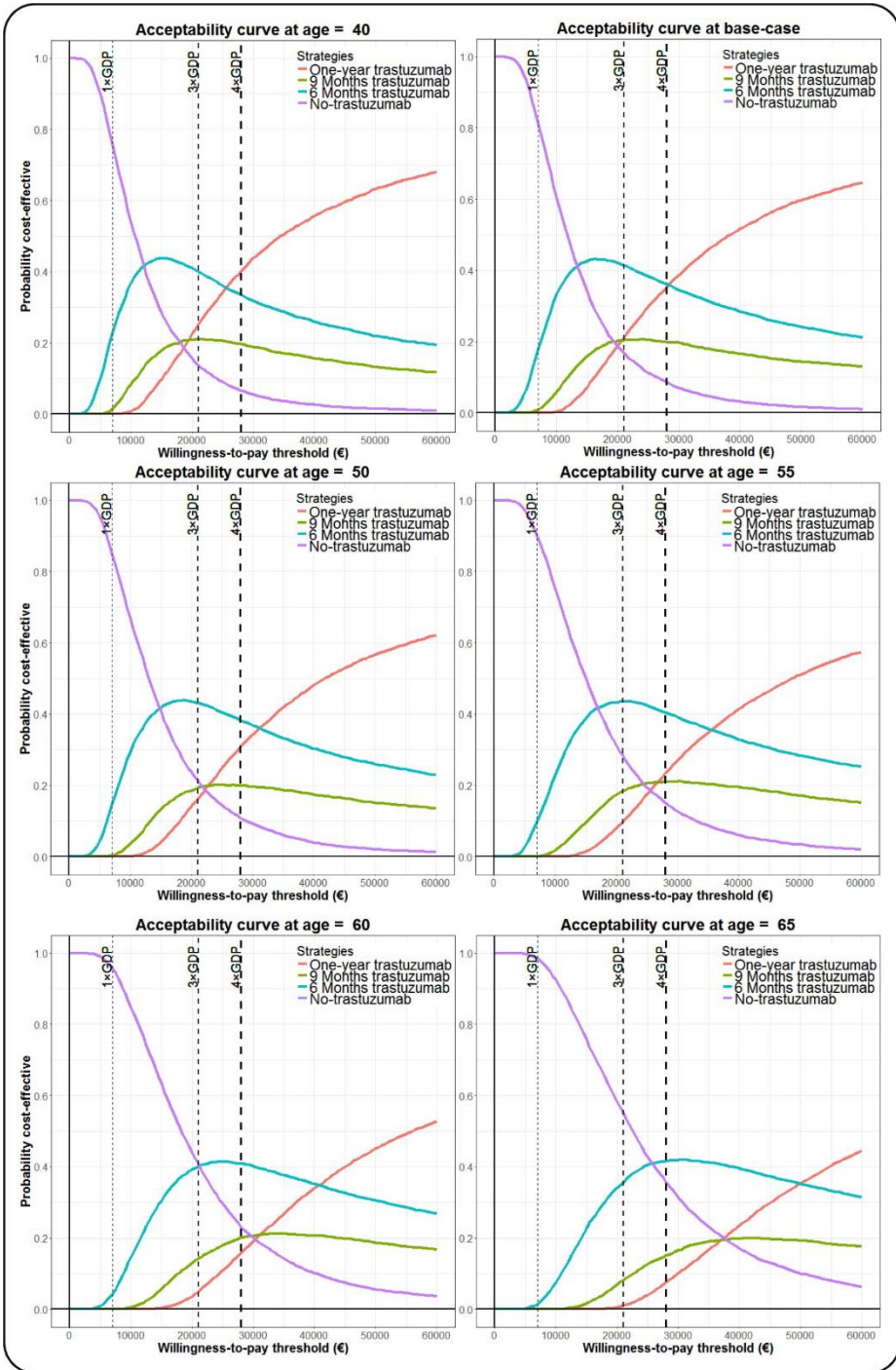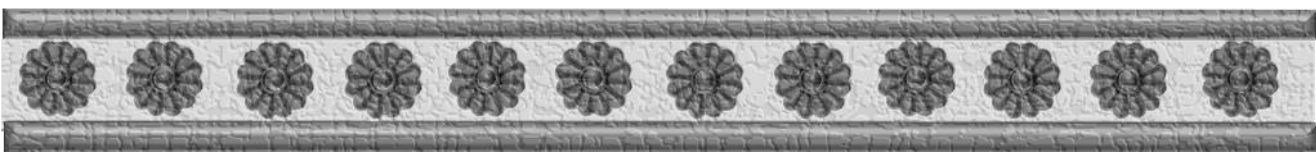

Appendix 5.2: Acceptability curves at the lower and upper limits of effectiveness of trastuzumab as the results of one-way sensitivity analysis. DFS HR: Disease-free survival hazard ratio.

Appendix 5.3: The impact of WTP thresholds and life expectancy on the probabilities being cost-effective among different treatment strategies at two WTP thresholds of 2×GDP and 4×GDP.

Appendix 5.4: Acceptability curves of various patient age at the onset of treatment as the results of one-way sensitivity analysis

Chapter 6

How can middle-income countries get a valid estimate of cost-effectiveness of a drug more efficiently and effectively?

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Abstract

Introduction: The results of cost-effectiveness analyses (CEAs) are often generalized between countries. However, the accuracy of their results is remaining uncertain when these countries have important differences in their economies and healthcare systems. The aims of this study are firstly to investigate compatibility between the results of transferred CEAs from high-income countries (HICs) with a previously published CEA in Iran (a middle-income country (MIC)). Secondly to identify bias factor(s) affected transferability from HICs to MICs, and finally to propose a method for estimating cost-effectiveness of a drug in MICs.

Method: We systematically searched and selected model-based CEAs in HICs which were based on the same method with an original country-specific CEA in Iran. The transferability of these studies to Iran was assessed using the Van Haalen method. Incremental quality-adjusted life-years (QALYs) were adjusted based on differences in life expectancy from age at treatment onset. Two methods were used to estimate incremental costs. In the conventional method, costs were corrected using consumer price indices and transferred to the Iranian setting using purchasing power parities (PPP). The proportional method involved estimating initial trastuzumab costs and combining them with the incremental downstream costs. Cost-effectiveness results using these methods were then compared with the results of an Iran-based CEA.

Results: Five of the nine CEAs identified were considered transferable. The transferred incremental costs of the conventional method (€21,419(USA); €5,115UK); €12,550(USA); €9,170(Portugal); €10,187(Belgium)) did not match the incremental costs of the Iranian CEA (€19,056). However, we could estimate closer incremental costs (€19,988(USA); €19,742(UK); €19,320(USA); €19,497(Portugal); €19,361(Belgium)) with the proportional method.

Conclusion: This study introduces a method to facilitate transferring the results of CEAs from HICs to MICs which is more efficient than the current methods. When there is a major economic gap between countries and external price referencing has a major impact on pricing in MICs, costs of expensive drugs should not be transferred using relative PPPs. The proportional method may be a solution to estimate a rough ICER in MICs while a country-specific CEA is recommended for a reimbursement decision-making.

Introduction

Cost-effectiveness analysis (CEA) is an important and valuable part of knowledge in health technology assessment (HTA) which is a prerequisite for pricing and reimbursement decision-making. The first CEAs of any new intervention are usually conducted in high-income countries (HICs) due to its preliminary market release and their results are used for initial pricing in these countries.

CEAs are time-consuming studies, need detailed information, and require an adequate research capacity. These factors mean that CEAs are not always possible to perform, particularly in middle-income countries (MICs). Using methods that help to transfer the results of CEAs in other countries may be a solution to overcome above limitations in MICs. Previous studies have focused on different methods to transfer the results of CEAs from a study country to a target country. The feasibility of transferring (due to lack of information) and accuracy of the results of a transferred CEA, however, remain uncertain, specifically when study and target countries have important difference in their economies and healthcare systems. To our knowledge, there is a lack of appropriate solution for transferring CEA when there is a lack of necessary information. Moreover, no study investigated the accuracy of the results of a CEA that has been transferred from a HIC to an MIC, even though this type of transferability is more complex than transferability between HICs. Therefore, the aims of this study are firstly, to investigate the transferred results of CEAs performed in HICs to an MIC. Secondly, to identify what potential bias factor(s) affected transferability from HICs to MICs, and finally to propose a method to estimate of cost-effectiveness of a drug considering the limitation of necessary information in MICs. We used the results of a previously published cost-effectiveness analysis in Iran as the gold standard [134].

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Methods:

We searched and used all model-based CEAs which assessed the cost-effectiveness of trastuzumab in early stage HER2-positive breast cancer in HICs. Subsequently, the Van Haalen method [135] was used to select transferable health economic evaluation models. In the next step, incremental QALYs and costs of selected CEAs were transferred to the Iranian setting. We used and compared the results of transferring costs to estimate the incremental cost-effectiveness ratios (ICERs) with the results of an Iranian-specific CEA, which was considered the "reference" study [134].

The recommendation from the World Health Organization's choosing interventions that are cost-effective (WHO-CHOICE) project [114] was used to determine cost-effectiveness of transferred ICERs. On this basis, the highest willingness-to-pay (WTP) threshold in Iran is 3×GDP/capita (€21,000) [134].

Search methods

A systematic literature review was conducted in PubMed in December 2016. The search strategy is shown in Table 6.1. Two MeSH terms ("Cost-Benefit-Analysis" and "Breast Neoplasms") were searched first, after which the term "trastuzumab" was included. As Table 6.1 shows, we then combined the above terms to find CEAs of trastuzumab in breast cancer and then added the term "early" in the search strategy to select studies in early-stage breast cancer. The search strategy was not limited to any publication year and language.

Diagnosing the transferability

The three-step approach by Van Haalen et al was used to select transferable CEAs to Iran. In the first step and due to our aim, we selected CEAs of trastuzumab in HICs. Moreover, only those studies were included that used the same method as the method used in the reference CEA. Therefore, we included model-based CEAs that used a healthcare perspective, a lifetime horizon and calculated direct medical costs and quality-adjusted life-years (QALYs) of one-year trastuzumab use among patients with an average age of 45-50 years. Studies were excluded if incremental costs and QALYs were not reported. In the second step of the Van Haalen method, Welte's specific knock-out criteria [136] were used to indicate for which criteria the results of CEAs are biased and need to be adjusted. Finally, Drummond's checklist [82] was used to assess the quality of CEA in the third step of the Van Haalen method. All studies that passed the Van Haalen method were then analyzed as the studies which were considered to be transferable between study and target country.

Analysis of included studies

We first checked whether patient-level cost estimates, including patient-level resource use data, were reported in sufficient detail. Lack of this level of detail meant we would be unable to estimate the cost for the Iranian setting. This was important because of differences in relative healthcare costs between study countries and Iran. Alternatively, we applied the following methods to transfer the utilities and costs:

Transfer of QALYs

In the five CEAs in HICs, there was a wide range of incremental QALYs across CEAs (Table 6.2), which was due to difference on source of effectiveness data. However, due to lack of good-quality publications on health-related quality of life in Iran, it was not possible to map the utilities between countries and therefore we assumed that trastuzumab lead to same QALY gains in Iran compared to other countries. However, the differences in discount rates and life expectancies need to be adjusted between

counties. The following steps describe how incremental QALYs adjusted from the selected CEAs to the Iranian setting

- **Adjusting the discount rates:**

We converted the incremental QALYs from those CEAs that used different discount rates than 3.5%, using the discount factors of the study country and target country. We also assumed that the main effectiveness appears in the first four years of treatment. This assumption was made based on the same approach which was used in the reference study [134] and also the CEA in the UK [31]. Then, the following formula used to adjust the incremental QALYs based on a 3.5% discount rate.

$$I\_QALYS_{3.5\%} = I\_QALYS \times \frac{DFS^4}{DFi^4}$$

Where I_QALYS is the incremental QALYs of the study country, $I\_QALYS_{3.5\%}$ is the adjusted incremental QALYs of the study countries based on a 3.5% discount rate and DFS and DFi are discount factors in the study countries and Iran, respectively.

- **Adjusting incremental QALYs based on the difference in life expectancies between study countries and Iran:**

The incremental QALYs calculated in the previous step, were adapted based on the ratio of the overall life expectancy of Iranian women at age 45 [137] compared to the life expectancy of the average age used in the study country, using the following formula.

$$I\_QALYi = I\_QALYS_{3.5\%} \times \frac{LEi}{LES}$$

Where I_QALYi is the incremental QALYs in Iran and LEi and LES are life expectancies among women in Iran and the study countries at a given age, respectively.

The overall life expectancies of European countries were obtained from the European health and life expectancy information system [138] and data from the USA Social Security were used for the life expectancy of American women [139].

Transfer of costs

Two methods were used to transfer costs in absence of patient-level resource use data.

-   **Conventional method**

In the conventional method, the costs for both arms (trastuzumab and no-trastuzumab) reported in CEAs performed in other countries were adjusted to the costs in 2015 using country-specific consumer price index (CPI) data. After that, costs were converted to the currency of Iran using purchasing power parity (PPP) data.

-   **Proportional method**

The basis of this method is a comparison of two simplified treatment strategies to treat HER2-positive breast cancer (Figure 6.1). As figure 6.1 shows, in this model, a combination of chemotherapy and trastuzumab is compared to chemotherapy alone. The chemotherapy regimens (Chemo) in two main stages of breast cancer (early and progressive) were assumed to be similar in both arms. Patients whose disease progressed, move to the progressed stage. Since the costs of trastuzumab can have an important impact on the incremental costs [96], we assumed that the incremental costs in the early stage could be estimated by calculating the costs of trastuzumab and its relative components using in this model. This meant cost components included trastuzumab acquisition costs, administration costs and the costs of trastuzumab-induced cardiac toxicity. These were defined as '*Incremental costs in early stage'* that were incurred by adding trastuzumab to routine care. However, it is possible that trastuzumab can reduce the risk of disease progression and thereby reduce '*downstream costs'*. We estimated the difference in downstream costs by combining the absolute difference in risk of progression (between trastuzumab and no-trastuzumab) with the costs of progression.
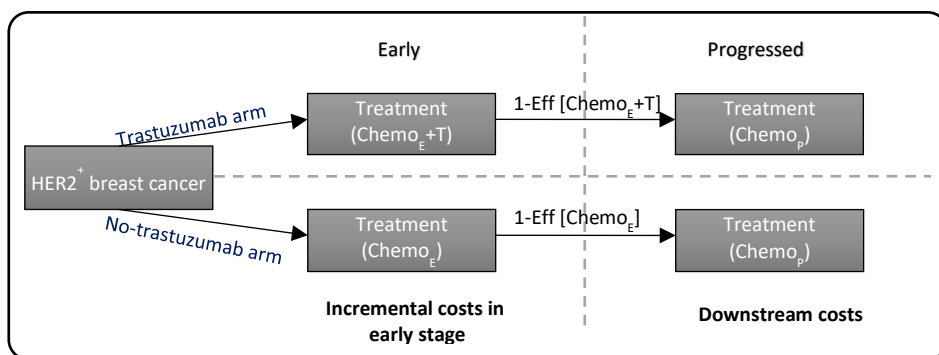
Figure 6.1: The model structure was used in the proportional costing method

Incremental costs (IC) are equal to the sum of the incremental costs in the early stage ($IC\epsilon$) and the difference in downstream costs (DC):

$$IC = IC\epsilon + DC$$

Therefore, DC was calculated by multiplying the reduction in risk of progression by the cost difference between the two arms.

$$DC = (1 - Eff[Chemo\epsilon + T]) \times Cp - (1 - Eff[Chemo\epsilon]) \times Cp$$

$$DC = (-Eff[Chemo\epsilon + T] + Eff[Chemo\epsilon]) \times Cp$$

Where DC represents the downstream costs, $Eff[Chemo\epsilon + T]$ and $Eff[Chemo\epsilon]$ are the probability of progression-free survival in trastuzumab and no-trastuzumab arms in early stage of breast cancer respectively, and Cp is the costs of treatment in progression stage.

In this study, we used the results of a cost analysis study [10] to estimate ICϵ in Iran and used the results of the HERA trial to estimate $Eff[Chemo\epsilon + T]$ = 0.790 and $Eff[Chemo\epsilon]$= 0.725 [11]. We assumed that Iranian policymakers can only estimate the extra costs relating to trastuzumab use and do not have sufficient data on other costs relating to current breast cancer treatment. To calculate an Iran-specific Cp, we first calculated the ratio between the costs of advanced breast cancer (CpS) and Incremental costs in the early stage ($IC\epsilon S$) in each of the five CEAs in HICs. Using the $IC\epsilon$ in Iran, we then estimated Cp using the following formula.

$$Cp = IC\epsilon \times (CpS \div IC\epsilon S)$$

Where CpS and $IC\epsilon S$ are the costs of progression and Incremental costs in the early stage in HICs respectively.

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Eventually, we calculated the discounted incremental costs during first four years (Based on our assumption that the main effectiveness appears in this period) with yearly discount rate of 3.5% in correspond with the Iran-specific CEA.

Results

Selection and transferability check of CEAs

Nine CEAs were found through the literature search (Table 6.1), and five of these fulfilled our criteria in the first step of van Haalen's method. Two of these studies were from the USA (Garrison et al [128] and Kurian et al [127]), while the other three were from the UK (Hall and et al [31]), Portugal (Macedo et al [140]) and Belgium (Van Vlaenderen et al [129]). Table 6.2 provides a summary of the methods and results of these five CEAs and the Iran-specific CEA [134]. As Table 6.2 shows, all six studies used the same overall methodology, although there were some differences regarding factors like age at onset of treatment, discount rate, and time horizon. The results of the second step showed that two main groups of costs and effectiveness need to be adjusted based

on Iran specifications (Table 6.3). Finally, the results of the third step of Van Haalen's method showed that all five studies passed Drummond's checklist and were considered as transferable CEAs to Iran.

Table 6.1: The search strategy and the number of founded publications at every step.

Search	Query	Items found
#1	Search cost-benefit-analysis [mesh]	66,909
#2	Search Breast Neoplasms [mesh]	243,752
#3	Search trastuzumab	8,238
#4	Search (#1 and #2)	1,440
#5	Search (#4 and #3)	95
#6	Search (#5 and early)	38
#7	Selected 9 document(s)	9

Table 6.2: A summary of the methods and results of CEAs in five high-income countries and Iran

Study	Kurian	Garrison	Van Vlaenderen	Marcedo	Hall	Ansaripour
Country	USA	USA	Belgium	Portugal	UK	Iran
Year of costing	2005	2006	2007	2007	2008	2015
Perspective	Healthcare	Healthcare	Healthcare	Healthcare	Healthcare	Healthcare
Modelling method	Markov	Markov	Markov	Markov	Markov	Markov
Time horizon	Lifetime	Lifetime	Lifetime	Lifetime	Lifetime	Lifetime
Duration of trastuzumab use	One year	One year	One year	One year	One year	One year
Measure of effectiveness	QALYs	QALYs	QALYs	QALYs	QALYs	QALYs
Average age at start	50	50	50	50	50	45
Duration of time horizon (Years)	50	50	45	45	50	55
Discount rate (Costs - effects)	3% - 3%	3% - 3%	3% - 1.5%	3% - 3%	3.5% - 3.5%	3.5% - 3.5%
Incremental cost	US$76,669	US$44,923	€30,878	€21,280	£12,629	€19,056
Incremental QALYs	0.53	1.70	2.98	2.01	0.49	1.14
ICER (Cost/QALY)	US$144,658	US$26,417	€10,315	€10,595	£25,803	€16,773

Results of transferring QALYs

The results of transferred incremental QALYs in all studies ranged widely between 0.46 and 2.54 (Table 6.4).

Transfer of CEAs using the conventional method of transferring costs

Table 6.4 shows the results of transferring costs using the conventional method. None of the incremental costs corresponded well with the reference incremental costs (based

on the Iranian CEA), usually because of an underestimation of incremental costs in most studies. Only the converted incremental cost obtained from the study by Kurian et al. (USA) estimated a higher incremental cost and a very different ICER compared to the results of the Iranian CEA. Figure 6.2A shows the dispersion of results obtained using the conventional method. Except for the transferred ICER from Kurian's study, the other transferred ICERs suggest that trastuzumab is cost-effective in the treatment of early breast cancer in Iran. Moreover, the transferred ICERs from two European studies (Macedo et al and Van Vlaenderen et al) suggested that trastuzumab is a very cost-effective intervention in Iran, since they were lower than the 1×GDP threshold.

Table 6.3: Transferability of the results of CEAs in HICs to Iran based on the Welte's specific knock-out criteria.

Transferability criteria	Impact on	Relevance for transferability HICs and Iran	Correspondence between HICs and Iran	Need to be adjusted
Perspective	Costs and effects	High	High	No
Discount rate	Costs and effects	High	High	Yes
Medical cost approach	costs	High	Low	Yes
Productivity cost approach	NA	NA	NA	NA
Absolute and relative prices	Costs	High	Low	Yes
Practice variation	Costs and effects	High	High	No
Technology availability	Costs	High	High	No
Disease incidence / prevalence	Costs and effects	High	High	No
Case mix	Costs and effects	High	?	?
Life expectancy	Costs and effects	High	Low	Yes
Health status preferences	Effects	High	?	?
Acceptance, compliance and incentives for patients	Costs and effects	?	?	?
Productivity and absenteeism	NA	NA	NA	NA
Disease spread	NA	NA	NA	NA

Abbreviation: NA: Not applicable, ?: Unknown

Transfer of CEAs using the proportional method of transferring costs

Based on the reference CEA, the $IC\epsilon$ was €24,046 in Iran. The results of ICϵ and Cp obtained from study countries are shown in Table 6.4. The ratios between $IC\epsilon S$ and CpS was ranged from 0.71-1.20. Using the proportional method, transferred incremental costs based on the five HIC-studies shifted to a narrow range (€18,828-€19,478) in Iran (Table 6.4). Figure 6.2B shows the distribution of the transferred incremental costs using the proportional method versus €19,056 in the Iran-specific CEA. According to three of the five results, trastuzumab was cost-effective in patients with HER2-positive breast cancer in Iran. In contrast, the transferred results from two

studies (Kurian et al, Hall et al) showed that trastuzumab was not cost-effective using a willingness-to-pay threshold of 3xGDP (Figure 6.2B).

Table 6.4: The results of transferring of CEAs in five HICs compared with the results of CEA in Iran.

	Study	Kurian	Garrison	Van Vlaenderen	Marcedo	Hall	Ansaripour
	Country	USA	USA	Belgium	Portugal	UK	Iran
Conventional method	PPP	1	1	0.82	0.59	0.69	8,120
	Incremental costs	€21,419	€12,550	€10,187	€9,170	€5,115	€19,056
	Incremental QALYs	0.49	1.58	2.54	1.74	0.46	1.11
	ICER (Cost/QALY)	€43,390	€7,926	€4,013	€5,261	€11,077	€16,773
Proportional method	Incremental costs in early stage (IC_ES)	US$64,185	US$56,066	€49,482	€49,619	£24,262	€24,046
	Costs of progression (CpS)	US$45,792	US$50,000	€59,616	€53,481	£28,434	-
	Ratio (CpS/IC_ES)	0.71	0.89	1.20	1.07	1.17	-
	Incremental costs in early stage (IC_E)	€24,046	€24,046	€24,046	€24,046	€24,046	€24,046
	Costs of progression (Cp)	€17,073	€21,401	€28,855	€25,729	€28,134	-
	Downstream costs (DC)	-€1,110	-€1,391	-€1,876	-€1,672	-€1,829	-
	Incremental costs (IC)	€22,936	€22,655	€22,170	€22,374	€22,217	-
	Incremental costs (IC) (Discounted)	€19,988	€19,724	€19,320	€19,497	€19,361	€19,056
	Incremental QALYs	0.49	1.58	2.54	1.74	0.46	1.11
	ICER (Cost/QALY)	€40,491	€12,469	€7,611	€11,187	€41,929	€16,773

Abbreviations: DC: *Downstream costs in Iran;* **Cp:** *costs of progression in Iran;* **CpS:** *costs of progression in study country;* **IC:** *Incremental costs in Iran* **IC_E:** *Incremental costs in early stage in Iran;* **IC_ES:** *Incremental costs in early stage in study country;* **QALY:** *Quality-adjusted life-year*

Discussion

Methods to transfer the results of CEAs between countries have enabled policymakers to obtain estimates of the cost-effectiveness of new technologies faster and more easily and they help to circumvent any lack of country-specific information and research capacity. However, the accuracy of these methods can be questioned when the study country and target country have important differences in their economies and/or healthcare systems. We aimed to examine and compare the compatibility of the results, which were obtained from transferring methods with the results of a previously published CEA in Iran.

To our knowledge, this is the first study that investigates the accuracy of transferring the results of multiple CEAs from HICs to an MIC and proposed a simple solution for
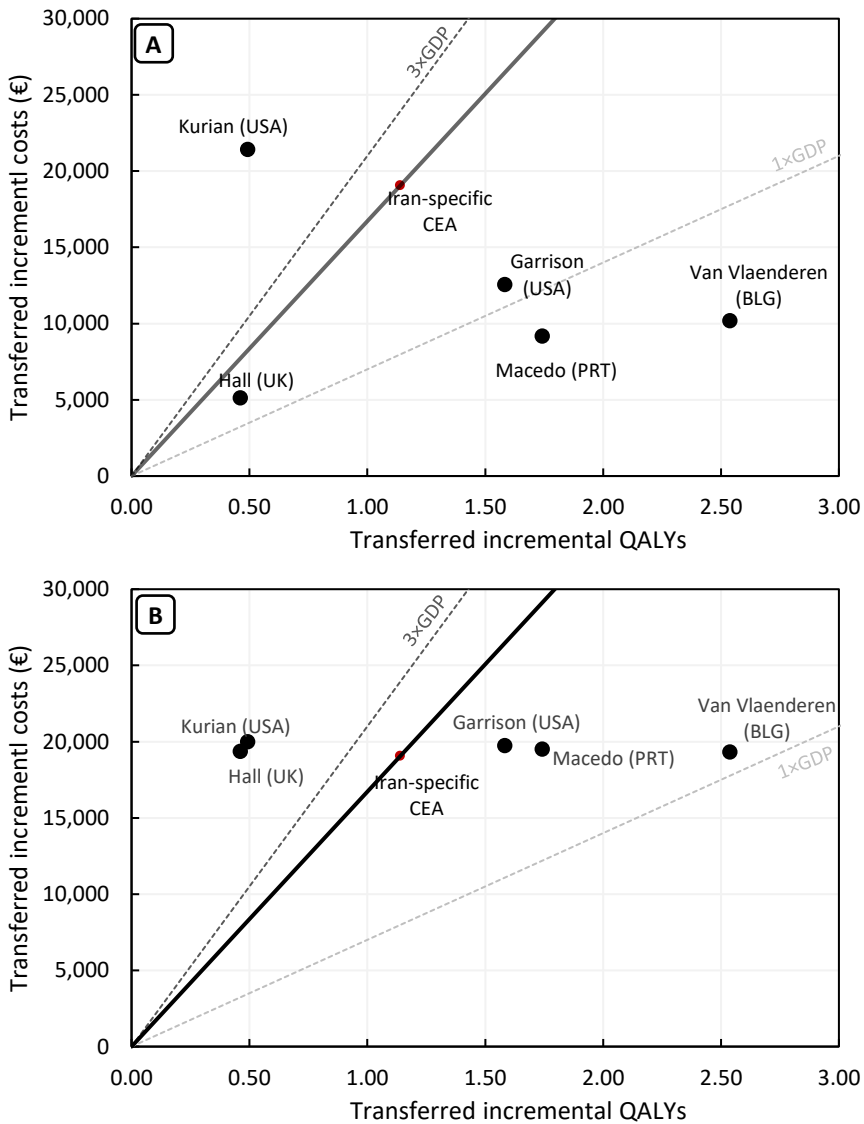
Figure 2: The comparison of the results of two methods that were used for transferring the results of CEAs in five high-income countries to Iran (the conventional method **(A)** and the proportional method **(B)**) with the results of an Iran-specific cost-effectiveness analysis as the gold standard.

transferring the results of CEAs in case of lack of information. We used standardized methods to search and select CEAs, and later to verify the possibility of transferring the results of these CEAs. This ensured comparability of methodology with other similar studies that transferred the results of a CEA between countries. However, the Van

Haalen method needs to be revised for transferring CEAs between HICs and MICs. Because it would not be easy to assess the quality of a CEA when the model and patient level data are not accessible. Different studies used various data sources to estimate costs and outcomes and it can result in a wide range of ICERs across countries, which is evident in this study. Therefore, in case of our study, it is difficult to select one of the five CEAs as the most accurate CEA when their results were transferred to an MIC setting. Perhaps one says that none of five CEAs are perfectly fitted to transfer in an MIC due to lack of patient level-cost and effectiveness estimates both in study and target counties. However, from a policymaking point of view in MICs, CEAs in HICs are probably the only information that they have access and this study tries to find a solution to overcome this gap of knowledge.

During our study, we had to address the lack of access to the patient-level costing information in all five studies. We used two methods in this study to calculate incremental costs. The conventional method was a naïve approach to transfer the results of CEA between HICs using PPP conversion factor after adjusting reported costs to 2015 costs. The proportional method was a more sophisticated approach where we divided costs into two general categories of incremental costs in the short term ($IC\epsilon$) and the long term (DC), based on a method applied by Redekop et al in a study [141] which was not aimed at transferring the results of a CEA. This alternative method bypassed the need for various calculations regarding cost adjustment, such as using CPI and PPP conversion factor, which meant that we only need to transfer the ratio between $IC\epsilon S$ and CpS from any study country. More explanations may make our strategy more clear. We all know that treatments strategies are basically identical throughout the world based on the results of the main randomized controlled trials. For example, a recent study showed that the different patterns of treatment HER2-positive breast cancer in Iran [96] were similar to the patterns that clinical guidelines were recommended in HICs [15,52,72]. Therefore, from a cost point of view, we can expect the same resource use and different unit costs across countries. For example, we have already determined a high correspondence in practice variation (resource use) between HICs and Iran in the Welte's specific knock-out criteria checklist (Table 6.3). Subsequently, if we assumed that the difference of unit costs for different healthcare services proportionally equal between HICs and MICs (regardless of the absolute values of service tariffs), then, our strategy seems to be reasonable because of same main cost drivers (the highest impact on ICER) for managing early and downstream health states in study and target countries. We used this method to estimate the downstream costs. However, this approach would not be relevant if there is a difference between the main cost drivers of the two health states. In this case, empirical data are needed to transfer the results of CEAs.

Our results showed that first method yielded estimated incremental costs that were highly influenced by the PPP conversion factor between countries and led to underestimates of the incremental costs and ICERs. Moreover, the transferred results from two of five studies suggested that trastuzumab was *'very cost effective'* (<1×GDP) in Iran, which is not logical for an expensive drug in an MIC. In contrast, the proportional method was very easy to conduct and led to more accurate results compared to the first method. Interestingly, this method resulted in a narrow range of incremental cost estimates even though these studies originally reported widely disparate incremental costs. For example, two studies (Kurian et al, Garrison et al) from the USA originally reported incremental costs of US$76,669 and US$44,923. When these two were transferred to the Iranian setting, the incremental costs were almost equal (€19,478 versus €19,240).

Regarding the causes of the differences between the results of the conventional and the proportional cost approach, we would like to point out the impact of external price referencing (EPR) on transferring the results of the CEAs from HICs to MICs. In many MICs, the price of expensive drugs is determined based on EPR. In this approach, external prices are converted based on currency exchange rates and not based on country-specific PPPs. While PPP is strongly correlated with GDP per capita, different studies have shown a poor correlation between drug prices and GPDs per capita across countries [78-80]. Moreover, another study which exclusively investigated trastuzumab price differentiation across 19 HICs and MICs showed that there was no association between price of trastuzumab and GDP per capita across countries [81]. Therefore, transferring costs, specifically costs of expensive drugs, using PPP conversion factors may cause a major underestimation of costs which is evident in the first method. Moreover, applying EPR means that the costs of medication accounts for a large share of the total health expenditure (due to imports from HICs) compared to other healthcare services such as hospitalization, surgery or diagnostic tests in MICs. A study on economic burden of cancer across the European Union showed that drug costs represented the highest share of total health expenditure in breast cancer (€3.07 billion, 46%) [142]. However, this proportion of cost in lower-income European counties was significantly higher than the European average. For example, this study reported that the share of drug costs was 81%, 79% and 76% in Cyprus, Hungary, and Malta, respectively (three MICs) [142]. Likewise, another study showed that trastuzumab alone accounts for almost 76% of total costs in early HER2-positive breast cancer in Iran [96]. Therefore, the EPR renders the PPP conversion factor essentially unusable in transferring of the results of CEAs and also causes heterogeneity in the absolute and relative cost components of an illness. According to reasons mentioned above, transferring the ratio between $IC\epsilon S$ and CpS from a study country would not be an appropriate approach if a) the key cost drivers were different between HICs and MICs

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and b) the key cost components in MICs were not affected by the external reference pricing (e.g. personnel wages or hospitalization costs).

Our study has some limitations worth noting. First of all, we had no access to patient-level cost estimations in all five CEAs and it was not possible to transfer CEA results in HICs by replacing prices of healthcare services in HICs with the healthcare services prices in Iran. Access to this information would have enabled us to compare the results of three methods instead of two. This is something that should be looked at more carefully in the future. While this might be interpreted as a major limitation of our study, the reality of reimbursement decision-making in MICs is that policymakers have to make decisions without access to sufficient and good-quality information. Another limitation might be the generalizability of our findings to other diseases and health technologies. Trastuzumab is used as an adjuvant therapy in breast cancer and does not affect the choice of drug combinations or decisions about dose adjustment of chemotherapies. While this made our calculations easier, it is important to examine how the proportional method, an approach of using simple formulas rather than complex cost-effectiveness models, could be applied in studies of other drugs.

This study showed that applying the conventional methods using PPP conversions, which are mostly used in transferring the results of CEAs between countries, may not be an appropriate approach when there is a notable difference between the economies of these countries. A proportional method which skips PPP conversions yielded incremental costs that came closer to the results of the Iran-specific CEA than the PPP conversion method. However, additional studies regarding the external validation are necessary to further develop the proportional method. For the time being, the preferred method for an MIC remains a country-specific CEA, despite the fact that transferring methods may be able provide reasonable cost-effectiveness evidence quickly.

Conclusion:

The transfer of CEAs between countries raises concerns regarding the accuracy of the transferred results, specifically when there are large economic gaps between the study and decision countries. The results of this study showed that the PPP converting factor should be used with caution when a CEA is transferring between HICs and MICs. Our proposed sophisticated method can be considered as an option in a preliminary-HTA analysis.
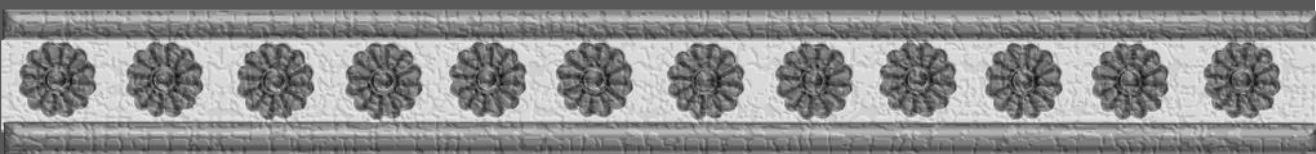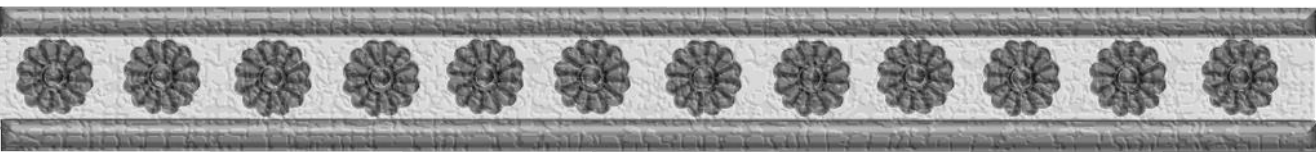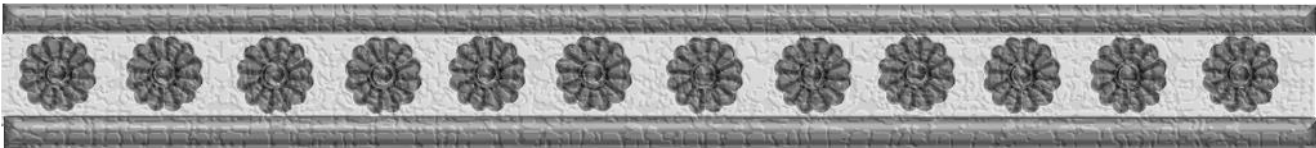
Part III

Recommendations to improve the drug reimbursement decision-making system in Iran

Chapter 7

Inequality in affordability and accessibility of drugs between high and middle-income countries

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Submitted

Abstract

Introduction: The WHO has included several expensive drugs in the essential drugs package while middle-income countries (MICs) cannot afford them as equally as high-income countries (HICs). We investigated the importance of price differentiation in enhancing drug affordability and provided recommendations to improve pricing systems in MICs.

Method: Using trastuzumab (Herceptin®) for treatment of HER2-positive breast cancer as a case study, we compared prices across 14 HICs and 5 MICs. We estimated the budget impact of trastuzumab on total health expenditure assuming equal access across all countries. Two scenarios were used to reflect relative affordability of trastuzumab: one where prices were estimated using purchasing power parity (PPP) conversion rates and one where assumptive prices were calculated using PPP conversion rates (with the US trastuzumab price as an external reference price).

Results: The relative budget impact of trastuzumab on total health expenditure was two times higher in MICs compared to HICs. There was no association between price and GDP/capita across countries (R^2 = 0.004). However, trastuzumab was three times less affordable in MICs compared to HICs (p-value=0.02). Using assumptive prices resulted in equal affordability in both MICs and HICs (p-value=0.31).

Conclusion: Current pricing systems do not facilitate access to expensive drugs in MICs. Equal affordability across countries can be improved by using price differentiation. Policymakers in MICs should base their price on national economic and social priorities. Implementation of value-based pricing using performance-based and finance-based risk-sharing arrangements is a critical need in lower income countries.

Introduction

Equal drug affordability for patients all over the world is a global aim spelled out in the constitution of the World Health Organization (WHO) [143]. The possibility of establishing equal affordability worldwide is totally dependent on the possibility of implementing price differentiation across countries based on their GDP/capita. In other words, people in high-income countries (HICs) should pay more for any particular drug than people in lower income countries so that patients or payers can afford (expensive) drugs equally throughout the world. However, multiple studies have found a poor correlation between drug prices and per capita GDP across countries [78-80]. Therefore, the aim of equal drug affordability worldwide does not seem to be easily attainable for expensive drugs due to current pricing systems.

For new pharmaceuticals, the majority of countries take into account prices of products in other countries where the product has already been launched. Consequently, the price in the country in which a new product was first launched is the most important price signal. This initial list price arises from a conflict between two interests upon initial market launch, namely the pharmaceutical manufacturer's desire to maximize profit and the payer's ability to pay. The target country of the first market launch is most certainly a HIC, followed by other HICs in the early phase [144]. The established list price in HICs is widely used as a reference price in lower-income countries, perhaps due to inadequate price negotiation with manufacturers. Consequently, people in lower income countries are 'condemned' to pay a high price based on HICs' ability to pay. This phenomenon is likely to be more evident with expensive drugs as their high budget impact is not easily affordable in low and middle-income countries.

Trastuzumab (Herceptin®) is an example of an effective and expensive drug and is used in targeted therapy for patients with HER2-positive breast cancer. It is a monoclonal antibody that can significantly improve both quality of life and survival and there are no other drugs with the same pharmacological effects. The therapeutic importance of trastuzumab is such that it was included in the WHO model list of essential medicines [145]. However, this does not guarantee access to the drug since countries also need to consider affordability. Therefore, price differentiation is an important and essential instrument for optimization of resource allocation and improvement of affordability. Many issues in healthcare systems may be related to how effectively policymakers use pricing instruments.

This study aimed to a) investigate the role of current pharmaceutical pricing in enhancing drug affordability in middle-income countries (MICs) and HICs and b) provide recommendations on how to improve the pricing system and thereby achieve more equal drug affordability worldwide.

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Methods

To investigate affordability and accessibility, we focused on the price of trastuzumab a widely used expensive drug, in 19 countries (14 HICs and 5 MICs). Table 7.1 shows their ranges of per capita GDP, total healthcare expenditure, and breast cancer incidence rates. We used this information to perform different analyses. 1) The relative budget impact of trastuzumab on total health expenditure across countries and 2) the relative affordability of trastuzumab across countries.

Relative budget impact of trastuzumab on total health expenditure across countries

To investigate budget impact of trastuzumab on total health expenditure, public list prices of 10mg trastuzumab in 19 countries were derived from internet or obtained from experts [125,146-159] and were converted using exchange rates against the US dollar (USD) [160]. Using the recommendations of the ISPOR 2012 Budget Impact Analysis Good Practice Task Force [3], we estimated the impact of trastuzumab on total healthcare expenditure using country-specific per capita GDP% spend on health care (in USD) in these countries, based on a 2014 report from the World Bank [118]. We assumed the same patient population and treatment regimen in all countries (i.e., patients with early HER2-positive breast cancer and a 52-week treatment regimen). Incidence rates for early HER2-positive breast cancer across different countries were obtained from GLOBOCAN 2012 [75]; the proportion of HER2-positive patients was assumed to be 25% [161,162]. The average weight was assumed to be 70kg [31,128,134,163], except from Chinese patients (they were assumed to weigh 57kg [126]). Using the above information, public list prices, and actual exchange rates against the USD [160], we calculated the country-specific budget impact of trastuzumab per million people. We, then, calculated the effect of the country-specific budget impacts of trastuzumab on total health expenditure and their relatively impacts compared to the budget impact of this drug in the US.

Relative affordability of trastuzumab across countries.

Two scenarios were performed to investigate inequality in affordability across different countries. In scenario I, list prices of trastuzumab (2015) were converted using country-specific purchasing power parity (PPP) [164] against PPP in the US. Scenario II addresses affordability and accessibility across countries by applying Ramsey pricing [165], which relates to the principle that the price of a drug should be varied based on differences in the income of a group of people or countries [166]. Assumptive prices were calculated using PPP conversion rates and the US trastuzumab price as an external reference price. Trastuzumab prices were considered as a sample of optimal price differentiation based

Table 7.1: Basic information of the target countries

Category	Country	Population 2015[S1]	GDP per capita 2014[S2]	GDP per capita 2014, PPP[S3]	Total health expenditure (% of GDP) 2014[S4]	PPP conversion factor, GDP 2014[S5]	Breast cancer incidence rate per 100,000[S6]
High-income economies[S7]	Denmark	10,510,566	60,770	47,848	10.80	7.59	105
	Greece	10,919,459	21,498	26,454	8.08	0.63	44
	Germany	80,889,505	41,726	47,100	11.30	0.79	92
	Hungary	9,861,673	12,958	25,517	7.40	132.00	55
	Ireland	4,612,719	47,904	51,311	7.78	0.84	92
	Italy	61,336,387	35,878	36,294	9.25	0.76	91
	Netherlands	16,979,729	50,341	49,055	10.90	0.83	99
	Oman	4,654,471	19,921	39,678	3.55	0.19	26
	Poland	37,995,529	12,530	25,730	6.35	1.83	52
	Saudi Arabia	32,157,974	18,754	52,268	4.68	1.74	30
	Spain	46,064,604	29,767	33,688	9.03	0.68	67
	Sweden	9,851,852	52,076	46,446	11.93	8.95	80
	UK	65,111,143	38,362	40,745	9.12	0.71	95
	USA	318,857,056	48,374	54,540	17.14	1.00	93
Upper-middle-income economies[S7]	Brazil	209,567,920	11,124	16,045	8.32	1.69	60
	China	1,382,323,332	4,515	13,440	5.55	3.53	22
	Iran	78,143,644	7,669	17,388	6.89	8,411.74	28
	Tunisia	11,375,220	4,212	11,358	7.00	0.63	32
	Turkey	79,622,062	10,530	19,654	5.41	1.20	39

S1: Data were obtained from The World Bank - Population, total [167];

S2: Data were obtained from The World Bank - GDP per capita (current US$) [118];

S3: Data were obtained from The World Bank - GDP per capita (current international $) PPP [168];

S4: Data were obtained from The World Bank - Health expenditure, total (% of GDP) [169];

S5: Data were obtained from The World Bank - PPP conversion factor, GDP (LCU per international $) [164];

S6: Data were obtained from the GLOBOCAN 2012 [75];

S7: The World Bank classification method. Upper middle-income economies are defined as those with a GNI/capita between (US$4,036 - US$12,475) and high-income economies are those with a GNI/capita of US$12,476 or more. [170]

Abbreviation: GDP: Gross Domestic Product; GNI: Gross National Income; LCU: Local Currency Unit; PPP: Purchasing Power Parity

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on country-specific PPP. The relative prices of trastuzumab across countries in the two scenarios were calculated by dividing the different trastuzumab prices by the reference price of trastuzumab in USD ($85.73) [158,159].

In both scenarios, an *'inability to purchase'* variable was calculated for trastuzumab and then compared across countries using the relative budget impact of trastuzumab on total healthcare expenditure based on country-specific PPPs. Inability can be defined as inequality in both affordability and accessibility of trastuzumab. The formula for inability to purchase was defined as:

$$Inability\ to\ purchase = \frac{Cost\ of\ drug_{PPP}}{Total\ health\ expenditure_{PPP}}$$
$$= \frac{N \times Price_{PPP} \times Dosage\ regimen}{GDP/capita_{PPP} \times THE_{\%\ of\ GDP} \times Population}$$

Where N=number of patients; $Price_{PPP}$, =price of the drug after conversion using PPP and GDP (Local currency unit (LCU) per international \$) [164]; Dosage regimen=total required amount of the drug. $GDP/capita_{PPP}$ =per capita GDP (current international \$) based on PPP [168]; $THE_{\%\ of\ GDP}$=total health expenditure as a percentage of GDP [169]; Population=total population of a given country.

The relative inability to purchase trastuzumab in a particular country was calculated by dividing the inability to purchase it in that country by the inability to purchase it in the US.

Results

Relative budget impact of trastuzumab on total health expenditure

Table 7.2 shows the budget impact in the 19 countries. In absolute terms, the budget impact per million people of trastuzumab use is the greatest in the US (USD: $10,951,362) and the lowest in Turkey (USD: $1,897,728). However, when the budget impact of trastuzumab is expressed as a percentage of total health expenditure, the impact is greatest in Tunisia (1.13%) and lowest in Sweden (0.08%). In fact, trastuzumab on average has a lower impact on total health expenditure in HICs than in MICs (0.21% vs. 0.68%, respectively). Figure 7.1 shows the relationship between relative public price of 10mg trastuzumab and GDP across the countries; the size of the bubbles reflects the relative budget impact. This figure shows that the budget impact of trastuzumab is 3.18 times greater in countries with a lower GDP than in countries with a higher GDP.

Table 7.2: The results of budget impact analysis and its impact on total health expenditure in different two scenarios.

Category	Country	Trastuzumab budget impact			Inability to purchase trastuzumab		
		per million people (US$)	Health expenditure	Relatively impact[1]	Scenario I[2]	Scenario II[3]	Scenario II – scenario I
High-income economies[S1]	Denmark	8,576,263	0.13%	0.99	1.25	2.31	1.05
	Greece	1,948,163	0.11%	0.85	1.11	1.44	0.33
	Germany	7,640,025	0.16%	1.23	1.40	1.52	0.12
	Hungary	3,353,781	0.35%	2.65	3.21	1.37	-1.84
	Ireland	7,748,453	0.21%	1.57	1.40	2.75	1.35
	Italy	5,649,868	0.17%	1.29	1.70	2.31	0.60
	Netherlands	6,306,813	0.11%	0.87	1.09	1.72	0.62
	Oman	3,047,722	0.43%	3.26	3.75	0.91	-2.84
	Poland	3,546,824	0.45%	3.37	3.82	1.55	-2.27
	Saudi Arabia	2,706,249	0.31%	2.33	2.04	0.56	-1.47
	Spain	4,644,827	0.17%	1.31	1.73	1.68	-0.05
	Sweden	5,142,610	0.08%	0.63	0.75	1.55	0.80
	UK	5,421,251	0.16%	1.17	1.15	2.79	1.64
	USA	10,951,362	0.13%	1.00	1.00	1.00	0.00
Upper-middle-income economies[S1]	Brazil	4,641,343	0.50%	3.80	5.85	2.27	-3.58
	China	2,601,139	1.04%	7.86	5.26	1.69	-3.58
	Iran	1,954,183	0.37%	2.80	4.80	0.68	-4.11
	Tunisia	3,342,792	1.13%	8.58	11.19	1.29	-9.90
	Turkey	1,897,728	0.33%	2.52	3.46	1.63	-1.83
Average (HICs)		**5,477,444**	**0.21%**	**1.61**	**1.81**	**1.68**	**-0.14**
Average (MICs)		**2,887,437**	**0.68%**	**5.11**	**6.11**	**1.51**	**-4.60**
P-value (HICs vs MICs)		**<0.01**	**0.03**	**0.03**	**0.02**	**0.31**	**0.02**

(For HICs Scenario I column: P-value=0.36[4]; for MICs Scenario I column: P-value=0.02[4])

S1: The World Bank classification method. Upper middle-income economies are defined as those with a GNI/capita between (US$4,036 - US$12,475) and high-income economies are those with a GNI/capita of US$12,476 or more. [170]

1- A comparison of the relative budget impact of trastuzumab on the total health expenditure across countries versus the USA. (The relative budget impact of trastuzumab on the total health expenditure in USA=1), **2-** A comparison of the current relative inequality in affordability of trastuzumab in target countries versus to the USA. (Inability to purchase trastuzumab in USA=1), **3-** A comparison of the relative inequality in affordability of trastuzumab in target countries versus to the USA using the assumptive prices. (Inability to purchase trastuzumab in USA=1), **4-** A pair comparison between inability to purchase trastuzumab in the first scenario versus the second scenario

Abbreviation: GDP: *Gross Domestic Product;* **GNI:** *Gross National Income;* **HIC:** *High Income Country;* **N:** *Number of patients;* **MIC:** *Middle Income Country;* **PPP:** *Purchasing Power Parity;* **THE:** *Total Health Expenditure*

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Relative affordability of trastuzumab across countries.

Figure 7.2 shows the results of scenario I, where list prices of trastuzumab were converted using country-specific PPP against PPP in the US. Here we see that the price of trastuzumab decreases as per capita GDP increases (R^2 = 0.510). This figure reveals that the inability to purchase trastuzumab, reflected by the size of the bubbles, is higher in countries with a lower GDP. Table 7.2 shows that the greatest inability to purchase trastuzumab (in Tunisia) was 11.19 times larger than the inability to purchase trastuzumab in the US (1.00). Comparing Tunisia with Sweden, the country with the lowest relative inability to purchase trastuzumab, trastuzumab was almost 15 times less affordable in Tunisia than it was in Sweden (Table 7.2). Overall, trastuzumab was 3.37 times less affordable in MICs compared to HICs (p-value=0.02); the mean ratio of inability to purchase in MICs versus in HICs was 3.37 (Table 7.2), which indicates inequality in affordability and accessibility.

Figure 7.3 presents the results of the scenario II which is a simulation of Ramsey pricing (price differentiation). The assumptive prices and per capita GDP increased simultaneously, indicating a significant price differentiation (p-value<0.01) across countries. Moreover, Table 7.2 shows that the ratio of inability to purchase trastuzumab in MICs versus in HICs was on average 0.91 in scenario II. This ratio is lower than the ratio of 3.37 seen in scenario I, which means that the inability to purchase trastuzumab in MICs improved 4.60 times in scenario II compared to scenario I (Table 7.2, final column, scenario II - scenario I). This change can also be seen in the smaller bubbles in Figure 7.3 in MICs compared to those in Figure 7.2. Scenario II also results in a nonsignificant difference in affordability and accessibility of trastuzumab between MICs and HICs (p-value=0.31). This approach affects countries differently. As Table 7.2 shows, the greatest loss in affordability and accessibility of trastuzumab was observed in the UK, where inability to purchase trastuzumab increased from 1.15 in scenario I (current situation) to 2.79 in scenario II. In contrast, the greatest gain in affordability and accessibility of trastuzumab was observed in Tunisia (change in inability to purchase= −9.90). However, in general, using scenario II resulted in improved equality of affordability and accessibility even in HICs (a 0.14 reduction in inability to purchase trastuzumab).

Discussion

Pricing is an instrument that policymakers can use to improve affordability of drugs in a healthcare system. This instrument is particularly valuable when an expensive drug is being considered for reimbursement in a lower or middle-income country. This study highlights the current differences in affordability and accessibility of trastuzumab, which is an expensive and important drug in HICs and MICs. We estimated the (relative)
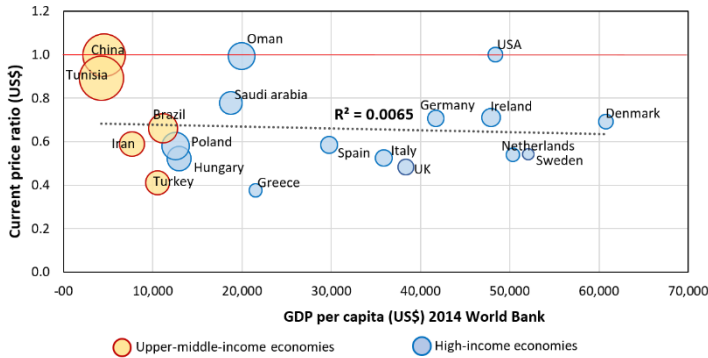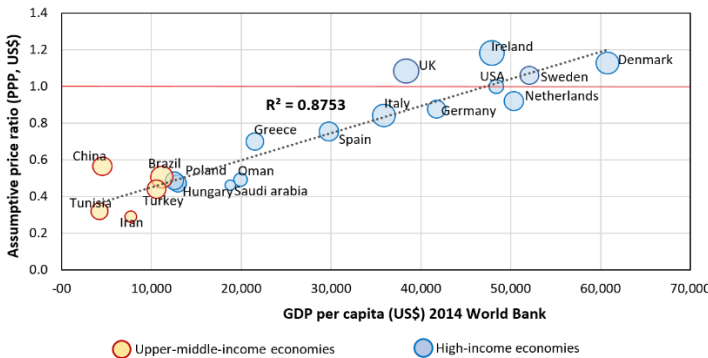
Note: Using the size of bubbles, Figure 7.1 represents a comparison of the relative budget impact of trastuzumab on the total health expenditure across countries versus the USA. (The relative budget impact of trastuzumab on the total health expenditure in USA=1)

Figure 7.1: GDP per capita (US$) 2014 world bank versus price ratios for trastuzumab. Real relative price of 10mg trastuzumab (Herceptin®) among some HICs and MICs based on the average currency exchange rate against USD in 2015[160] (price in USA=1)
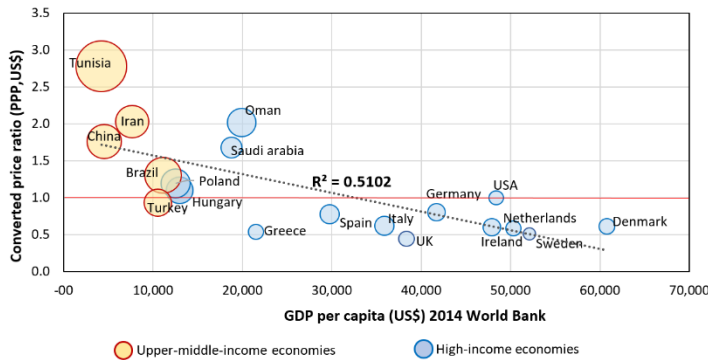
Note: Using the size of bubbles, Figure 7.2 illustrates a comparison of the inequality in affordability of trastuzumab in these countries versus to the USA. (Inability to purchase trastuzumab in USA=1)

Figure 7.2: GDP per capita (US$) 2014 World Bank versus price ratios for trastuzumab. Comparison of converted prices of 10mg trastuzumab based on the PPP conversion factor, GDP lowest unit cost (LUC international $) obtained from the World Bank [164] (PPP in USA=1)

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Note: Using the size of bubbles, Figure 7.3 illustrates a comparison of the inequality in affordability of trastuzumab in these countries versus to the USA. (Inability to purchase trastuzumab in USA=1)

Figure 7.3: GDP per capita (US$) 2014 world bank versus price ratios for trastuzumab: An assumptive comparison price of 10mg trastuzumab when price of this drug in USA directly converted based on PPP conversion factor for each country.

budget impact of trastuzumab and inability to purchase trastuzumab in order to draw some conclusions about differences in affordability and accessibility between HICs and MICs.

External price referencing is a widely applied method to control pharmaceutical prices. If differences between the economic status of reference countries are not taken into account, this will limit the ability of individual MICs to adjust drug prices to their affordability constraints, because it will result in a fairly narrow international price corridor [171]. Since the potential price indicated by this narrow price corridor is usually too high for lower income countries, it may reduce affordability and patient access to new pharmaceuticals in MICs.

HICs often have a greater degree of negotiation power when setting pharmaceutical prices due to their larger market potential (4). However, because they often apply performance-based and finance-based risk-sharing arrangements (PFRSA), which are not publicly available due to confidentiality agreements [144], reference prices are most likely higher than actual paid prices. If other countries base their drug prices on publicly available reference prices in other countries, this will only increase inequality in affordability. In addition, external price referencing using prices of HICs results in other issues in MICs. For example, one of the main consequences is that the budget impact of expensive drugs account for a larger share of total health expenditure in MICs than in HICs. As an example, a study on economic burden of cancer in the European Union showed that on average €3.07 billion (46%) in total health expenditure were allocated to medication in treatment of breast cancer [142]. However, the proportion of pharmaceutical expenditure was much higher in several lower European income countries, such as Cyprus (81%), Hungary (79%), and Malta (76%), than the European average [142]. This means that money must be shifted away from other healthcare services to finance expensive drugs. This phenomenon may cause health and efficiency loss, and lead to compression elsewhere in the healthcare system. Illegal and informal payments [93,172] by patients to underpaid healthcare providers for difficult to access health care services due to insufficient budget allocation in MICs may be an example of this issue.

From a pharmaceutical point of view, the domino effect is an undesirable consequence of external price referencing. If the lowest price is always considered a benchmark for other countries, this may result in a 'race to the bottom' and lower prices in many countries. To solve this issue, most countries keep their real price confidential. However, due to confidential price discounts specifically for expensive drugs in HICs, policymakers in MICs may not know actual paid prices of drugs in the reference countries. Therefore, uncertainty about the real price of drugs in reference countries is an additional issue associated with external price referencing [144].

Ramsey pricing is a method which enables pharmaceutical companies to price their products according to a country's ability to pay [165]. If Ramsey pricing is implemented, pharmaceutical prices are lower in MICs compared to HICs, which improves affordability and accessibility, as illustrated in our study. However, it creates additional policy problems related to parallel trade between countries and domino effect of reducing the floor price of the pharmaceutical price corridor. Therefore, Ramsey pricing is not a reasonable strategy for pharmaceutical companies as long as there are deficiencies in external price referencing [166]. The companies, hence, may lose interest in launching their products in MICs at lower prices. On the other hand, Ramsey pricing should be considered by payers in MICs as the target price or starting point for price negotiations. Therefore, implementation of only one of these two methods may affect patient access to drugs in different countries (Figure 7.3 vs Figure 7.1).

Policymakers in MICs must improve their pricing and reimbursement policies in order to ensure access to essential treatments. Our study shows that this means differentiating prices across countries based on the ability to pay. MICs should work towards establishing a value-based pricing system instead of only applying external price referencing. Furthermore, if MICs aim at implementing price differentiation, they have to solve issues related to parallel trading and the domino effect. Some procedures, such as a confidential rebate mechanism for MICs and restrictions on selecting reference countries with a similar GDP, may provide feasible opportunities for price differentiation. However, an improvement in capability for price negotiation would be a significant milestone in MICs.

The capability to negotiate prices can be improved by using two strategies. The first strategy is to maximize the power for price negotiation in the pharmaceutical market. Different approaches could be used here. For example, one approach is to establish regional health technology assessment (HTA) bodies (like the collaboration among Belgium, Netherlands, Luxemburg and Austria [173]) to organize the pharmaceutical market in multiple countries with the same economic power. Another approach is to let brands launch in the market only under a regional brand name using a different package. This may reduce parallel trading and facilitate the implementation of price differentiation. The second strategy is to improve HTA knowledge in MICs. With more knowledge, MICs can improve their price negotiations based on the expected (value-based) and assessed (real-world) value of a drug in a particular market and provide country-specific pricing standards rather than rely on the price of drugs in other countries. This would help policymakers to combine price negotiations with performance-based and finance-based arrangements (PFRSAs) [174,175].

The implementation of PFRSAs is an approach to allocate the healthcare resources efficiently and based on our finding, it may be highly important in MICs. MICs may use

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the experience of other countries to improve their pricing system. The UK may be a good example of this as instead of using external price referencing [144] they have a strong PFRSA system [175] based on HTA and fairly low explicit thresholds compared to their GDP per capita. The greatest price increase of trastuzumab between scenarios I and II was in the UK (Table 7.2). This means that the UK has the cheapest list price based on PPP conversion factor across the target countries. Moreover, due to some confidential rebates, it can be expected that trastuzumab is likely to be even cheaper in the UK. This price balance between payers and manufacturer is made based on ability to negotiate on price and/or measure the real-world effectiveness of drugs. An ability to negotiate price can be obtained by improving the knowledge production infrastructure in different areas of HTA analysis such as cost-effectiveness analysis and multiple criteria decision analysis. Moreover, the healthcare governance structure should be such that it can facilitate implementation of PFRSA. The UK has successfully implemented these two prerequisites to achieve value-based pricing. The power of pricing system in the UK is such that policymakers in many countries consider the NICE recommendations as an important document in reimbursement decision-making process. Therefore, manufacturers are willing to offer huge discounts to the UK for a positive NICE recommendation which can facilitate a successful international marketing. In summary, implementation of PFRSA can support a pricing system independent from other countries. However, PFRSA would not be easy to implement in countries that have not yet established a strong knowledge production infrastructure, and their healthcare governance would need to be upgraded to improve capacity for implementing PFRSAs.

This study has two limitations worth noting. Firstly, the price of trastuzumab has only been studied in a limited number of countries, which may affect the generalizability of the results. Secondly, GDP per capita of Hungary and Poland - two HICs in Eastern-Europe - is closer to MICs than to other HICs. Listing these two countries among HICs may reduce the power of our conclusions. However, it would have been difficult to justify an arbitrary 15,000 USD per capita GDP threshold to distinguish lower-income from higher-income countries. Regardless of these limitations, our result show that there is no correlation between price and per capita GDP across countries, which corresponds with results of other studies [78-80]. Therefore, we expect that our limitations do not affect the calculated inability to purchase.

Our main message is a strong recommendation for MICs to improve their healthcare infrastructures with the goal of implementing innovative policies which facilitate establishing an independent pharmaceutical pricing system. International organizations such as the WHO can help lower income countries to improve their healthcare infrastructure in favor of implementation of price differentiation. An implemented
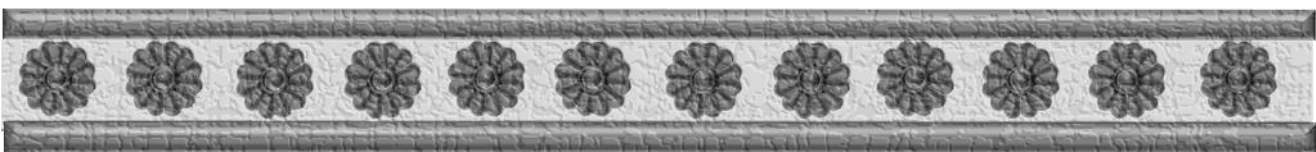
strong pricing system will improve patient access to (new) essential drugs, including expensive drugs, in MICs.

Conclusion

Equal drug affordability is an important aim emphasized by the WHO but current pricing methods result in affordability and accessibility issues in MICs. Population health and quality of care are both affected by limited access to essential drugs. Trastuzumab, an essential drug according to the WHO, is less affordable and accessible in MICs than in HICs. Equal affordability across countries can be improved by using price differentiation. Specifically, PFRSA can relieve inequality in affordability and accessibility and may help in price differentiation in MICs.
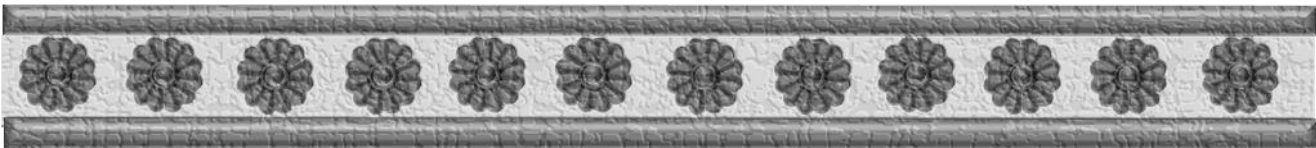
Acknowledgment

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Chapter 8

Moving forward to innovative pricing and reimbursement policies for expensive drugs in a middle-income country

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Submitted

Abstract

In the coming years, performance-based and finance-based risk-sharing arrangements (PFRSA) are expected to be more prominent in middle-income countries (MICs). This study examined the pharmaceutical pricing and reimbursement in one MIC (Iran) to identify prerequisites for the implementation of PFRSAs.

In the first step, a SWOT (strengths, weaknesses, opportunities and threats) analysis was used to compare the current pharmaceutical pricing and reimbursement decision-making system in Iran with the PFRSA governance and infrastructures in six reference countries (England, Germany, Hungary, Italy, Poland and Turkey) that have implemented PFRSA policies. We then developed recommendations to improve system capacity for implementing PFRSA policies in Iran.

The SWOT analysis showed that distributed responsibilities, conflicts of interest, a lack of post-decision market monitoring, and time-consuming procedures are important weaknesses of the current system in Iran. The results of country comparisons showed that four important phases of PFRSA process (i.e., evaluation, negotiation, resolution, and observation) were not implemented continuously and consistently. Moreover, to improve performance of the current process, improvement in two areas of reorganizing healthcare governance and improving infrastructure and process would be instrumental in Iran.

In conclusion, Iran can strengthen its pricing and reimbursement system by centralizing governance duties and responsibilities. The current process must be improved by using a cyclic and dynamic pricing and reimbursement process. Subsequently, implementing finance-based arrangements would be a good start point to implement PFRSA policies in Iran. Implementation of performance-based schemes needs more efforts on improvement of post-decision market monitoring and real-world evidence.

Introduction

Performance-based and finance-based risk-sharing arrangements (PFRSA) between payers and manufacturers have been widely implemented in high-income countries (HICs) [32] to achieve an optimal balance between ensuring timely access and managing affordability. PFRSA is an overarching term that includes various policies related to price negotiation, post-decision-making monitoring of costs and outcomes, and evaluation of the cost-effectiveness of new technologies in a real-world setting [175]. These policies have been given a variety of names, including outcomes-based schemes, patient access schemes, and pay-for-performance [175]. They share, however, one main aim, which is to base reimbursement on real-world outcomes by addressing both value for money and cost containment.

Implementation of PFRSA in middle-income countries (MICs) is of utmost importance to achieve equal affordability of a drug [81]. In countries where PFRSA is not implemented, payers and patients must endure possible finance and performance-based risks [81]. Iran, as an MIC, is facing the consequences of its lack of implementation of such policies. Tracking the story of one drug can illustrate the shortcomings of the current Iranian pharmaceutical pricing system. The drug trastuzumab, used for early breast cancer treatment, is a good example as historically, the price of trastuzumab remained mostly stable over the years even though its use continued to increase (Figure 8.1). This means that all of the finance-based risks have been aggregated for payers. Moreover, from a cost-effectiveness point of view, a recently published article studying different strategies of trastuzumab therapy [134] showed that with the current price of trastuzumab in Iran [176], a six-month course of trastuzumab is an optimal strategy only for patients who are younger than 59. In contrast, most clinical guidelines recommend a one-year treatment regimen for trastuzumab use. This means that the price of trastuzumab should be significantly reduced in Iran. In other words, if payers only want to cover six months of trastuzumab use and the manufacturer does not reduce the price, performance-based risks such as lower quality-adjusted life year (QALY) gains are imposed on the patient. Therefore, Iran needs to upgrade its pricing and reimbursement system to improve its capacity to implement policies like PFRSA.

The implementation of PFRSA in MICs will, however, encounter serious issues. Some of these issues relate to a country's limited infrastructure to produce health economic data or its inefficient healthcare governance [51], but there are also issues of patients already having a lower life expectancy than HICs and insufficient health care budget [134]. To move forward, it is important to know how policymakers in MICs can both use and improve their current available knowledge and how to strengthen their systems to ensure a better decision-making in order to get better health outcomes. This raises the question of how MICs can establish an appropriate process and infrastructure to

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implement PFRSA. As there are many similarities in healthcare systems and above mentioned issues between Iran and other low- and middle-income countries [177], we will focus on the situation in Iran.
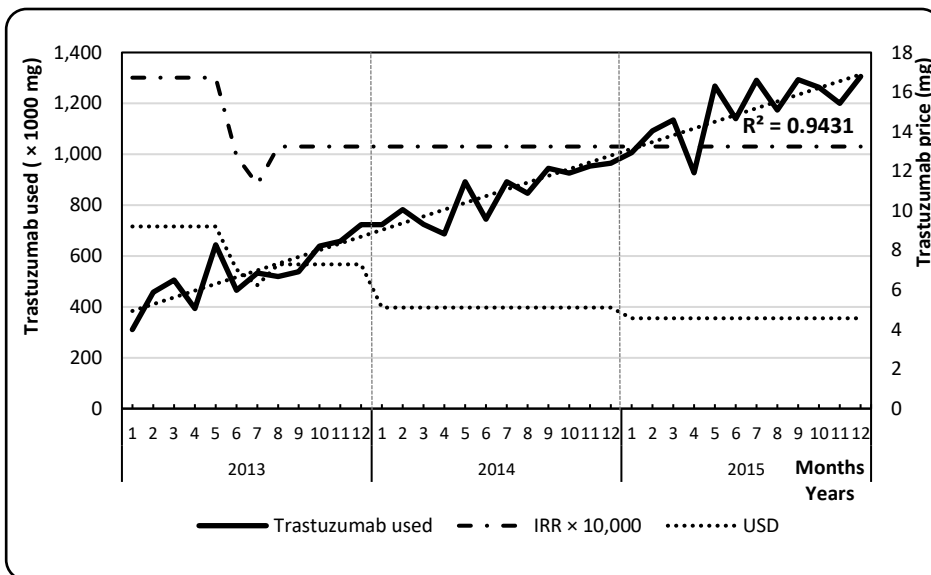
Figure 8.1: The trend of trastuzumab use and changes in average price per mg over three years since the reimbursement date (01/2013) in Iran. The average price obtained from the prices of both 150mg and 440mg vials over a 3-years period [125].
Abbreviation: IRR: *The Iranian rial,* ***USD:*** *The United states dollar*

The aim of this study is to investigate the prerequisites for improving pharmaceutical pricing and reimbursement in Iran. Firstly, the shortcomings and successes of the current drug pricing and reimbursement system are explained using an analysis of the relevant strengths, weaknesses, opportunities, and threats (SWOT analysis). The SWOT analysis helps create a framework to identify and analyze the internal and external factors that can have an impact on the pricing and reimbursement system [178] in Iran. Then, using the experiences of six other countries (England, Germany, Hungary, Italy, Poland, and Turkey) regarding their implementation of innovative policies such as PFRSA, recommendations for policymakers in Iran are outlined. These recommendations may also be relevant for other MICs.

The current drug pricing and reimbursement system in Iran

The pharmaceutical pricing is managed by the Iranian Food and Drug Organization (FDO), under the supervision of the Ministry of Health (MoH) [179]. The pricing method for domestic pharmaceutical products is based on a "cost-plus" pricing strategy, which means that the pricing is based on the final cost of drug production plus marginal

benefits in various layers of wholesale and pharmacy retail. Prices in other countries (Greece, Spain, and Turkey [14]) and currency exchange rates are considered in order to set the prices of imported drugs [179]. The prices of branded and generic drugs are different; however, four main payers [51] which cover more than 95% of Iranian population, mostly cover the price of the generic form. Although prices for expensive drugs are negotiated before reimbursement decisions [51], the implementation of finance-based risk sharing arrangements is uncertain because of three main issues. Firstly, in the case of rapid changes in the currency exchange rate [117], the agreed price may change if the currency exchange rate changes significantly. Secondly, the regulating body for drug pricing (FDO) is not sensitive to the budget impact of drugs in Iran [51] because payers are responsible for healthcare expenditures. Finally, although payers are responsible for the pharmaceutical budget [51], they do not participate in the pricing commission [179] and are not allowed to negotiate directly with manufacturers. However, the pharmaceutical companies have a representative on the pricing commission.

The drug reimbursement decision-making process in Iran can be described as a shared responsibility process as it is divided between two different ministries, the MoH and the Ministry of Welfare (MoW) [51]. New drugs must first be approved by the MoH. Once a drug is approved, patients can have access to them even though the reimbursement phase of the process is still incomplete. Next, pharmaceutical firms must apply for reimbursement of expenses by payers at the MoW. Ultimately, the Iranian Cabinet approves a drug when they get a positive reimbursement recommendation from the MoW. In addition, other stakeholders are involved in the reimbursement process, including the Iranian Medical Council and two members of the Iranian Parliament. Under the supervision of the MoW, payers are also involved and mostly focus on economic considerations [51].

To identify ways to improve the reimbursement decision-making process, both internal and external factors that may impact the current drug pricing and reimbursement system in Iran need to be analyzed. Therefore, a SWOT analysis was performed by reviewing the administrative rules and interviewing experts and policymakers in Iran.

SWOT analysis; shortcomings and success of the pricing and reimbursement system in Iran

Table 8.1 shows the results of the SWOT analysis. In terms of strengths, Iran's strong generic market and universal health insurance coverage are the most important strengths of its pharmaceutical system. These strengths help reimbursed drugs to be affordable to all patients. Moreover, Iran has an existing pharmaceutical pricing and reimbursement system and drugs must undergo a formal process of assessment and

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appraisal to be reimbursed. On the other hand, the system has some weaknesses such as the fact that two ministries share the responsibility for the drug pricing and reimbursement system, which leads to inefficient management. The fact that the process is non-transparent and time-consuming is another important weakness that causes unequal affordability among patients. Moreover, Iran has not been defined any correction methods on the previous decisions and also flexibility on the process of reimbursement decision making for drugs with different specifications. There are many opportunities to overcome the weaknesses, such as Iran's large population size, that can bolster the price negotiating power of Iranian policymakers, and Iran's generally strong health information infrastructure that can facilitate post-market monitoring. In contrast, there are important threats to improving the system. For example, pharmaceutical firms may be unwilling to reform the system and to implement of PFRSA. Another major threat that policymakers are face is a decrease in social accountability of payers due to budget constraints.

Based on the results of the SWOT analysis, the main challenges seen in the Iranian pricing and reimbursement process are the inconsistency between the two ministries, the time-consuming and opaque process, and the lack of process dynamism (flexible process execution to improve performance) [51]. Therefore, policymakers should try to consolidate the strengths and eliminate the weaknesses through the proper use of their opportunities. They also should try to turn threats into opportunities by creating new policies. Furthermore, to improve the performance of the pharmaceutical pricing and reimbursement decision-making process, Iran may benefit from the experiences of other countries. That is, a careful examination of the systems in other countries could help Iranian policymakers recognize how weaknesses can be improved using the current strengths and opportunities of the Iranian system.

What can Iran learn from the experiences of other countries?

The experiences of HICs regarding the implementation of PFRSA provide a useful resource when considering how to implement these policies in MICs. Due to the results of SWOT analysis (Table 8.1), this study focused on two main aspects which affect the pricing and reimbursement system: healthcare institutions and governance and infrastructure and process.

A comparison of healthcare institutions and governance

Table 8.2 presents an overview of the pharmaceutical pricing and reimbursement institutions and governance seen in six HICs and one MIC (Iran), including information

Table 8.1: SWOT analysis of the pharmaceutical pricing and reimbursement process in Iran.

Strengths	Weaknesses	Type of issue
1. Long-established generic drug market	1. Pharmaceutical governing bodies distributed across two ministries	HG
2. Universal health insurance coverage policy	2. Non-transparent drug registration and reimbursement decision-making process	HG, IP
3. National basic package for all Iranians	3. Conflicts of interest in the pricing and reimbursement process	HG
4. Drug assessment and appraisal protocols for the drug reimbursement process	4. Time-consuming procedure of reimbursement decision-making	HG, IP
5. Existence of national level pricing and reimbursement policies	5. Payers are not involved in the pricing process	HG, IP
6. Appropriate financial contribution particularly by payers for severe diseases with catastrophic costs (almost 100% of costs are covered)	6. No correction method for previous pricing and reimbursement decisions	IP
7. Drugs are properly available in all regions of the country	7. Inflexible process for drug reimbursement with different specifications such as administrative burden and budget impact.	IP
8. Price negotiation and budget impact analysis during the reimbursement process	8. New and expensive drugs can be launched while they are not reimbursed and affordable	HG, IP
	9. Risk aggregation is centered on payers and patients. There is a no-risk market for the manufacturers after the reimbursement decision-making process	HG, IP
	10. Uncertainty regarding implementation of the price negotiation agreements	HG, IP
	11. Lack of a systematic reimbursement revision process after a decision to health insurance coverage of drugs	HG, IP
	12. Unwillingness of payers to reimburse new technologies, such as expensive drugs	HG, IP
	13. Redundancy of information provided by applicants for the registration and reimbursement decision-making processes	HG, IP

Opportunities	Threats	Can be handled by improvement in
1. Large population size, which can provide a stable market for manufacturers	1. Scarcity of health and drug financing	HG, IP
2. Strong general tendency for implementing strategic purchasing among the Iranian policymakers and governors	2. Growth of expensive pharmaceutical products, medical devices, targeted therapies, and patient-centered therapies in the global market	HG, IP
3. Strong HIT infrastructure for outpatient services and rapidly improving HIT infrastructure for inpatient services	3. Decreasing social accountability of payers due to drug budget limitations.	HG, IP
4. Developing production of expensive drugs inside the country, which means lower costs for payers	4. Increasing patient copayments	HG, IP
5. Developing health economy and outcome research	5. Resistance of manufacturers to novel pricing and reimbursement policies	HG, IP
6. Increasing export rate of branded-generic products to other countries	6. Insufficient research capacity for HTA studies	HG, IP
	7. High rate of fluctuation in the currency exchange rates	Others
	8. Phenomenon of increasing intermediaries among drug import companies	HG

Abbreviations: HIT: *Health Information Technology,* **HTA:** *Health Technology Assessment,* **HG:** *Healthcare Governance,* **IP:** *Infrastructure and Process.*

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about the main actors involved in the drug pricing and reimbursement decision-making process in these countries. The number of institutions that are involved in the process is remarkable. In most of the six HICs, pricing and reimbursement decision-making is centralized in the same body or in various institutions administered by a single governing body. In Iran, however, these processes are divided between two ministries with partly divergent missions [51].

In the six countries, the pricing authorities are also governing bodies for health insurance payers. Moreover, pharmaceutical companies do not appear to be directly involved in the process of price determination by the governing bodies in these countries. In contrast, pharmaceutical pricing in Iran are centralized in a non-finance-related organization. Moreover, representatives of the manufacturers have been directly and legally involved in pricing decision-making since 1988 [180]. This can be seen as an example of conflict of interest in the Iranian drug pricing process.

Within the hierarchical governance structure, Table 8.2 shows that the difference between the assessment-appraisal layers and the layer of final reimbursement decision-making is greater in Iran compared to the six countries. In other words, a longer process can be expected in Iran. As European countries are committed to implementing the Transparency Directive regulation of the European Union [181], there is a maximum duration of their pricing and reimbursement decision-making process. With 2 layers and without a directive about maximum duration it is expected that the process in Iran will take longer [51].

A comparison of infrastructure and process

Table 8.3 shows the differences and similarities in infrastructure and process of pharmaceutical pricing and reimbursement between Iran and the six other countries, including information regarding drug pricing, reimbursement, and post-market monitoring. The first remark is that Iran, as in the other countries, has implemented some parts of the reimbursement infrastructure, such as having a national drug formulary and a national level pricing system. However, considerable differences in the current process exist as well. Iranian policymakers manage the demand side by using reimbursement restrictions (e.g. restrictions regarding indication or prescriber). In contrast, the other six countries use easy-to-implement risk-sharing policies to contain costs. Until now, Iranian policymakers have shown little interest in any of the PFRSA.

In the six countries, the pharmaceutical market is monitored by governing bodies that investigate real-world drug utilization, adherence to treatment or guidelines, and long-term clinical outcomes. However, the results of these systematic audits may lead to revision of reimbursement status. It means a cyclic process for the drug reimbursement

Table2: Pharmaceutical reimbursement Institutions and governance

	England	Germany	Hungary	Iran	Italy	Poland	Turkey
Main actor for clinical safety and effectiveness assessment	NHS	IQWiG	NHIFA	FDO (MoH)	AIFA	URPLWMiPB	TİTCK
Appraisal main actor	NICE (NHS)	IQWiG	NHIFA	SCoHI (MoW)	AIFA	AOTMiT	TİTCK
Final reimbursement decision-making body	NHS	G-BA	NHIFA	Government cabinet	AIFA	Minister of Health	SGK
Price negotiation	Yes	Yes	Yes	Yes	Yes	Yes	SGK
Price negotiation main actor	NHS	GKV-SV	NHIFA	SCoHI (MoW)*	AIFA	MoH	SGK
Price regulator main actor	NHS	GKV-SV	SSH (MoHR)	FDO (MoH)	AIFA	MoH	SGK
Payer(s) operational supervisor	NHS	GKV-SV	NHIFA	MoW	SSN (MoH + AIFA + ISS + ASLs)	MoH	SGK
Time limitation for reimbursement process (Days)		180 (+180 for pricing)	90 (+90 for pricing)	No binding deadline	350	90 (+90 for pricing)	No binding deadline
Health care system model	Beveridgien[1]	Bismarckian[2]	National health insurance[3]	Bismarckian[2]	National health insurance[3]	National health insurance[3]	Bismarckian[2]

1- **Beveridgien:** The National Health Service– Funded from general government revenues, coverage for entire population [200]
2- **Bismarckian:** Social Health Insurance – Compulsory funding by employers and employees, administered by pre-existing "sickness funds" [200]
3- **National health insurance:** A system which would be established by a government to cover whole population of the country and funded with tax money [201]

Abbreviations: ***AIFA:*** *The Italian Medicines Agency (Agenzia Italiana del Farmaco),* ***AOTMiT:*** *the state agency for HTA and tariff system (Agencja Oceny Technologii Medycznych i Taryfikacji),* ***ASLs:*** *Local health units (Azienda Sanitaria Locale),* ***CEPS:*** *The Economic Committee for Medical Products (Comité Economique des Produits de Santé),* ***FDO:*** *Food and Drug Organization,* ***G-BA:*** *Federal Joint Committee (Gemeinsamer Bundesausschuss),* ***GKV_SV:*** *Federal Association of Social Health Insurance Funds (GKV-Spitzenverband),* ***ISS:*** *The Superior Institute of Health (Istituto Superiore di Sanità),* ***SGK:*** *Social Security Institute (Sosyal Güvenlik Kurumu),* ***SSH:*** *State Secretariat of Health (Egészségügyi Szakállamtitkárság),* ***SSN:*** *National Health System (Servizio Sanitario Nazionale),* ***IQWiG:*** *The Institute for Quality and Efficiency in Healthcare (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen),* ***MoH:*** *Ministry of Health,* ***MoHR:*** *Ministry of Human Resources (Emberi Erőforrások Minisztériuma),* ***MoW:*** *Ministry of Welfare,* ***NFZ:*** *National Health Fund (Narodowy Fundusz Zdrowia),* ***NHIFA:*** *National Health Insurance Fund Administration,* ***NHS:*** *National Health System,* ***NICE:*** *National Institute for Health and Care Excellence,* ***SCoHI:*** *Supreme Council of Health Insurance,* ***TİTCK:*** *Turkish Drug and Medical Device Institution (Türkiye İlaç Ve Tıbbi Cihaz Kurumu),* ***URPLWMiPB:*** *The Office for Registration of Medicinal Products, Medical Devices and Biocidal Products (Urząd Rejestracji Produktów Leczniczych, Wyrobów Medycznych i Produktów Biobójczych)*

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decision-making system. The situation in Iran is different; neither systematic nor ad-hoc reimbursement revision is possible in the current process unless important drug safety concerns arise later. Therefore, it seems that drug manufacturers operate in a secure market after reimbursement because all of the risks of low performance or high budget impacts are pushed onto the payer or patient, which leaves the pharmaceutical firms with no concern about revision of reimbursement decision-making.

With this comparative analysis of the six target countries, four phases of drug pricing and reimbursement should be considered in order to implement PFRSA policy: evaluation of a new drug, negotiation of the price, resolution of the price and reimbursement of the new drug, and observation of the outcomes followed by a decision. These phases not only must be in line with the other phases, but also the results of the observation phase, based on real-world evidence (RWE), should be used for the next evaluation phase. A self-correcting system, like revision of reimbursement status which already discussed, is needed such that for each new decision to be made, it corrects what issues were found in the past. Therefore, to enhance reimbursement revision, as shown in Table 8.3, it is crucial to make the reimbursement process more cyclical (Figure 8.2) [182]. To achieve this proposed structure, policymakers need to provide some prerequisites.

What is needed to move forward?

A series of recommendations can be formulated based on a SWOT analysis of Iran's system and a comparison of Iran's system with the systems found in six other countries. Each recommendation has an impact on different components of the SWOT analysis and leads to consolidation of strengths and improvement of weakness. Table 8.4 shows the impact of the recommendations on each item of the SWOT analysis given in Table 8.1.

Eliminate conflicts of interest and maximize process transparency

It is very important that healthcare governors identify and eliminate all current conflicts of interest. Otherwise, upgrading actions and the adoption of various recommendations will be affected by the multi-faceted characteristics of personal (member composition of the pricing commission) or organizational purposes (Inconsistency between MoH and MoW). Moreover, by increasing transparency, the risk of conflicts of interest can be decreased. If these two actions (eliminating conflicts of interest and maximizing process transparency) are not fulfilled, this will not only mean that the ultimate aims of PFRSA will not be achievable but it can also increase the risk of poor performance in the healthcare system.

Table 8.3: Pharmaceutical reimbursement infrastructure and process [51,198,199]

	England	Germany	Hungary	Iran	Italy	Poland	Turkey
National drug formulary (NDF)	Yes	Yes	Yes	Yes (Doctors can prescribe drugs out of NDF)	Yes	Yes	Yes
Positive reimbursement list	No	No	Yes	Yes	Yes	Yes	Yes
Reimbursement restrictions							
Clinical indication	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Doctors' specialization	Yes	No*	Yes	Yes	Yes	No	Yes
Using in inpatients or outpatient services	Yes	No	Yes	Yes	Yes	No	Yes
National level pricing	Yes	Yes	Yes	Yes	No	Yes	Yes
Reference pricing system							
Internal	Yes	Yes	Yes	No	Yes	Yes	Yes
External	No	Yes	Yes	Yes (Only for imported drugs)	Yes	Yes	Yes
Being reference for other countries	Yes	Yes	Yes	Unknown	Yes	Yes	Yes
Risk Sharing arrangements	Yes	Yes	Yes	No	Yes	Yes	Yes
Non-outcomes based implemented schemes							
Market share	No	Yes	No	No	No	Yes	Yes
Price volume	Yes	Yes	Yes	No	Yes	Yes	Yes
Budget caps	Yes	No	Yes	Yes	Yes	Yes	Yes
Manufacturer funded treatment	Yes	Yes	Yes	NO	Yes	Yes	Yes
Health outcomes based implemented schemes							
Coverage with evidence development (CED)	Yes	No	No	No	Yes	No	No
Conditional treatment continuation (CTC)	Yes	No	Yes	No	Yes	No	Yes
Performance linked reimbursement (PLR)	Yes	Yes	Yes	No	Yes	Yes	No
post-market monitoring	Yes	Yes	Yes	No	Yes	Yes	
Reimbursement revision							
Ad hoc	Yes	Yes	Yes	Yes (Only if the safety rejected)	Yes	Yes	Yes
systematically	Yes	No	Yes#	No	Yes	Yes (2,3 or 5 years)	No

* With a few exceptions; # When the initial risk sharing agreement expires

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Establish integrity in operation

According to the experiences of other countries, the reimbursement decision-making and pricing process should operate as a unified process. Accountability, performance, and timeliness suffer if the process is fragmented. Some of the weaknesses of the Iranian pharmaceutical system exist because this process is shared between two ministries whose objectives are not necessarily (or perfectly) aligned (Table 8.1). Therefore, a reorganization is required to integrate the operation of the pricing and reimbursement system. The experiences of other countries show that the pricing and reimbursement process is mostly performed by the governing bodies that coordinate the payers. The FDO (MoH), as the drug price regulator in Iran, may not be sensitive to the actual impact on payers' budgets or may not be the most appropriate organizer of risk-sharing agreements between producers and payers. Based on the experiences of other countries, price negotiations can be better implemented when the body responsible for price regulation is directly involved with healthcare financing. Ultimately, budget responsibility and the management of all pricing and reimbursement process components, including the final decision-making, should be centralized in one organization. Centralized responsibility will stimulate policymakers to establish and maintain a sustainable balance between healthcare resources and expenditures. In the case of Iran, the responsibility for the healthcare system should be centralized in the

MoH, and its authority should be increased correspondingly. This transfer of responsibility would include shifting final reimbursement decisions from the cabinet to the MoH. The establishment of a health technology assessment (HTA) body as a department of the MoH is recommended in order to ensure cohesive management of the components of the proposed structure (Figure 8.2). Therefore, a reorganization of the MoH would be necessary to move all processes associated with the reimbursement system from various departments, such as the FDO, to the HTA body. Due to the country comparisons, in addition to the HTA body, it is highly recommended that another governing body, a health insurance administration (HIA) responsible for the pricing phase and coordination among payers (like the GKV-SV in Germany), be implemented in the MoH. The duties of these two main governing bodies (HTA and HIA) in collaboration with the MoH are shown in Figure 8.2.

Start a PFRSA system with a finance-based scheme

Finance-based schemes, such as market share or price-volume agreements, can help to contain costs quickly and create an appropriate context in which to introduce performance-based policies. Large population size, a rapid growth of health economics studies, and the use of a positive reimbursement list are important components of the current Iranian system (Table 8.1) that can lead to efficient price negotiation. When

finance-based schemes are extended, other pharmaceutical infrastructures should be simultaneously upgraded by improving skills such as post-decision monitoring, data management, value measurement, and the implementation of internal reference pricing. Moreover, improvements in the health information technology infrastructure are necessary for the implementation of health-outcome-based schemes (like PBRSAs).

It is important to remember that the implementation of outcomes-based schemes is difficult, even in HICs. Missing data in electronic health records, administrative burden, and biases related to clinical outcome measurement and patients' adherence to treatment are some of the implementation obstacles. This is probably why policymakers tend to focus on finance-based schemes, which are easier to implement. However, outcomes-based schemes seem optimal to ensure real value-for-money and should therefore be considered as a long-term goal by further developments in the generation of RWE.
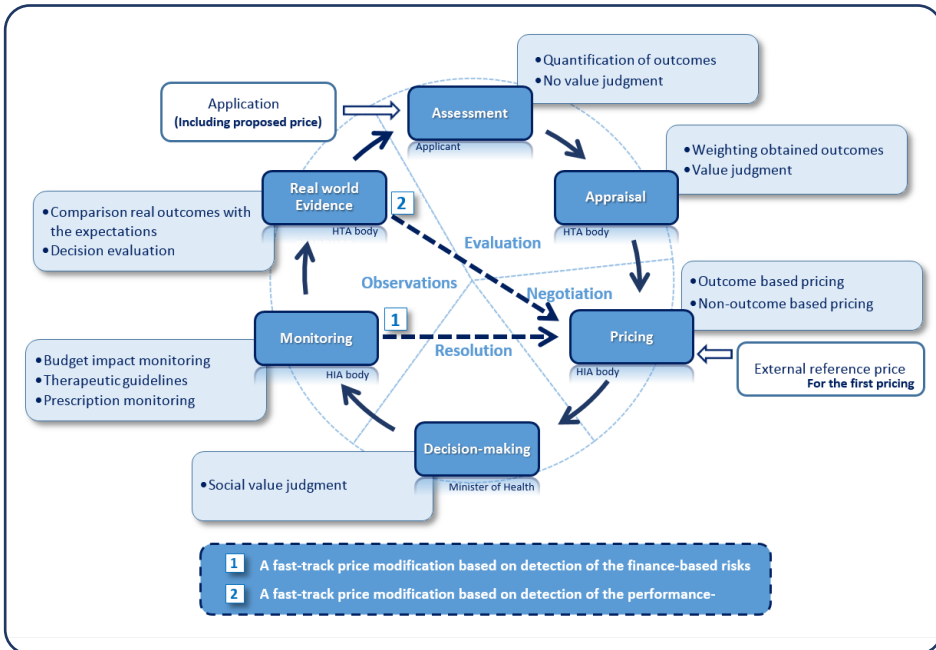
Figure 8.2: Schematic illustration of the proposed cyclic and dynamic reimbursement process. *Abbreviations: **HIA:** health insurance administration; **HTA:** health technology assessment*

Improve real world evidence

PFRSA could be implemented based on a platform of RWE generation. If this platform is stable, it will result in an efficient pay-for-performance system. Policymakers may use external reference pricing when they decide to negotiate a drug's price and determine the national price, but they must monitor the actual consequences. Based on national

RWE, previous decisions ought to be re-evaluated and modified, if necessary, in a cyclic and dynamic reimbursement process (Figure 8.2).

RWE generation requires the development of a health information technology (IT) infrastructure, but MICs may not be able to create the necessary infrastructure due to difficulties in its financing and implementation. There is, in fact, a vicious circle in MICs regarding PFRSA implementation and health IT infrastructure. PFRSA requires proper information flow through the health IT systems while health IT needs sufficient financing to be implemented. Thus, the lack of financing is the main obstacle to implementing a comprehensive health information technology system, but financial resources are currently wasted due to a lack of PFRSA policies. Therefore, a transitional action plan is necessary to improve health IT in MICs based on a priority-setting program. Moreover, the potential cost-savings derived from a finance-based arrangement can (partly) be shifted to improve the health information systems.

Make the system more dynamic

In order to improve the system, the assessment and appraisal of new evidence about a drug should lead to a change in the pricing and reimbursement (Figure 8.2). In some cases, however, policymakers can achieve cost savings using a fast-track price modification based on the results of monitoring the process or RWE (the shortcuts between monitoring or real-world evidence and pricing, as seen in Figure 8.2). In other words, a cyclic and dynamic reimbursement process produces an evidence-based pricing method. In this method, drug prices can be modified so as to correspond with the revised estimate of added-value. Modified prices should be considered as the new references for other drugs, which means that they can be applied to new drugs (within a therapeutic class) to estimate the initial prices when starting a new reimbursement decision-making process. Accordingly, an initial price will be determined by pharmacological similarity, differences in effectiveness, and other criteria that apply to national priority setting.

Table 8.4: The impact of recommendations on different components of SWOT analysis.

Recommendations	Consolidation of strengths	Addressing of weakness	Use of opportunities	Elimination of threats
Eliminate conflicts of interest and maximize process transparency	1, 3, 4, 5, 7, 8	2, 3, 4, 5, 8	2	3
Establish integrity in operation	1, 3, 4, 5, 7, 8	1, 2, 3, 4, 5, 8, 12		5, 8
Start a PFRSA system with the finance-based schemes	5	2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12	1, 2, 3, 4	1, 2, 3, 4, 8
Improve real world evidence	4, 8	2, 3, 4, 6, 7, 12, 13	1, 3,	6
Improve dynamicity of the system	1, 3, 4, 5, 7, 8	3, 4, 6, 7, 9, 10, 11, 12	2	5

The numbers represent the number of items for columns of strengths, weaknesses, opportunities and threats in Table 8.1.
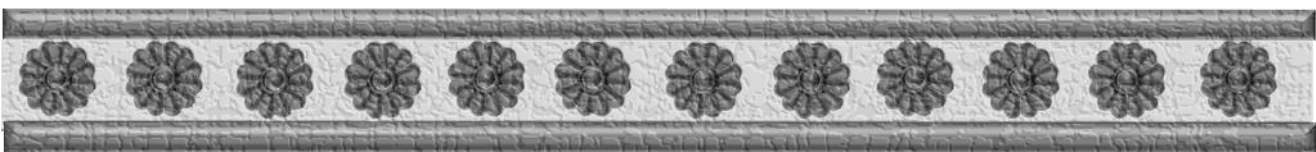
Conclusion

MICs face difficult challenges with their pricing and reimbursement decision-making policies while HICs have addressed similar challenges by improving their systems using innovative policies for better resource allocation. Using PFRSA schemes is a tested policy in HICs that it can improve timely access and affordability of an expensive drug.

There are numerous barriers that prevent a PFRSA system from being implemented in Iran, such as dysfunctional healthcare systems, various conflicts of interest, and the lack of a comprehensive health information technology infrastructure. Iran can start improving its pharmaceutical pricing and reimbursement decision-making system by using various finance-based schemes. Most importantly, increased use of RWE will enable the implementation of various performance-based schemes (e.g. pay-for-performance policy). Duties and responsibilities must be centralized in new HTA and HIA bodies that manage the tasks of the cyclic and dynamic reimbursement process under the leadership of the MoH. These changes will provide better functionality for pharmaceutical pricing and reimbursement decision-making system to make Iran ready for the implementation of PFRSA policies and ultimately to improve the affordability and accessibility of expensive drugs.

Acknowledgment

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Chapter 9
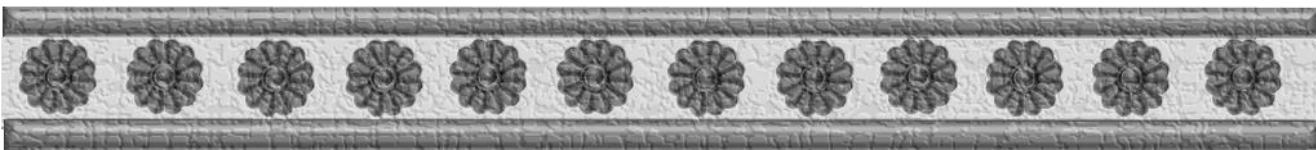
Discussion

Introduction

To discuss the results of this thesis, it would be appropriate to flashback to the overall goals of a drug reimbursement decision-making system which is described in the first chapter. It is noted that the best decision is made when the three goals relating to **quality of care**, **population health**, and **affordability** have been accomplished simultaneously. To make sure whether or not these goals are met at any decision, decision-makers need to reach maturity and wisdom on different areas of the subject of the decision. This chapter explains how Iran can move toward achieving the overall goals and improving its drug reimbursement decision-making system by using the findings of this thesis. The general discussion has been structured in three sections. In the first section, the main issues and subsequent consequences of the current drug reimbursement decision-making system in Iran are explained and then applying our findings in this thesis, some possible solutions are suggested. In the second section, some general recommendations are proposed to facilitate improvement of the drug reimbursement decision-making system. Finally, in the third section, studies' limitations and general conclusion are explained followed by the final remarks.

1. Dilemmas and Solutions

1.1- The main issues of the current drug reimbursement decision-making system in Iran

As outlined in chapters two and eight, the current drug reimbursement decision-making system in Iran has some important issues such as inconsistency among different stakeholders, lack of transparency, and a time-consuming process. As an example, using trastuzumab to treat breast cancer may help to illustrate these current issues. Trastuzumab was launched in 2007 after issuing a marketing license by the Ministry of Health in Iran while the reimbursement process started at the Ministry of Welfare was later on. As a result, patients had to pay the total costs of trastuzumab; consequently, trastuzumab was not affordable for many patients due to its high cost. Iranian health insurance organizations (payers) were not interested in reimbursing this drug due its significant budget impact. Therefore, trastuzumab was available but not affordable for many patients at least for 5 years after its market launch in 2007. Doctors and patients tried to force payers to reimburse trastuzumab in different ways that are explained in chapter three. Subsequently, Iranian policymakers decided to reimburse trastuzumab in 2012 with no reasons. This example clearly shows that there is an inconsistency between the two ministries of health and welfare in Iran. According to the Ministry of Health policy, patients should have access to all essential drugs and that any drug with no safety issues can be launched in Iran. However, the Ministry of Welfare and payers are not interested in covering all drugs approved by the Ministry of Health, due to economic issues. Therefore, payers try to postpone the reimbursement of expensive

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drugs with high budget impacts. Consequently, these issues make the drug reimbursement decision-making system a non-transparent and time-consuming process in Iran. These main issues lead to lack of solidarity and mutual understanding between different stakeholders. For example, the Ministry of Health in Iran recommends nine weeks of trastuzumab for patients with HER2-positive breast cancer, since the high cost of this medication. Payers therefore covered only a nine-week treatment strategy. However, as described in chapter three, most Iranian doctors did not follow this recommendation and treat patients in longer periods. Therefore, those patients who use trastuzumab longer than nine weeks, should pay 100% of the costs of trastuzumab and incur the financial risks for the extra treatment. Due to the huge out of pocket payments caused by implementation of the national guideline, both doctors and patients argued against the decision made by payers regarding coverage of the short duration of trastuzumab therapy. This way resulted in one-year treatment strategy was reimbursed for trastuzumab. These events call into question the full dominance of policymakers on the pharmaceutical market in Iran. In other words, while payers are working under pressure of healthcare budget constraints, as chapter eight explains, drug manufacturers can release their product almost without taking any substantial financing or performance risks. Patients and payers, however, have to incur these risks.

In summary, the performance of the current drug reimbursement decision-making system is affected by inconsistency between the two ministries. To solve the current problems, Iran has to prepare some new arrangements.

1.2- Requirements to improve the drug reimbursement decision-making system

As chapter eight recommends, to improve the system, Iran should eliminate conflict of interests and inconsistency throughout the healthcare system and increase transparency of the drug reimbursement processes. These two important recommendations should be viewed by the Parliament members and non-governmental organizations as societal important needs. As chapter eight also explains, these two issues can be solved by improving health economics-related evidence and healthcare governance. Therefore, this section has focused on how to improve these two parts.

Improving evidence for better decision making concurrently with eliminating conflict of interests would be an important step to achieving the overall goals of decision-making. This is possible only through a proper infrastructure which helps in providing proper knowledge for decision-making. In other words, the existence of a knowledge-production infrastructure is a key item in moving forward to an optimal decision-making system. This infrastructure could manage the flow of data from the healthcare

environment to policymakers. However, the quantity and quality of necessary information are dependent on how well the infrastructure generates, collects and integrates the data (Figure 9.1). As Figure 9.1 shows, the healthcare system is composed of different layers, and various stakeholders are involved in each layer. Healthcare providers and patients are found in the environment layer and their activities generate patient level data. This data must be collected at a higher layer (data layer) by patient registry centers and payers. This layer is a source of many necessary patient-level data like observational and claims data. Researchers can use these data to generate valuable information such as the costs of illness and quality of life values. This information can then be used to support various cost-effectiveness and budget impact analyses of any intervention or be used to conduct priority setting studies such as multi-criteria decision analysis in the healthcare system. This knowledge is provided by researchers in the academic field or by governmental bodies like health technology assessment (HTA) agencies and can be used to help policymakers to obtain important insights in to the particular area of interest, which will prepare them to make a balanced decision. This infrastructure for reimbursement decision-making consists of two main parts in general. The first part is *'Production of health economics-related evidence'* and the second part is an *'Efficient healthcare governance structure'* that supports the continuity and quality improvement of the first part. These two parts are indispensable and are the main requirements of a proper decision-making system in healthcare, as concluded in chapter eight. If all components of this healthcare platform work perfectly, then we can expect perfect knowledge and an appropriate decision.

1.2.1- Production of health economics-related evidence

As stated in the previous subsection, knowledge production is a necessity to make better decision. Indeed, HTA studies yield an important part of the knowledge required for evidence-based decisions. Providing this part of knowledge, however, needs a strong platform based on health information technology to manage the flow of data and information. It is worth noting that implementation of a perfect infrastructure is costly and sometimes infeasible in many middle-income countries (MICs). Therefore, in parallel with the improvement of different components of the current infrastructure, we need to find solutions to overcome some missing elements. This subsection illustrates the knowledge gaps in the current Iranian healthcare system and provides some solutions to improve it.

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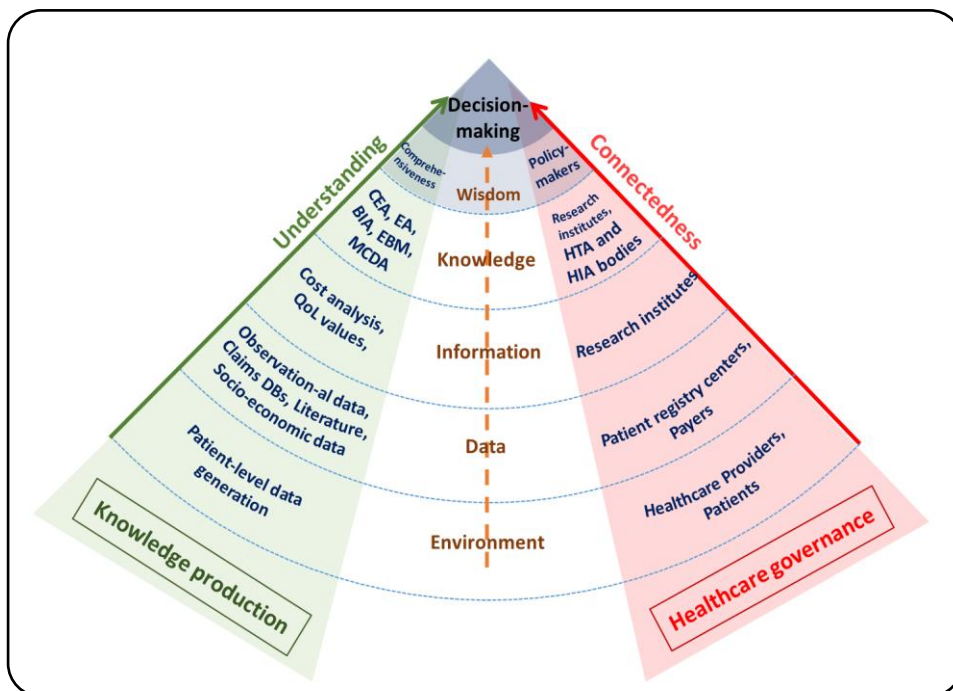
Figure 9.1: An appropriate infrastructure for a reimbursement decision-making system.
*Abbreviations: **BIA:** budget impact analysis, **CEA:** cost-effectiveness analysis, **DBs:** data bases, **EA:** equity analysis, **EBM:** evidence-based medicine, **MCDA:** multi criteria decision analysis, **QoL:** quality of life*

1.2.1.1- Knowledge gaps in drug reimbursement decision-making

Limitations of health information technology lead to various obstacles for HTA studies. Any platform for health information technology should be able to manage two important parts of patient level information including clinical and resource used data. In general, patient registries and claims databases are the two important sources of data for HTA studies. However, implantation of country-level patient registries is very costly and time-consuming [183] even in high income countries (HICs). Patient registries in HICs can be created and maintained through different potential sources of funding, including funding by governments and manufacturers [184] due to mutual interests in performing observational studies between pharmaceutical firms and HTA bodies in HICs. This collaboration, however, would not be possible in MICs and governments must mostly fund patient registries. Accordingly, a comprehensive and national patient registry is not available in Iran and various academic institutes track different clinical outcomes of treatments in a local population of patients. As explained in chapter four, the generalizability issues are explicitly expressed in most patient-level studies due to lack of patient registries. On the other hand, Iran has implemented universal health

insurance coverage that involves various payers. Chapter two notes that two payers (Social Security Organization (SSO) and Health Insurance Organization (HIO)) insure more than 85% of the Iranian population. This means that a good source of claims data potentially is available to provide important information such as patient level resource used and costing. However, despite the huge data collection from the health care providers by payers, Iran does not have a comprehensive database representing a country-level healthcare resource use data. Therefore, researchers should find a solution to deal with limitations of patient-level data in Iran.

Another important knowledge gap is lack of reliable health-related quality of life data, both in the general population and in specific types of disease. This gap exists due to the lack of research capacity (human and finance resources) in the field of health economics in Iran. Lack of health-related quality of life data can influence the results of various HTA studies like cost-effectiveness analyses, as clearly discussed in chapters five and six of this thesis.

In summary, there are different limitations to perform HTA studies and many country-specific studies cannot easily be conducted in Iran. Therefore, short-term and long-term solutions are needed to improve knowledge production in Iran. In the next subsection, some possible solutions are presented based on the previous chapters of this thesis as the short-term solutions for dealing with the lack of necessary information. The long-term solution, however, is to improve the knowledge-production infrastructure (Figure 9.1) in general.

1.2.1.2- Possible solutions to address the knowledge gaps

This thesis described two solutions that were proposed and tested by researchers. The idea was that the knowledge gaps described above can be addressed through the appropriate use of available data sources. In other words, Iranian researchers and policymakers should use what is available to obtain what they need. For example, the strong claims databases in Iran may help researchers and policymakers to obtain the information that is vital for HTA studies. One possibility (first solution) is to produce the necessary information, which are normally obtained from patient registries, using various patient classification techniques on the claims databases. As this thesis shows in chapter four, validated patient classifications could support a real-world cost analysis in Iran. Data-mining techniques, in this case, facilitated the acquisition of valuable information to estimate health care utilization and understand the contribution of diverse cost components of treatment of HER2-positive breast cancer in Iran.

Another solution is to use the results of economic evaluations performed in other countries. Iran may use these evaluations but should be careful with the interpretation.

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This strategy may also introduce extra uncertainties regarding the outcomes, resulting in less reliable information for the drug reimbursement decision making. Simplifying the problems based on important factors with high impact on the results of a cost-effectiveness analysis can be an option, as shown in chapter six. This strategy of transferring the results of cost-effectiveness analyses to Iran can facilitate the process of knowledge production and therefore decision-making. Chapter six shows how a relatively simple transfer method could lead to a good estimation of incremental costs of an expensive drug in Iran. There is a strong argument that the simplification technique may not provide an accurate estimation of ICER. That may be the case, however, there are always uncertainties around any estimations and the simplification technique is no exception to that rule. On the other hand, simplification method can be considered as an option to overcome various limitations such as time-limitation for a reimbursement decision-making, necessary detailed information, and adequate research capacity for economic evaluation studies. In other words, this technique can be used as a preliminary-HTA analysis. However, despite the fact that transferring methods may be able to provide reasonable cost-effectiveness evidence quickly, the preferred method remains a country-specific cost-effectiveness analysis which can be an important segment of a post-marketing analysis.

Improving research capacity in Iran is a prerequisite for improvements in reimbursement decision making. Increased funding for research can provide incentives for researchers to improve the quantity and quality of HTA knowledge production by some fundamental studies. For example, some studies are essential like measuring utility weights and quality of life both in population and individual levels. These are very important studies which provide knowledge that is useful for many economic evaluations and financial contributions are needed to conduct. However, these studies may not be interesting enough to invest by some third party financial contributors such as pharmaceutical firms in middle-income countries. Therefore, knowledge production must be supported mostly by governing bodies in middle-income countries.

1.2.2- Efficient healthcare governance structure

To support the process of knowledge production an efficient healthcare governance is essential. From a governance perspective, chapters two and eight describe the structural deficiencies in the Iranian healthcare system. In fact, without an efficient healthcare governance, the process of knowledge production and application of this knowledge in decision-making would not be possible. The role of an efficient healthcare governance is to support the process of knowledge production and provide the connectedness among different stakeholders in healthcare system (Figure 9.1). Only a guaranteed and effective collaboration among the different stakeholders who are involved in different levels of healthcare system can help the decision-making process.

A strong healthcare governance can guarantee effective collaboration. This subsection explains the issues and provides solutions to improve healthcare governance.

1.2.2.1- Healthcare governance issues in drug reimbursement decision-making

Chapters two and eight explain how the responsibilities of drug reimbursement decision making are inappropriately split between two ministries. The Ministry of Health in Iran is trying to expand patient access to different medications without considering affordability of treatments and budget impact. This strategy may mean that expensive drugs are made available for patients with a high socio-economic status. However, other patients in lower socio-economic classes, who cannot afford easily the costs of unreimbursed expensive drugs are condemned to incur the catastrophic costs of expensive drugs [185]. On the other hand, a very time-consuming reimbursement process by the Ministry of Welfare can make it impossible for patients to obtain early access to effective in an affordable manner. This time-consuming decision-making process by the Ministry of Welfare and payers may be existing because of uncertainty about the potential consequences beyond reimbursement of expensive drugs. The payers try to postpone reimbursement until they have enough information about the financing of expensive drugs. However, as explained in chapter eight, it may not be possible to reduce the degree of uncertainty regarding reimbursement decisions due to lack of information and an inability to implement innovative policies like performance-based and finance-based risk sharing arrangements (PFRSAs). Therefore, payers are not enough active in reimbursement decision-making process [179] while they have to pay the costs of drugs with very high budget impact. In fact, in this governance structure, payers are not able to perform risk assessments and therefore try to shift the risks caused by reimbursing drugs to patients by increasing out-of-pocket payments [62] or delaying payments to healthcare providers such as pharmacies [186,187]. Both of these two strategies limit the ability to achieve the overall goals of a drug reimbursement decision-making system (i.e., quality of care, population health, and affordability). Therefore, drug availability and affordability do not necessarily go hand in hand in Iran. While a drug may be available on the market, its purchase price may not be reimbursed and its high price may not make it easily affordable for the majority of patients.

In recent years, many efforts have been made to reduce patients' out-of-pocket payments since the first term of president Rouhani in 2014 [188-190]. Under the "Healthcare Reform Plan", the state has allocated 1% of value added tax (VAT) to healthcare system in order to facilitate the achievement of the plan's objectives including eliminate of informal payments [191]. However, improvements in financing alone may not be helpful in sustaining the reform plan. Sustainability and improvements in the performance of any plan are depend on how the decision-making bodies are well organized in healthcare system [192]. As chapter seven explains, use of external price

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referencing can influence the costs of expensive drugs in Iran or other MICs and can lead to more waste of healthcare resources. Therefore, as chapter eight concludes, improvements in healthcare governance is necessary to optimize budget allocation. Otherwise, policymakers have to increase the healthcare budget to cover governance inefficiencies. This sounds like what is happening for the "Healthcare Reform Plan" in Iran. In other words, increase in healthcare budget without improvement in healthcare governance cannot necessarily lead to a better quality of care.

1.2.2.2- Possible solutions to improve healthcare governance

As chapter eight explains, integrity in operation is the most important solution to overcome inefficiencies. Centralizing responsibilities at the Ministry of Health will help to improve the overall performance of different organizations, which are involved in the healthcare system. To express this simply, when an organization is responsible for both healthcare resources and expenditure, its decisions will be based on a balancing act between various expectations and available resources. Policymakers then must focus to make an optimal decision considering budget constraints rather than trying to resolve the conflicts [193].

Chapter eight proposes a new structure for the reimbursement decision-making process in the Ministry of Health. Two important governing bodies are responsible for clarification about the various uncertainties about reimbursement and pricing of any new drug. A governing body for health technology assessment (HTA body) should provide a strong connection between different research institutes in the country to facilitate performing comprehensive researches. Real-world evidence of new interventions should be monitored by the HTA body. Another governing body which is responsible for health insurance administration (HIA body) should be a coordinator of various health insurance organizations and should be responsible for negotiating prices with pharmaceutical firms. Monitoring different financial consequences would be an obvious task for this governing body. Indeed, these two governing bodies must be completely synchronized to perform the cyclic and dynamic reimbursement process shown in Figure 8.2. The Minister of Health will be responsible for establishing coordination and management of these two governing bodies and must be an eligible figure for making and revising decisions regarding drug reimbursement and pricing. Due to this new reorganization, the current responsibilities found in different departments of the Ministry of Health should be centralized in the two governing bodies of HTA and HIA. Specifically, the process of registration, evaluation and pricing needs to be disconnected from the FDO. On the other hand, the process of reimbursement decision making in the Ministry of Welfare and the Cabinet should be transferred to the two governing bodies. Obviously, the final decision would be made by the Minister of Health.

The solutions explained in the first section of this chapter were based on the opinion of the researchers involved in this thesis. Other researchers may suggest alternative solutions to improve both knowledge production and healthcare governance. However, policymakers should understand that all of these possible solutions should lead to achieve the overall goals of a drug reimbursement decision-making system. Therefore, some important steps should be implemented in the Iranian healthcare system which are explained in the second section.

2. Improvements needed in the drug reimbursement decision-making

This section provides and explains general recommendations to achieve more effective drug reimbursement decision-making in Iran. In contrast with the first section that contains some solutions to improve the system, the second section provides key points suggested to implementing in Iran.

Chapter eight shows that the drug reimbursement decision-making system should be designed as a cyclic and dynamic process. Policymakers should pay attention to the fact that pharmaceutical market is always changing; new products are launching continuously and new effective interventions are potentially available. Meaning that the previous reimbursement decisions would not be relevant forever and may if needed, be modified. Moreover, the healthcare market has its own complexities and the priorities of policymakers and other stakeholders in any healthcare system can be changed over time. Therefore, under this circumstance, a drug reimbursement decision-making process should not be considered like a one-way street and pros and cons of the decisions made should be monitored in the real world. In other words, the four main sections of the proposed cyclic and dynamic reimbursement process (evaluation, negotiation, resolution, and observation), as introduced in chapter eight, should be performed regularly. If the cyclic and dynamic process is implemented fundamentally, it can certainly help to achieve the overall goals of a drug reimbursement decision-making system in the long term. To improve the performance of the process, implementation of some actions is strongly recommended to policymakers in Iran.

2.1- Development a country-specific guideline for economic evaluations

As evident in chapters five and six, the WHO-CHOICE recommendations [114] were used to conduct these studies in the absence of Iran-specific guidelines for economic evaluations. The development of guidelines, that clearly define the framework of the economic evaluations, analytic approaches, input data, and reporting, is one of the requirements for improving quality and standardization of various economic evaluations.

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A country-specific guideline for economic evaluation can reduce uncertainties around decision-making process. For example, the World Health Organization recommends a unique willingness-to-pay threshold of 3×GDP/capita for lower-income countries [114]. Implementation of this threshold does not help countries in their reimbursement decision-making process, due to the following weaknesses that it can potentially affect reimbursement decision-making. Firstly, it is changeable with fluctuations of the GDP over years and policymakers then cannot make a long-term decision based on a threshold at the year of study. Secondly, it does not necessarily reflect the total health expenditure which is allocated to healthcare system. And thirdly, it is relatively higher than the threshold in HICs (e.g.: 3×GDP/capita estimates almost £100,800 in the UK in 2015 [118] while the reference threshold for the NHS is ranged between £20,000 and £50,000). Therefore, introducing a range of willingness-to-pay thresholds based on severity of disease can be more effective and operative in Iran. Similar to the willingness-to-pay threshold, other important parameters such as budget impact analysis, different perspectives and discount rates also need to be defined based on socio-economic specifications in Iran.

2.2- Development a good governance standard for drug reimbursement decision-making

With respect to chapter eight, responsibilities of different governing bodies for health insurance administration, health technology assessment, and also the Minister of Health, should be clearly defined in the cyclic and dynamic process (Figure 8.2). It is necessary that Iranian policymakers design and implement principles of good governance like those standards for public services recommended by the Independent Commission on Good Governance in Public Services in the UK [194]. Six principles have been introduced in this guideline, which can be considered and adapted to improve the performance of the drug reimbursement decision-making system. These standards should help governing bodies to: a) being clear about their purposes and intended outcomes for patients and healthcare providers; b) being clear about their functions and roles; c) being attentive to transparent decisions in their governing bodies; d) Making sure that personnel have the skills, knowledge and experience they need to perform well; and e) engaging effectively with stakeholders in healthcare system [194].

2.3- Development an independent pricing system

Chapter four shows how the healthcare budget allocated for the treatment of breast cancer can quickly be consumed by an expensive drug in Iran. This is due to use of external reference pricing which has reduced the affordability of expensive drugs in lower income countries. Chapter seven, however, explains why a strong pricing system is necessary to improve affordability and accessibility of drugs. This thesis recommends

that payers should first improve their ability to negotiate the price of drugs through improvement of health economics-related evidence generation and then establish a value-based pricing. It would be understandable if payers wanted to reference the price of drugs in other countries for the first price determination. However, price modification might be necessary as soon as real-world evidence suggests an unpredictable risk on financial resources or improvement population health (Figure 8.2).

2.4- Implementing risk sharing arrangements

Sharing risk between payers and pharmaceutical firms is an important missing piece in Iranian healthcare system. This is due to limitations in the current healthcare governance in Iran which hinders the implementation of risk sharing arrangements. This thesis provides some recommendations to distribute risks between payers and pharmaceutical firms and thereby improve accessibility to expensive drugs.

Two main groups of risks should be taken into consideration. Firstly, financial risks, which have an impact on healthcare expenditures, will appear as an early consequence of any reimbursement decision-making. Therefore, financed-based risk sharing arrangements would be a necessity to reduce budget allocation uncertainties. It seems that implementation of this type of risk sharing policies would be easily feasible for both payers and pharmaceutical firms, due to existence of an adequate developed infrastructure for health information technology in Iran. The second group of risks are those that affect population health or quality of care. Therefore, implementation of a performance-based risk sharing arrangement can reduce uncertainties around improvements in population health and quality of care. Feasibility of implementing this policy, however, is uncertain due to a series of shortcomings and deficiencies in Iran that have already been mentioned in chapter eight. Indeed, such problems are not limited to Iran and even high-income countries are facing with difficulties and challenges [195,196]. Perhaps Iranian policymakers can take the first step by focusing on orphan drugs and some other expensive drugs administered in relatively low disease frequency. Because of a small number of patients, policymakers can easily prepare requirements for measuring and monitoring treatment responses.

2.5- Pricing based on a max-age threshold

Price determination based on a fair price that ensures a drug remains cost-effective for a large patient population might be among important goals for policymakers. In the absence of a performance-based risk schemes using max-age threshold may be a possible solution to improve affordability and accessibility of expensive drugs. As chapter five shows, an expensive drug might be cost-effective but only for a small

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number of patients. We need to reach an optimal price to implement in a larger group of patients. This idea will be discussed more later.

2.6- Improvement of post-marketing observations

Post-marketing monitoring helps policymakers to check the accuracy (moving toward the overall goals) and precision (achieving the overall goals) of the conclusions derived in pre-decision steps (assessment, appraisal and pricing) (Figure 8.2). Chapter eight has explained that lack of post-marketing monitoring in Iran is one of the main issues leading to increase decisions uncertainties. Perhaps the most obvious part of post-monitoring process is the monitoring of the actual budget impact of any new intervention and its deviation from the budget impact that was estimated before making the reimbursement decision.

This thesis showed that post-marketing analyses are important to correct previous decisions by policymakers. Some of the research described in this thesis performed shortly after reimbursement of trastuzumab in Iran. Therefore, the results of some chapters can be considered as examples of post-marketing analyses. For example, chapter three showed that Iranian doctors did not adhere to the national guideline published by the Ministry of Health in Iran which recommended a very short duration of trastuzumab (9 weeks). The contribution of trastuzumab to medical costs of health care services associated with HER2-positive breast cancer in Iran was investigated in a real-world cost analysis described in chapter four. This analysis showed two things. Firstly, the average duration of 21 weeks trastuzumab therapy in patients was not consistent with the Iranian national guideline or the clinical guideline in HICs (52 weeks for trastuzumab therapy). Secondly, trastuzumab costs comprised the largest share of total costs in all three stages of breast cancer. Chapter five is an example of how policymakers should be aware about the updated evidence and then modify their previous decisions. This study used the results of PHARE trial [89], which compared six months versus one year of adjuvant trastuzumab therapy. The PHARE trial was published almost two years after reimbursement of trastuzumab in Iran. Consequently, using this updated evidence, it is possible to improve the affordability and accessibility of expensive drugs in MICs. Finally, chapter eight showed that trastuzumab use in Iran continually increased in the three years after the reimbursement date and discussed what steps should be taken to adjust budget impact of trastuzumab using different risk sharing schemes. Moreover, to make sure about the real-word effectiveness of trastuzumab, the real-world outcome in Iran could be compared with the results of different randomized control trials such as HERA and PHARE trials. However, we were limited to perform this comparative analysis. Despite this limitation, there is enough evidence to express the importance of post-marketing observations. All of the above evidence suggests that the current policies based on previous decisions do not

effectively improve quality of care, population health, and affordability simultaneously and lead to the conclusion that these decisions must be modified.

Two proposed governing bodies in chapter eight (HTA and HIA) should be responsible for post-marketing monitoring and real-world evidence generation after drug reimbursement decision making. Specifically, these two institutions should make sure about the moving toward and achieving the overall goals at any decision. If there is a deviation from achieving the goals, as shown in Figure 8.2, these two governing bodies should provide an appropriate solution to fix the deviation. Depending on the issue, it may lead to a new evaluation phase or using two fast-tracks price modification (Figure 8.2).

2.7- Correcting former decisions

New and updated evidence may present additional and important information. This provide an opportunity for policymakers to review their former decision and think about other options to improve quality of care, population health, and affordability at the same time. Therefore, an alert system is necessary to follow evidence and consider their potential impact on previous decisions.

As chapter eight suggested, healthcare services costs and their impacts on healthcare budgets need to be monitored regularly after any decision. A higher than expected budget impact and off-labeling use of drugs may cause consequences on total health expenditure and, therefore, correction of the former decision need to be considered persistently. Chapter eight suggests a cyclic and dynamic reimbursement process (Figure 8.2) to monitor and correct the previous decisions. In the medium or long term, this process provides considerable knowledge and evidence on various pharmacological categories. Policymakers can use this knowledge and evidence not only to improve internal price referencing, but also to enhance predictability of an appropriate price for other new drugs in future. Ultimately, this structure helps countries to eliminate the use of external price referencing and ensure that their decisions are independent from the decisions which were made regarding the price of a drug in other countries. Pharmaceutical firms will then be faced with an efficient healthcare governance that can detect and measure various possible risks for reimbursing a drug. Therefore, they should convince policymakers by both reducing the possible risks (financial and performance-based risks) for healthcare system and asking a reasonable price.

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3. General conclusions and policy implications

Reimbursement and pricing decision-making is a complicated process and it is not very easy to find two similar cases in this process. The system should be designed in a way that policymakers are able to be flexible in applying the various techniques already mentioned in different chapters of this thesis. The main aim is to achieve all three overall goals for drug reimbursement decision-making. To manage uncertainties around the decision, policymakers can use different techniques to ensure that they achieve the goals. Figure 9.2 illustrates how and what techniques must be applied to improve decision-making regarding reimbursement of a drug in MICs. When drug
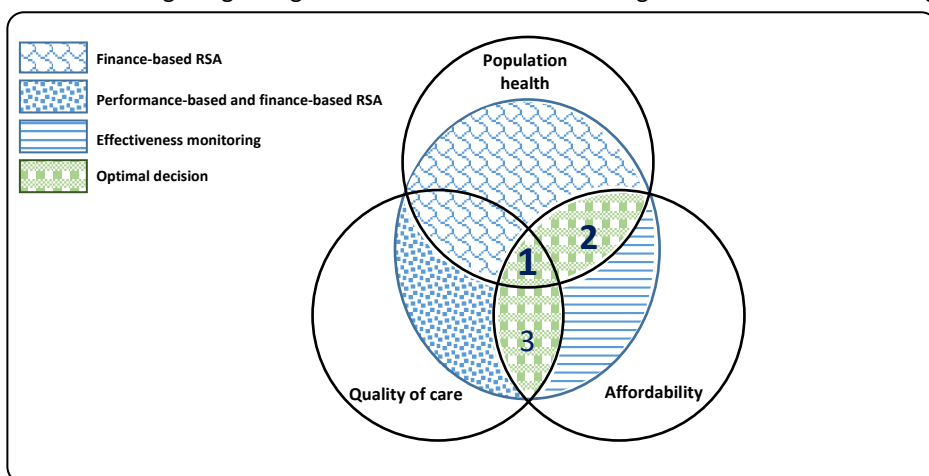
Figure 9.2: Using different strategies to facilitate the overall goals achievement in a reimbursement decision-making system.

reimbursement cannot help achieving all three goals simultaneously, policymakers should apply various strategies to reduce uncertainty. For example, if specific drug is effective and improves population health but it is not affordable, finance-based risk sharing arrangements need to be applied to help improving affordability. In another situation, if the drug improves quality of care but there are uncertainties about affordability and improvement of population health, both finance-based and performance-based risk sharing arrangements can be applied to achieve them.

It is quite likely to not achieve the three overall goals of reimbursement decision making for any new drug despite using the various techniques explained in section two. Therefore, if the best decision (area number 1 in the figure 9.2) is not possible, policymakers should prioritize the three overall goals of reimbursement decision making. Due to severe budget limitations in MICs, affordability of a drug may be the most important goal; indeed, if drugs are not affordable, they cannot improve population health or quality of care. However, using an affordable drug is also useless

when it is not effective and cannot improve population health or quality of care. Therefore, affordability of a drug is an integral part of an optimal decision. In conclusion, when it is not possible to make the best decision, an optimal decision happens when an affordable drug can improve population health or quality of care.

From a policymaking point of view, improving population health is more important than quality of care. The obvious reason is that a drug or intervention (such as vaccination) that saves lives is more important than any intervention that can only improve quality of care (such as robotic surgery). Moreover, as chapter five shows, it is likely that MICs have a lower overall population health [197] than HICs and a lower life expectancy can affect the cost-effectiveness of expensive drugs. Therefore, as much as life expectancy improves probability of being cost-effectiveness for expensive drugs will be improved as well. Therefore, an optimal decision that covers affordability and population health is more preferable than a decision which covers affordability and quality of care. Figure 9.2 shows the area of an optimal reimbursement decision making which is the green zone. As the figure shows, the priority of decision will decrease from the first to the third section of the green zone and a decision made in other areas cannot be considered as a proper decision and should be avoided by policymakers.

To make these concepts clearer, as an example, we can consider our case study and explain three scenarios for decision-making on trastuzumab reimbursement in Iran. The first scenario is to make a decision on trastuzumab reimbursement with the current price in Iran. In this situation, chapter three explains that one year of trastuzumab is not an affordable strategy due to its huge budget impact, despite the fact that it can improve population health. On the other hand, chapter five showed that 6-month trastuzumab use is an optimal strategy that can improve both population health and affordability. However, this strategy is cost-effective only in patients younger than 59 years. Based on what was explained before, both strategies cannot fulfill the overall goals of reimbursement decision making. Therefore, policymakers should not reimburse trastuzumab with the current price in Iran and should seek a price reduction (through finance-based or performance-based risk sharing arrangements) to make trastuzumab more affordable. The second scenario could be when policymakers reduce the price of trastuzumab in Iran using different strategies of risk sharing schemes. Supposing a 30% price reduction for trastuzumab has been achieved in Iran. In this situation, chapter five explains that with a 30% reduction in trastuzumab price, one year of trastuzumab can also be considered as an optimal strategy but only for patients younger than 49.5 years (Figure 5.5). One year compare to 6 months of trastuzumab duration may provide better individual quality of care, however, due to smaller group of patients for whom the strategy remains optimal (max-age 49.5 vs 68), it is less cost-effective than the 6-month strategy. It looks like the one-year and 6-month strategies

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can be assumed in areas number 3 and 2 in the figure 9.2 respectively. According to the above-mentioned, both strategies can be considered as the optimal strategies (green zone). However, from a healthcare point of view, 6-month trastuzumab use would be more preferable in Iran. The third scenario is a significant trastuzumab price reduction using the max-age threshold. Depending on how much the price of trastuzumab can be reduced, the one-year treatment regimen may be closer to the best decision area. For example, chapter five shows that if Iranian policymakers decide to consider the max-age threshold for pricing and it should be equal to the average life expectancy of Iranian women (75.6 years), then the best decision happens when the price of trastuzumab is reduced by ~70% (Figure 5.5). In this situation, most women can undergo a cost-effective and standard treatment regimen (one-year) of trastuzumab which is recommended by many clinical guidelines worldwide [65-67,69-74]. Subsequently, trastuzumab not only would be an affordable medication but also it improves both population health and quality of care. In other words, all three goals of a drug reimbursement decision-making system can be accomplished simultaneously.

3.1- Limitations and recommendations for future research

There are some limitations related to the fact that although different methods are used for improving evidence in the field of HTA in Iran; some other methods are missing in this thesis. Firstly, as it has been noted, quality of life measurement is one of the missing research areas in this thesis. Specifically, there is an important lack of information regarding generic utility weights that helps calculating quality adjusted life years (QALYs) in Iran. Utility measurement is one of the most important parts of HTA knowledge due to its significant impact on the results of cost-effectiveness analyses. In the absence of country specific information in this area, utility weights in other countries were used in different chapters of this thesis. The results of studies included in this thesis should be examined using Iran-specific utility weights in the future. Secondly, this thesis does not include a multi-criteria decision analysis (MCDA) [7] in Iran. This method may help policymakers to improve their decision regarding reimbursement of an expensive drug. Performing a MCDA, however, seems to be affected by budget impact (affordability) of an intervention. Therefore, it would also necessary to investigate the role of a MCDA approach in improvement of reimbursement decision-making in a middle-income country in the future studies.

3.2- Final remarks

This thesis opens a window toward a less well-known part of the HTA-related sciences. At first glance, the drug reimbursement and pricing system in an MIC may look like the same system in HICs. However, various studies in this thesis showed that improvement of the system in lower income counties is relatively more difficult than in counties with

more financial resources and more stable infrastructures. Although this thesis only focused on drug reimbursement and pricing system in Iran, we believe that other MICs can also use our findings to improve their system where the limitations on knowledge production and healthcare governance represent the most important obstacles to improve the system in these countries.

Different chapters of this thesis show that the drug reimbursement decision-making system in Iran needs to be improved. The shortcomings of the current system are categorized into two main types: those that have impact on understanding to make a good decision and those that improve the connectedness among different stakeholders in this system (Figure 9.1). To overcome these shortcomings, two strategies should be used. Some solutions may be useful in the short term while others need some structural changes in the long term. Improving decision-making system for drug reimbursement in Iran is feasible but it is a tough task to provide necessary infrastructure for **'Production of health economics-related evidence'** and to achieve an **'Efficient healthcare governance structure'**. All changes must be targeted toward improving the ability to achieve the best decision through the accomplishment of the three goals of **quality of care**, **population health**, and **affordability** simultaneously.

The final conclusion of this thesis is that good decision making happens when the pharmaceutical market can be controlled by monitoring and correcting previous decisions. A national commitment is needed to implement the recommendations provided in this thesis. We hope that this thesis helps Iranian policymakers in this way.

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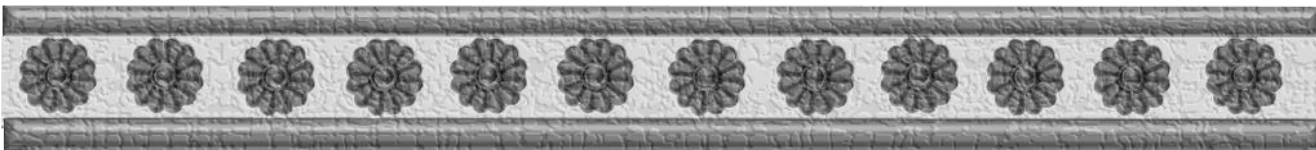
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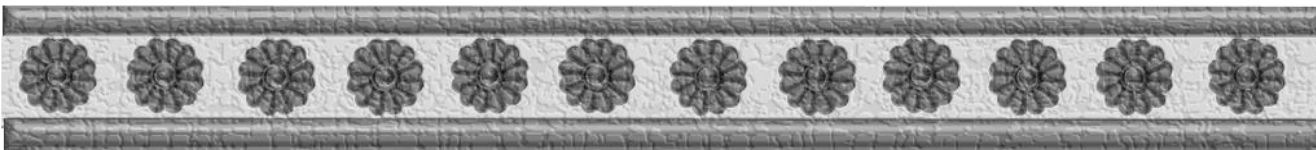
Introduction

Reimbursement decision making in any healthcare system is an important process to ensure patient access to various healthcare services in an affordable manner. A proper reimbursement decision making happens when it can concurrently pursue three main goals including quality of care, population of health, and affordability. However, achieving the goals requires enough knowledge and proper healthcare governance. In middle-income countries (MICs) improving the three main goals is likely to be difficult due to weakness in the knowledge production infrastructure and healthcare governance. To investigate possible solutions for improving the drug reimbursement decision-making system in MICs, this thesis focuses on the drug reimbursement decision-making system in Iran. Subsequently, we focus on use of a monoclonal antibody in breast cancer. Trastuzumab (Herceptin®) is widely used in the treatment of overexpressed human epidermal growth factor receptor 2 (HER2-positive) breast cancer. Trastuzumab, as an expensive drug, has continued to be a topic of conversation in many healthcare systems since its launch into the pharmaceutical markets.

The overall aim of this thesis is to investigate how an MIC (in this case, focusing on Iran) can improve its drug reimbursement decision-making system. Therefore, this thesis provided important information on how an MIC can improve the drug reimbursement decision-making system in three parts. Firstly, we discussed the current situation and subsequent consequences of the drug reimbursement decision-making system in Iran. Secondly, we provided some solutions to improve limited health economics-related evidence in Iran. And finally, some recommendations are provided to improve the system.

Part I: The current drug reimbursement decision-making system in Iran

In **chapter two**, we focus on the current drug reimbursement process in Iran. The entire drug reimbursement process and the stakeholders are explained in this chapter. We reviewed the documents describing the administrative rules and directives of stakeholders. Moreover, we used published statistics and interviewed with experts and policymakers. The Food and Drug Organization and the Supreme Council of Health Insurance are two most qualified organizations in this process. Ultimately, the Iranian Cabinet approves and recommends a drug to all health insurance organizations. Despite its strengths, the system faces various issues. Important shortcomings in the system include out-of-pocket contributions due to lengthy decision-making, lack of transparency, and conflicting interests amongst stakeholders

To obtain insight about routine practice of treatment HER2-positive breast cancer in Iran, **chapter three** assessed the extent to which current routine practice in Iran

matches the recommendations found in the national guideline published by the Iranian Ministry of Health. The Iranian national guideline recommends a nine-week trastuzumab regimen while most national standard therapeutic guidelines in the world recommend a 52-week trastuzumab regimen for breast cancer treatment. To investigate clinician adherence to the Iranian guideline for treating HER2-positive breast cancer, an online anonymous questionnaire was sent to 128 Iranian oncologists and asked them about their approach when they treat a patient with HER2-positive breast cancer. Moreover, a 3-year retrospective claims database analysis was conducted using data from the Social Security Organization, a health insurer which covers approximately 50% of the Iranian population, to enable comparisons with the questionnaire results. Iranian doctors reported a low rate of absolute adherence (6%) to the guideline for duration of trastuzumab treatment. The general trends found in the survey were confirmed in the claims database analysis of 1,295 HER2-positive patients. Therefore, Iranian physicians appear to rely more on the medical literature than on national guidelines regarding trastuzumab use.

Part II: Production of health economics-related evidence in Iran

To fill the gap of knowledge to make better reimbursement and implementation decisions, **chapter four** explains how middle-income countries can use claims data and data mining to achieve a good understanding of real-world healthcare costs. This chapter examine the fraction of total costs related to trastuzumab use into three disease stages of HER2-positive BC in Iran. A retrospective analysis of claims data was performed from the Iran Social Security Organization, a health insurer which covers approximately 50% of the Iranian population (~40 million). We performed data-mining algorithms using R software. After validating the data-mining using patient dossiers in the Cancer Research Center, we identified 1,295 patients and divided them into the three main HER2-positive breast cancer stages (early, loco-regional and advanced). The number of women totaled 802 (early), 125 loco-regional and 218 (advanced). Average costs of direct medical care in early, loco-regional and advanced stages were €11,796 (95%CI: €9,356-€12,498), €8,253 (95%CI: €6,843-€10,002) and €17,742 (95%CI: €15,720-€19,505), respectively. The results of **chapter four** show that wherever comprehensive patient registries are infeasible or costly, real-world costs can be estimated through claims databases and data-mining strategies.

To investigate an optimum duration of trastuzumab use in Iran, a cost-effectiveness analysis was performed from the Iranian healthcare perspective in **chapter five**. We compared four treatment strategies comprising chemotherapy with different durations of trastuzumab use (no-trastuzumab, 6-month, 9-month, and one-year). A Markov model and probabilistic sensitivity analysis were used to estimate the costs and the effects of these strategies. The cost-effectiveness of these strategies at different

willingness-to-pay thresholds, and ages at the onset of treatment were examined. In contrast to the clinical guidelines in high-income countries, six months of trastuzumab may be the most cost-effective option to apply in Iran. As a result, this chapter showes that the lower absolute willingness-to-pay threshold and lower life expectancy compared to high-income countries are the two crucial parameters in cost-effectiveness of interventions in MICs.

Generalizing the results of cost-effectiveness analyses between countries is one of the solutions to overcome knowledge gaps in middle-income countries. However, the accuracy of their results is remaining uncertain when these countries have important differences in their economies and healthcare systems. To investigate accuracy of the results of a transferred cost-effectiveness analysis from high-income countries to a middle-income country, **chapter six** compared the results of five transferred cost-effectiveness analyses with a previously published CEA in Iran. This chapter also identified bias factor(s) affected transferability from high-income countries to middle-income countries, and finally it proposed a new method to estimate cost-effectiveness of a drug in middle-income countries. We systematically searched and selected model-based CEAs in five high-income countries based on the same method with an original country-specific CEA in Iran. In this chapter, two methods were used to estimate incremental costs. In the conventional method, costs were corrected using consumer price indices and transferred to the Iranian setting using purchasing power parities. The proportional method involved estimating initial trastuzumab costs and combining them with the incremental downstream costs. Cost-effectiveness results using these methods were then compared with the results of an Iran-based CEA. The transferred incremental costs of the conventional method (€21,419(USA); €5,115UK); €12,550(USA); €9,170(Portugal); €10,187(Belgium)) did not match the incremental costs of the Iranian CEA (€19,056). However, we could estimate closer incremental costs (€19,988(USA); €19,742(UK); €19,320(USA); €19,497(Portugal); €19,361(Belgium)) with the proportional method. The results of this study showed that when there is a major economic gap between countries and external price referencing has a major impact on pricing in middle-income countries, costs of expensive drugs should not be transferred using relative purchasing power parities. However, the proportional method might be a solution to estimate cost-effectiveness of a drug in a middle-income country.

Part III: Recommendations to improve the drug reimbursement decision-making system in Iran

To investigate the importance of price differentiation in enhancing drug affordability and provide recommendations to improve pricing systems in middle-income countries, **chapter seven** compares prices of trastuzumab for treatment of HER2-positive breast cancer across 14 high-income countries and five in middle-income countries. We

estimated the budget impact of trastuzumab on total health expenditure. Two scenarios were used to reflect relative affordability of trastuzumab: one where prices were estimated using purchasing power parity conversion rates and one where assumptive prices were calculated using purchasing power parity conversion rates (with the US trastuzumab price as an external reference price). The relative budget impact of trastuzumab on total health expenditure was two times higher in middle-income countries compared to high-income countries. It means that trastuzumab was three times less affordable in middle-income countries compared to high-income countries. Therefore, current pricing systems do not facilitate access to expensive drugs in middle-income countries. Equal affordability across countries can be improved by using price differentiation.

Chapter eight examines the pharmaceutical pricing and reimbursement in Iran as a middle-income country to identify prerequisites for the implementation of performance-based and finance-based risk-sharing arrangements. As the previous chapter showed performance-based and finance-based risk-sharing arrangements facilitate implementation of price differentiation in different countries. Therefore, performing a SWOT (strengths, weaknesses, opportunities and threats) analysis, we compared the current Iranian pharmaceutical pricing and reimbursement decision-making system with the performance-based and finance-based risk-sharing arrangements governance and infrastructures in six reference countries (England, Germany, Hungary, Italy, Poland and Turkey) that have implemented PFRSA policies. The results of SWOT analysis showed main weaknesses points of the Iranian system including distributed responsibilities, conflicts of interest, a lack of post-decision market monitoring, and time-consuming procedures. To improve performance of the current process, improvement in two areas of reorganization of the Iranian healthcare governance and improving infrastructure and process would be instrumental in Iran. In conclusion, a cyclic and dynamic pricing and reimbursement process should be used to improve the current process. Iran can start improving the system by implementing finance-based arrangements and concurrently provide necessary infrastructure (including post-decision market monitoring and real-world evidence) for implementation of performance-based schemes.

Discussion

Chapter nine, the general discussion, discusses the key findings of this thesis based on the results of different chapters. Previous chapters showed that the drug reimbursement and pricing decision-making is a complicated process. Improvement in knowledge production infrastructure and health governance are two main and important necessities in Iran. Iranian policymakers should be able to applying the various techniques already mentioned in different chapters of this thesis to achieve all

three overall goals for drug reimbursement decision-making. This thesis also recommends some key points that must be implemented in Iran including development a country-specific guideline for economic evaluations, development a good governance standard for drug reimbursement decision-making, development an independent pricing system, implementation of risk sharing arrangements, implementation of pharmaceutical pricing based on a max-age threshold, Improvement of post-marketing observations, and correcting former decisions. All changes must be targeted toward improving the ability to achieve the best decision through the accomplishment of the three goals of **quality of care**, **population health**, and **affordability** simultaneously.

Samenvatting
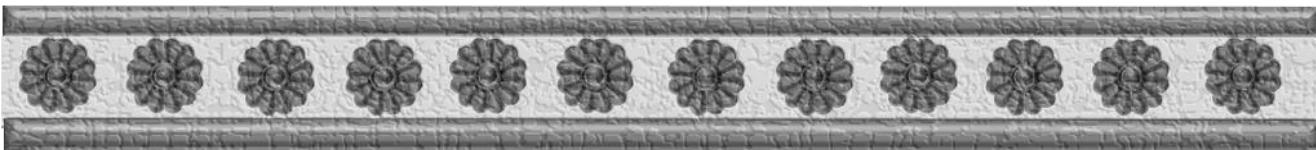
Introductie

De besluitvorming rondom geneesmiddelvergoeding is een belangrijk proces in elk zorgsysteem om betaalbare zorg voor patiënten te verzekeren. De vergoedingsbeslissing kan als goed worden bestempeld als het achtereenvolgend de volgende doelen nastreeft; **kwaliteit van zorg**, **gezondheid van de samenleving**, en **betaalbaarheid van zorg**. Om verbetering op deze drie punten te bereiken moet er voldoende kennis beschikbaar zijn en goed zorgbeleid uitgevoerd worden. Doordat midden-inkomenslanden een minder sterk zorgbeleid en een minder sterke infrastructuur hebben om deze kennis te vergaren ondervinden zij meer problematiek in het verbeteren van de drie punten. Deze thesis is opgezet om de mogelijkheden tot verbetering van het besluitvormingsproces rondom geneesmiddelenvergoedingen in midden-inkomenslanden te onderzoeken. Het onderzoek is gedaan op basis van het besluitvormingsproces in Iran aan de hand van het geneesmiddel trastuzumab (Herceptin®), een monoklonaal antilichaam dat veel gebruikt wordt bij de behandeling van borstkanker patiënten die een verhoogde aanwezigheid hebben van het humane epidermale groeifactor receptor type 2 (HER2 positief). Trastuzumab is een duur geneesmiddel, waarover vraagtekens bestaan over de hoogte van vergoeding sinds zijn intrede in de farmaceutische markt.

Onderzoek naar de mogelijkheden tot verbeteren van het vergoedingsproces in midden-inkomenslanden (met focus op Iran) staat centraal in deze thesis. De thesis bestaat uit drie delen. In het eerste deel staat de huidige situatie rondom het Iraanse geneesmiddelvergoedingssysteem en zijn gevolgen centraal. Het tweede deel biedt verschillende oplossingen tot het verbeteren van de Iraanse kennis met betrekking tot gezondheidseconomie. Het derde en laatste deel doet verschillende aanbevelingen ter verbetering van het vergoedingssysteem in Iran.

Deel I: Het huidige besluitvormingsproces rondom geneesmiddelvergoeding in Iran

In **hoofdstuk 2** ligt de nadruk op het huidige besluitvormingsproces rondom geneesmiddelvergoeding in Iran. Het gehele proces en alle betrokken partijen worden toegelicht in dit hoofdstuk. Om deze informatie in kaart te brengen zijn alle documenten die het huidige beleid beschrijven onderzocht. Daarnaast is er gebruik gemaakt van openbaar beschikbare statistieken en zijn er experts en

relevante beleidsmakers geïnterviewd. De Iraanse '*Food and Drug Organization*' en de '*Supreme Council of Health Insurance*' zijn de kernorganisaties in dit besluitvormingsproces, maar het Iraanse kabinet neemt uiteindelijk de beslissing of een geneesmiddel wordt goedgekeurd en dus wordt vergoed door de zorgverzekeraars. Ondanks dat het Iraanse systeem sterke kanten bevat, ondervindt het ook verscheidene problemen. Tekortkomingen van het systeem bestaan onder andere uit *out-of-pocket*-kosten voor patiënten (kosten gemaakt door patiënten zelf). Dit wordt veroorzaakt door een vertraagde besluitvorming, gebrek aan transparantie en door tegenstrijdige belangen van de belanghebbenden.

Om inzicht te krijgen in de dagelijkse praktijk van het behandelen van HER2-positieve borstkanker patiënten in Iran, beschrijft **hoofdstuk 3** de huidige praktijk in Iran en in hoeverre deze overeenkomt met de nationale behandelrichtlijnen van het Ministerie van Gezondheid. De Iraanse nationale richtlijnen adviseren een negen-weken trastuzumab regime aan, terwijl de richtlijnen van de meeste andere landen een 52-weken regime hanteren. Om de naleving van de Iraanse richtlijnen door Iraanse oncologen te onderzoeken is er een online-enquête ontwikkeld en gestuurd naar 128 oncologen. Zij zijn gevraagd naar hun aanpak in de behandeling van HER2-positieve borstkanker patiënten. De uitkomsten van deze enquête zijn vergeleken met data over een periode van 3 jaar afkomstig uit de retrospectieve *claim database* van de *Social Security Organization*, een Iraanse zorgverzekeraar die ongeveer 50% van de bevolking dekt. Slechts een klein deel van de Iraanse artsen (6%) rapporteerde absolute naleving van de richtlijnen omtrent de duur van trastuzumab-behandeling. Deze uitkomst komt overeen met wat werd gevonden in de analyse van de *claim database* van 1295 HER2-positive borstkanker patiënten. Daaruit blijkt dat Iraanse oncologen zich meer berusten op de medische literatuur, dan op de nationale richtlijn wat betreft het gebruik van trastuzumab bij deze groep patiënten.

Deel II: Ontwikkeling van farmaco-economische data in Iran

Hoofdstuk 4 bekijkt hoe het gebruik van de *claims database* en *datamining* het besluitvormingsproces omtrent geneesmiddelenvergoeding in midden-inkomenslanden kan ondersteunen, door middel van het verkrijgen van meer kennis rondom de zorgkosten in de klinische praktijk. Een retrospectieve

analyse is uitgevoerd op basis de *claims database* van de Iraanse *Social Security Organization* (dekking 50% van de Iraanse bevolking; ~40 miljoen inwoners). *Datamining* algoritmes zijn uitgevoerd in R software. Patiëntendossiers van het Kanker Onderzoek Centrum (*Cancer Research Center*) zijn gebruikt om de *datamining* te valideren, resulterend in de identificatie van in totaal 1295 patiënten. Deze patiënten hebben allen HER2-positieve borstkanker en zijn ingedeeld naar de volgende stadia, vroeg stadium (802 vrouwen), locoregionaal stadium (125 vrouwen) en geavanceerd stadium (218 vrouwen). De gemiddelde directe kosten in het vroege stadium, locoregionaal stadium en geavanceerd stadium zijn €11.796 (95% betrouwbaarheidsinterval (BI): €9.356-€12.498), €8.253 (95%BI: €6.843-€10.002) en €17.742 (95%BI: €15.720-€19.505), respectievelijk. De uitkomsten in dit **hoofdstuk 4** laten zien dat in het geval dat het opzetten van patiëntenregistraties onmogelijk of te duur is, de kosten van de dagelijkse praktijk ook geschat kunnen worden op basis van *claims databases* en *datamining*.

Om de optimale duur van trastuzumab gebruik in Iran te onderzoeken is er een kosteneffectiviteitsanalyse uitgevoerd vanuit het Iraanse zorgperspectief ((**hoofdstuk 5)**. Hierbij zijn vier behandelstrategieën onderzocht en ingedeeld op basis van tijdsduur van trastuzumab behandeling , te weten geen trastuzumab, 6-maanden, 9-maanden, en 1-jaar trastuzumab. Een Markov-model en een probabilistische sensitiviteitsanalyse werden toegepast om de kosten en effectiviteit van elk van de vier behandelstrategieën te schatten. Voor elk van deze vier strategieën is de kosteneffectiviteit bepaald op basis van verschillende betalingsbereidheid grenzen *(willingness-to-pay-thresholds),* en de leeftijd van start van behandeling. In tegenstelling tot de behandelrichtlijnen in hoog-inkomenslanden, lijkt de 6-maanden trastuzumab behandeling de meeste kosteneffectieve optie te zijn in Iran. Dit hoofdstuk maakt inzichtelijk dat de lagere betalingsbereidheid grens en de lagere levensverwachting in midden-inkomenslanden cruciale factoren kunnen zijn in het bepalen van de kosteneffectiviteit van medische behandelingen.

Het tekort aan kennis in midden-inkomenslanden kan overkomen worden door het generaliseren van resultaten van kosteneffectiviteitsanalyses tussen landen. Echter, verschillen in economie en zorgsystemen tussen landen maken dat het overdragen van deze resultaten mogelijk onbetrouwbaar en onnauwkeurig is. **Hoofdstuk 6** verdiept zich in het generaliseren van resultaten

van kosteneffectiviteitsanalyses van hoog-inkomenslanden door midden-inkomenslanden. De resultaten van vijf gepubliceerde kosteneffectiviteitsanalyses zijn vergeleken met een eerder gepubliceerde Iraanse kosteneffectiviteitsanalyse. Daarnaast staan in dit hoofdstuk factoren die mogelijk een effect hebben op de overdraagbaarheid van de resultaten tussen de hoog- en midden-inkomenslanden, en presenteert het een nieuwe methode om de kosteneffectiviteit van een medicijn te bepalen in een midden-inkomensland. Na een systematisch onderzoek zijn vijf modelgebaseerde kosteneffectiviteitsstudies uit hoog-inkomenslanden, die een eenzelfde methode toepasten, en een originele Iraanse kosteneffectiviteitsanalyse geselecteerd. Er zijn twee methoden gebruikt om de incrementele kosten te bepalen. In de gangbare methode zijn de kosten gecorrigeerd op basis van de consumentenprijsindex en vertaald naar de Iraanse situatie aan de hand van Iraanse koopkrachtpariteitsindices. In de proportionele methode zijn de initieel geschatte trastuzumab kosten gebruikt en gecombineerd met incrementele downstream kosten. De resultaten van deze twee methoden zijn vergeleken met de resultaten van de originele Iraanse kosteneffectiviteitsanalyse. De naar Iran-gecorrigeerde incrementele kosten op basis van de traditionele methode (€21.419 (Verenigde Staten, eerste studie); €5.115 (Verenigd Koninkrijk); €12.550 (Verenigde Staten, tweede studie); €9.170 (Portugal); €10.187 (België)) komen niet overeen met de incrementele kosten van de Iraanse kosteneffectiviteitsanalyse. Echter, de proportionele methode schatte de incrementele kosten nauwkeuriger (€19.988 (Verenigde Staten, studie 1); €19.742 (Verenigd Koninkrijk); €19.320 (Verenigde Staten, studie 2); €19.497 (Portugal); €19.361 (België)). De resultaten van dit onderzoek laten zien dat in het geval dat er grote economische verschillen zijn tussen landen, en in het geval dat externe prijsreferenties een grote rol spelen in midden-inkomenslanden, de kosten van dure geneesmiddelen niet overgedragen kunnen worden op basis van de relatieve koopkrachtpariteiten. De proportionele methode biedt dan een uitkomst in het schatten van kosteneffectiviteit van een medicijn in midden-inkomenslanden.

Deel III: Aanbevelingen voor het verbeteren van medicijnvergoeding besluitvorming in Iran

Om het belang van prijsdifferentiatie in het verbeteren van de betaalbaarheid van medicijnen te onderzoeken wordenin **hoofdstuk 7** de prijzen van

trastuzumab in de toepassing bij HER2-positieve borstkanker patiënten vergeleken tussen veertien hoog-inkomenslanden en vijf midden-inkomenslanden. Tevens worden aanbevelingen gedaan tot het verbeteren van de prijssystemen in midden-inkomenslanden en is de budget impact van trastuzumab op de totale zorgkosten geschat. Twee scenario's zijn toegepast om de relatieve betaalbaarheid van trastuzumab te evalueren. In het eerste scenario zijn prijzen geschat op basis van koopkrachtpariteiten wisselkoersen. In het tweede scenario zijn de prijzen berekend op basis van koopkrachtpariteiten wisselkoersen, waarbij de prijs van trastuzumab in de Verenigde Staten als referentieprijs diende. De relatieve budgetimpact van trastuzumab ten opzichte van de totale zorgkosten is twee keer groter in midden-inkomenslanden vergeleken met hoog-inkomenslanden. Dat betekent dat trastuzumab drie keer minder betaalbaar is in midden-inkomenslanden vergeleken met hoog-inkomenslanden. De huidige prijssystemen dragen daarom niet bij aan het toegankelijk maken van dure medicijnen in midden-inkomenslanden. Gelijke betaalbaarheid tussen landen kan worden verbeterd aan de hand van prijsdifferentiatie.

Hoofdstuk 8 onderzoekt het prijs- en vergoedingssysteem van Iran als midden-inkomensland om de voorwaarden van het implementeren van prestatie-gebaseerde en financieel-gebaseerde risicodeling ('*risk-sharing*') (PFRSA) regelingen. Het voorgaande hoofdstuk maakte inzichtelijk hoe deze prestatie-gebaseerde en financieel-gebaseerde regelingen kunnen bijdragen aan de implementatie van prijsdifferentiatie in verschillende landen. Aan de hand van een SWOT-analyse (sterktes, zwaktes, kansen, en bedreigingen) is er een vergelijking gemaakt tussen het huidige Iraanse medicijnprijs- en vergoedingsbesluitsysteem en de prestatie-gebaseerde en financieel-gebaseerde regelingen, beleid en infrastructuren van zes referentie landen met een PFRSA beleid, te weten Engeland, Duitsland, Hongarije, Italië, Polen en Turkije. Uit de SWOT analyses bleek dat verdeelde verantwoordelijkheden, tegenstrijdige belangen, een gebrekkig post-market monitorbeleid, en het tijdrovende proces de zwakke punten in het Iraanse systeem zijn. Om het huidige systeem te verbeteren, is een reorganisatie op twee terreinen van het Iraanse zorgbeleid, alsmede het verbeteren van de infrastructuur en van het proces, noodzakelijk. Concluderend wordt een cyclisch- en dynamisch prijs- en vergoedingsproces aangeraden om het huidige systeem te verbeteren. Deze

verbeteringen kunnen in gang gezet worden door het implementeren van financieel-gebaseerde regelingen en het opzetten van een juiste infrastructuur (inclusief post-market monitoren en het gebruiken van '*real-world evidence'*) voor het implementeren van prestatie-gebaseerde regelingen.

Discussie

Hoofdstuk 9 bespreekt de hoofdbevindingen van deze thesis op basis van de bevindingen van elk hoofdstuk. Voorgaande hoofdstukken concludeerden al dat het prijs- en vergoedingsproces met betrekking toelating van geneesmiddelen gecompliceerd is. Het verbeteren van de kennis infrastructuur en het zorgbeleid zijn de twee noodzakelijkheden in Iran. Iraanse beleidmakers moeten in staat zijn de verschillende technieken, besproken in deze thesis, toe te passen om de drie doelen voor een goed werkend systeem te behalen. Deze thesis biedt ook kernaanbevelingen voor Iran, waaronder het ontwikkelen van land-specifieke richtlijnen voor economische evaluaties, het ontwikkelen van beleidstandaarden voor besluitvorming omtrent het vergoeden van medicijnen, het ontwikkelen van een onafhankelijk prijssysteem, het implementeren van risicodeling regelingen, het verbeteren van post-market observaties, en het evalueren en aanpassen van eerdere beslissingen. Alle veranderingen moeten gericht zijn op het bereiken van de juiste vergoedingsbeslissingen door middel van het tegelijkertijd behalen van de drie doelen; **kwaliteit van zorg**, **gezondheid van de samenleving**, en **betaalbaarheid van zorg**.
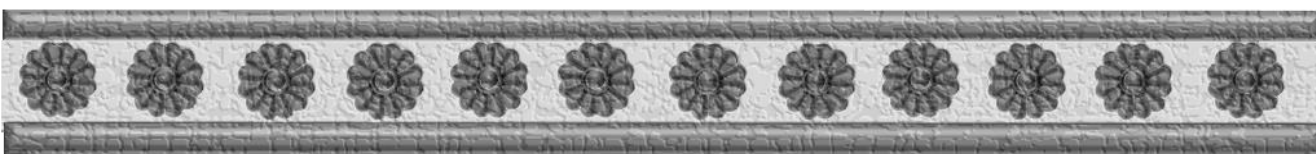
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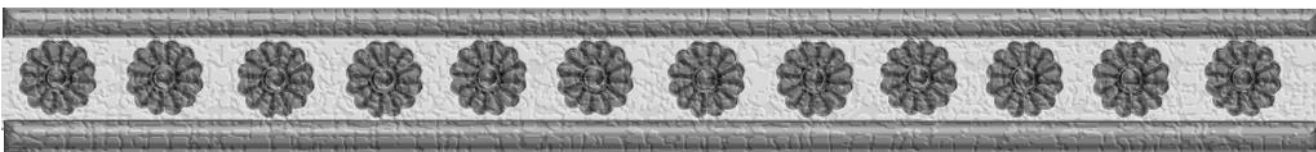
Now, it is time to write the most read part of this dissertation. Over the course of the PhD program during the past years, I have very often fantasized about this moment; what it would really feel like when I start writing the acknowledgements part. But words cannot fully explain my feelings now, honestly. There are a huge number of people to whom I owe gratitude for their support over this chapter of my life. It is not very easy now to single out the people; I genuinely hope I have not missed anyone.

My deepest gratitude and the most special thanks go to my supervisors, Prof. dr. Carin A. Uyl-de Groot and Dr. W. Ken Redekop, as the most deserving ones. Thank you for not only giving me the opportunity to pursue this degree but also steadfastly guiding me through it. There were many aspects you have really taught me through the process of progressive learning and how to deal with various issues. Your help was essential and I am quite sure that I would have never made it without your help. Dear Carin, I feel myself privileged for having been able to undertake my thesis under your guidance. I will never forget all your supports and for making it possible for me to overcome difficulties. Dear Ken, thanks for your efficient and quick feedback, your guidance and your patience. Never ending enthusiasm for scientific research and your creative thinking have inspired me and opened my eyes to the fascinating world of science during these years. You are the kindest and the most amazing person as a scientist, teacher and human being. I truly enjoyed meeting with you and talking about politics once in a while!

I am grateful to all my co-authors for their constructive criticisms and comments which have certainly improved this thesis. While obtaining a PhD is a lonely business on principle, I had the good fortune of working with many people from the Netherlands as well as other countries. Thanks to all my co-authors for spending time on my studies and giving me very useful comments to improve them. Special thanks go to Prof. dr. Zoltán Kaló from Institute of Economics at the Faculty of Social Sciences at Eötvös Loránd University (ELTE) in Budapest and Prof. dr. Hans Severens from ESHPM, I am really grateful for all your help and work on my studies; your motivation and enthusiasm for research is adorable. I would also like to single out two people here: Dr. Margreet Franken from ESHPM and Dr. Kazem Zendehdel from the Institute for Cancer Researches, Tehran University of Medical Sciences. Dear Margreet, thank you very much for all your kind notes and encouragement; I really appreciate your help and support with my studies. Dear Kazem, I really appreciate your collaboration and for allowing me to use patient-level data in your institute.

I want to take the opportunity to thank the members of my thesis reading committee: Prof. dr. Werner Brouwer, Prof. dr. Anthonius de Boer, and dr. A. Agnes Jager. I am grateful to have had you on board and thank you for taking time to review the dissertation.

supports especially during my PhD. Mojtaba jan, I owe you for your goodness and your supports.

Can't think of a better distraction from the monotonicity of the research life; I have made a good number of friends during my PhD project who have made this journey much more enjoyable. I enjoyed our picnics, trips, parties, Persian BBQs, restaurants and celebrating the new year with Ali and Mehrnoosh, Yaser and Neda, Soulmaz and Hamid, Farshad and Mazda, Mohadeseh and Ali, Vida and Kamal, Marzieh and Mehdi, Sima and Tomas, Negar, Neda, Peyman, and Soheil.

I am also very grateful to my friends and former neighbours Majid and Lidian; words cannot easily express my great appreciations to you both for being such a true friend of family. Thank you so much for your friendship and kindness.

Special thanks go to Frederick and Menno as my paranimfen. Dear friends, thanks for being my paranimf and helping me with organizing things for the promotion, but more importantly, I am grateful for your precious friendship. Thank you for being there for me!

I am grateful of my in-law family for their kindness and support through my life; Maman Esmat, Dr. Fardin Ahmadizar and Parisa Salour, Voria Ahmadizar and Sara Naghshbandi, Hiva Ahmadizar and Foad Ahmadizar.

To my dear family; I am grateful to my dear parents for all the care and love they have given to me during my life. Dear mom and dad, I could not have been here without your guidance, unconditional love and courage in the first place. You support me in every possible way that helps to keep going on even in the most difficult moments. To my dear brother Dr. Emad Ansaripour, my dear sister Dr. Nafiseh Ansaripour and her husband Dr. Reza Davar and their daughter Donya joon, for being at different points in my life and for their strong support. I always feel much stronger when I am thinking about you; thanks for your presence. You are always close to me, in my heart and mind.

No words can express the gratitude and love for the three people who have the strongest claim to this accomplishment. To my dear wife, Fariba, I wish to express my unlimited love to you and thank you for all your patience, for your love and for your kindness. Fariba, not only are you my partner in life, but also my best friend; I would have never been able to finish this work without you. To my lovely angels "Yasaman and Ariana", I want to thank you both for just being in my life and thus making life worth of living. Hope you both always reach to *whatever is true and whatever is honorable. Yasi and Ari! get prepared, your time to shine is approaching. So, just look forward and continue to pursue your dreams.*
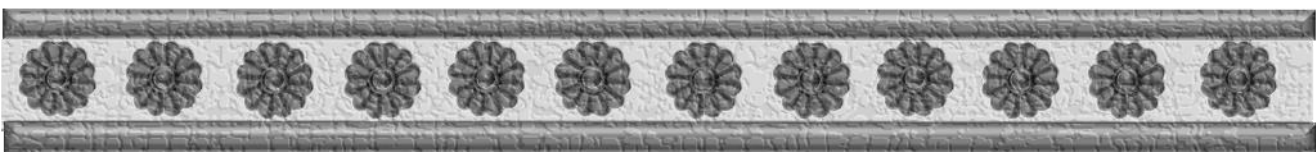
Finally, my most sincere thanks belong to insurees of the Social Security Organization. I started, countinued and now I am closing this chapter of my life, with the honor of serving you.

Amir Ansaripour,

Rotterdam, July 2018
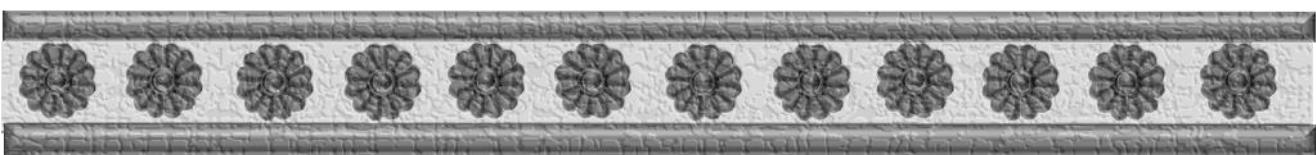
PhD Portfolio

PhD Portfolio:

PhD student:	Amir Ansaripour
Faculty:	Erasmus School of Health Policy and Management
PhD Period:	2012 - 2018
Promotor:	Prof. dr. Carin A. Uyl-de Groot
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PhD traning

Academic writing in English for PhD students, Language & training center, Erasmus university Rotterdam (2012)

Economic of health and health care, Erasmus School of Health Policy and Management (2012)

Health Technology Assessment, Erasmus School of Health Policy and Management (2013)

Reimbursement Systems for Pharmaceuticals in Europe, International Society for Pharmacoeconomics and Outcomes Research (2014)

Advanced Economic Evaluation, Erasmus School of Health Policy and Management (2014)

Using Multi-criteria Decision Analysis in Health Care Decision Making: Approaches & Applications, International Society for Pharmacoeconomics and Outcomes Research (2015)

Pharmaceutical Pricing and Market Access, International Society for Pharmacoeconomics and Outcomes Research (2016)

Patient Registries, International Society for Pharmacoeconomics and Outcomes Research (2016)

Transferability of Cost-effectiveness Data Between Countries, International Society for Pharmacoeconomics and Outcomes Research (2016)

Risk-Sharing/Performance-Based Arrangements for Drugs and Other Medical Products, International Society for Pharmacoeconomics and Outcomes Research (2016)

Presentations at international conferences

    Podium presentations

Drug reimbursement decision-making; The First National Congress of Health Economy Academy, Tehran, Iran (2015)

Implementation of resistive economy in the Iranian healthcare system; The Iranian PhD Candidates Association in Europe, Embassy of the Islamic Republic of Iran, The Hague, the Netherlands (2016)

Use of data-mining to perform a real-world cost analysis of HER2-positive breast cancer in Iran"; International Society for Pharmacoeconomics and Outcomes Research, 19th Annual European Congress, Vienna, Austria (2016) (Nomination)

Use of data-mining to perform a real-world cost analysis of HER2-positive breast cancer in Iran; Faculty of Pharmacy (Department of Pharmacoeconomics), Shahid Beheshti University of Medical Sciences, Tehran, Iran (2016)

How can middle-income countries get a valid estimate of cost-effectiveness of a drug more efficiently and effectively?" lolaHESG, Rotterdam, the Netherlands (2018)

Poster presenations

Which is more important for doctors in a low-middle income country: A national guideline or the medical literature? A guideline adherence survey of trastuzumab use for breast cancer in Iran; International Society for Pharmacoeconomics and Outcomes Research, 17th Annual European Congress, Amsterdam, the Netherlands (2014)

Direct medical costs of HER2-positive breast cancer management in Iran: A claims database and data-mining analysis; International Society for Pharmacoeconomics and Outcomes Research, 20th Annual International Meeting, Philadelphia, USA (2015)

Is external reference pricing a threat to internationally equal affordability?"; International Society for Pharmacoeconomics and Outcomes Research, 19th Annual European Congress, Vienna, Austria (2016)

What is an efficient and affordable trastuzumab therapy in a middle-income country? - Adjuvant therapy with trastuzumab in management of early HER2-positive breast cancer in Iran"; International Society for Pharmacoeconomics and Outcomes Research, 19th Annual European Congress, Vienna, Austria (2016)

The cost-effectiveness of bluelight therapy vs fixed combination of calcipotriol and betamethasone dipropionate gel in the treatment of mild-to-moderate psoriasis"; International Society for Pharmacoeconomics and Outcomes Research, 19th Annual European Congress, Vienna, Austria (2016)

How can middle-income countries get a valid estimate of cost-effectiveness of a drug more efficiently and effectively?"; International Society for Pharmacoeconomics and Outcomes Research, 20th Annual European Congress, Glasgow, Scotland (2017) (Nomination)

Teaching

NIHES health economics summer course, Workgroups (2013, 2014, 2015, 2016)

Pharmaceutical Pricing and Market Access, Workgroups (2017)

Health Technology Assessment, Workgroups (2017)

Supervising master theses (2014, 2017)

Scientific publications not included in this thesis

Ansaripour A., Thio H.B., Maessen R., Redekop. W.K.; 2017; The cost-effectiveness of bluelight therapy in the treatment of mild-to-moderate psoriasis; Journal of Comparative Effectiveness Research, DOI:http://dx.doi.org/10.2217/cer-2017-0007.
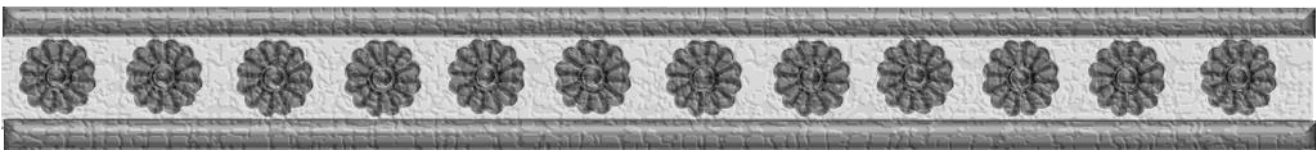
Scientific awards

Best student podium presentationfor the presentation of Use of data-mining to perform a real-world cost analysis of HER2-positive breast cancer in Iran"; International Society for Pharmacoeconomics and Outcomes Research, 19th Annual European Congress, Vienna, Austria (2016)
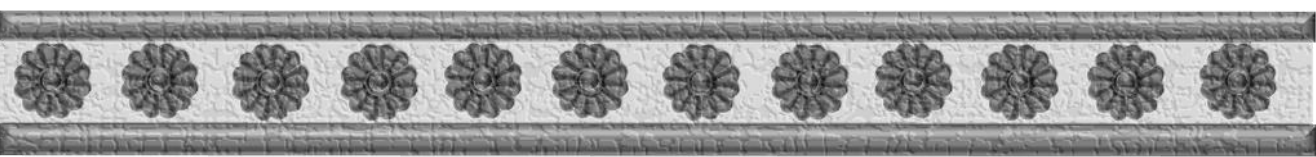
About the author

About the author:

Amir Ansaripour was born in Mashhad, on June 16th, 1973. Having spent his childhood in Sabzevar in Khorasan province, he started his study on pharmacy at the Shahid Beheshti University of Medical Sciences in Tehran in 1992. During this time, he was an active member of the Research Committee for Students at the Faculty of Pharmacy and he was appointed the chair of this committee in 1997. He graduated with a degree of Doctorate of Pharmacy in 1998. Afterward, he started working at the Social Security Organization (SSO)[1] at a polyclinic in Sanandaj. He quickly promoted to manager of purchasing of healthcare services in Kurdistan province in 2002 and was selected as the best provincial manager for two consecutive years (2003 and 2004). In 2005, Amir was asked to work at the headquarter office of the SSO in Tehran.
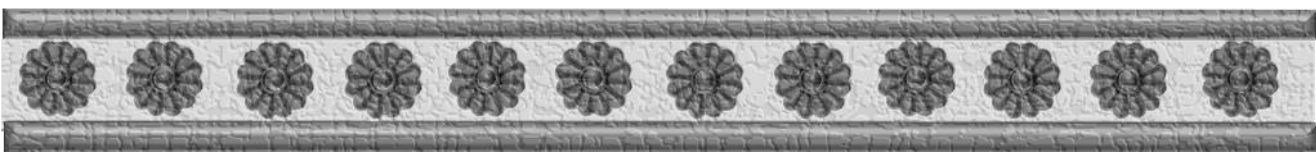
After working in different positions, he realized the importance of electronic medical records in decision-making. Therefore, he decided to conduct a project of data collection from over 46,500 healthcare providers in Iran. The project was started under his supervision in 2007 and it is operational throughout the country now. The data obtained from this project were used for one of the studies of this dissertation. Amir was also involved in different national-level projects such as implementation of family physicians program in Iran. At the same time, he was the SSO's delegate at the expert committee for reimbursing of the medical technologies at the Supreme Council for Health Insurance in Iran.

Experiencing many issues that could ultimately lead to mismanagement regarding reimbursement decision-making process, he decided to start a new chapter in his life, far away from home and in a new field of science; doing research. From 2012 onward, he has been in a PhD-working for the department of Erasmus School of Health Policy and Management in Rotterdam. He was focused on the area of cost-effectiveness analyses, modeling, and reimbursement policy in Iran. During past years, he has applied various methods in his PhD project which are explained in different chapter of this dissertation. As a result, Amir has received the best podium presentation award at ISPOR 2016 in Vienna.

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[1] The biggest social insurance organization in Iran (~32,000 employees) and also the biggest health insurance company with over 40 million insureds.

References
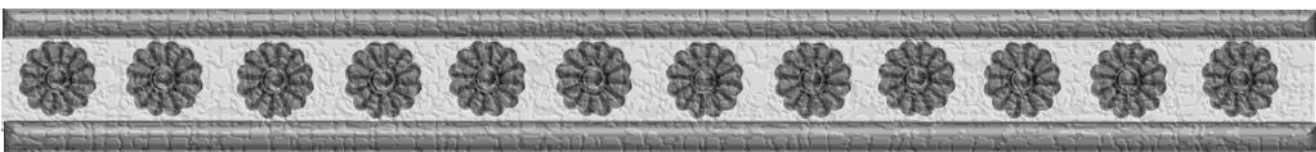
References

1. Claxton K, Sculpher M, Drummond M. A rational framework for decision making by the National Institute For Clinical Excellence (NICE). . 2002;360: 711-715. doi: http://dx.doi.org/10.1016/S0140-6736(02)09832-X.

2. Drummond M.F., O'Brien B., Stoddart G.L., Torrance G.W. Methods for the economic evaluation of health care programes. Second ed. England: Oxford Medical publication; 1997.

3. Sullivan SD, Mauskopf JA, Augustovski F, Jaime Caro J, Lee KM, Minchin M, et al. Budget Impact Analysis—Principles of Good Practice: Report of the ISPOR 2012 Budget Impact Analysis Good Practice II Task Force. Value in Health. 2014;17: 5-14. doi: 10.1016/j.jval.2013.08.2291.

4. World Health Organization. About the Health Equity Monitor. , WHO. 2016: 1. Available: http://www.who.int/gho/health_equity/about/en/.

5. Baltussen R, Niessen L. Priority setting of health interventions: the need for multi-criteria decision analysis. . 2006;4: 14. doi: 10.1186/1478-7547-4-14.

6. Guyatt G, Cairns J, Churchill D,et al. Evidence-based medicine: A new approach to teaching the practice of medicine. JAMA. 1992;268: 2420-2425. doi: 10.1001/jama.1992.03490170092032.

7. Marsh K, IJzerman M, Thokala P, Baltussen R, Boysen M, Kaló³ Z, et al. Multiple Criteria Decision Analysis for Health Care Decision Making—Emerging Good Practices: Report 2 of the ISPOR MCDA Emerging Good Practices Task Force. Value in Health. 2016;19: 125-137. doi: 10.1016/j.jval.2015.12.016.

8. The Agency for Healthcare Research and Quality. National Strategy for Quality Improvement in Health Care. Report to Congress. 2011.

9. Wija Oortwijn, Judith Mathijssen, David Banta. The role of health technology assessment on pharmaceutical reimbursement in selected middle-income countries. Health Policy. 2010;95: 174-184.

10. Babigumira JB, Jenny AM, Bartlein R, Stergachis A, Garrison LP. Health technology assessment in low- and middle-income countries: a landscape assessment. . 2016;7: 37-42. doi: 10.1111/jphs.12120.

11. Ngorsuraches S, Meng W, Kim B, Kulsomboon V. Drug Reimbursement Decision-Making in Thailand, China, and South Korea. . 2012;15: S120-S125. doi: http://dx.doi.org/10.1016/j.jval.2011.11.002.

12. Zelle SG, Baltussen RM. Economic analyses of breast cancer control in low- and middle-income countries: a systematic review. . 2013;2: 20-20. doi: 10.1186/2046-4053-2-20.

13. The Iran Official Gazette. The Iran universal health insurance for health care law. . Available: http://www.dastour.ir/brows/?lid=154352. 1997, Updated:12/30/1997, Accessed:2012, 06/20.

14. FDO. Pharmaceutical pricing policy. . Available: http://www.fda.gov.ir/item/1370. 2015, Updated:14/10/2015, Accessed:2016, 02/18.

15. World Health Organization. Guidelines for management of breast cancer. 1st ed. Cairo, Egypt: World Health Organization, Regional Office for the Eastern Mediterranean; 2006.

16. WHO. Breast cancer: prevention and control. . Available:
http://www.who.int/cancer/detection/breastcancer/en/index1.html. 2016, Updated:2016, Accessed:2016,
05/17.

17. Mariotto AB, Robin Yabroff K, Shao Y, Feuer EJ, Brown ML. Projections of the Cost of Cancer Care in the
United States: 2010–2020. . 2010;103: 117-128. doi: 10.1093/jnci/djq495.

18. Kiadaliri AA. Social Disparity in Breast and Ovarian Cancer Incidence in Iran, 2003-2009: A Time Trend
Province-Level Study. . 2013;16: 372-377.

19. Mousavi SM, Montazeri A, Mohagheghi MA, Jarrahi AM, Harirchi I, Najafi M, et al. Breast Cancer in Iran:
An Epidemiological Review. Breast J. 2007;13: 383-391. doi: 10.1111/j.1524-4741.2007.00446.x.

20. Afsoon Taghavi, Zeinab Fazeli, Mohsen Vahedi, Ahmad Reza Baghestani, Asma Pourhoseingholi,
Farnoosh Barzegar, et al. Increased Trend of Breast Cancer Mortality in Iran. APJCP. 2012;13: 367-370.

21. ENAYATRAD M, AMOORI N, SALEHINIYA H. Epidemiology and Trends in Breast Cancer Mortality in Iran. .
2014;44: 430-431.

22. Davari M, Yazdanpanah F, Aslani A, Hosseini M, Nazari AR, Mokarian F. The Direct Medical Costs of
Breast Cancer in Iran: Analyzing the Patient's Level Data from a Cancer Specific Hospital in Isfahan.
International Journal of Preventive Medicine. 2013;4: 748-754.

23. Daroudi R, Akbari Sari A, Nahvijou A, Kalaghchi B, Najafi M, Zendehdel K. The Economic Burden of Breast
Cancer in Iran. Iranian Journal of Public Health. 2015;44: 1225-1233.

24. General administration of affordable health insurance coverage in Iranian Social Security Organization.
Annual health care costs. . 2015.

25. Scott AM, Allison JP, Wolchok JD. Monoclonal antibodies in cancer therapy. . 2012;12: 14.

26. Glassman PM, Balthasar JP. Mechanistic considerations for the use of monoclonal antibodies for cancer
therapy. . 2014;11: 20-33. doi: 10.7497/j.issn.2095-3941.2014.01.002.

27. Emens LA, Davidson NE. Trastuzumab in breast cancer. Oncology (Williston Park, N Y). 2004;18: 1117-
28; discussion 1131-2, 1137-8.

28. Moja L, Tagliabue L, Balduzzi S, Parmelli E, Pistotti V, Guarneri V, et al. Trastuzumab containing regimens
for early breast cancer. Cochrane Database of Systematic Reviews. 2012;4: CD006243. doi:
10.1002/14651858.CD006243.pub2.

29. Joensuu H, Bono P, Kataja V, Alanko T, Kokko R, Asola R, et al. Fluorouracil, Epirubicin, and
Cyclophosphamide With Either Docetaxel or Vinorelbine, With or Without Trastuzumab, As Adjuvant
Treatments of Breast Cancer: Final Results of the FinHer Trial. Journal of Clinical Oncology. 2009;27: 5685-
5692. doi: 10.1200/JCO.2008.21.4577.

30. Smith I, Procter M, Gelber RD, Guillaume S, Feyereislova A, Dowsett M, et al. 2-year follow-up of
trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. .
2007;369: 29-36. doi: http://dx.doi.org/10.1016/S0140-6736(07)60028-2.

31. Hall P, Hulme C, McCabe C, Oluboyede Y, Round J, Cameron D. Updated Cost-Effectiveness Analysis of Trastuzumab for Early Breast Cancer. Pharmacoeconomics. 2011;29: 415-432. doi: 10.2165/11588340-000000000-00000.

32. Garrison LP, Jr., Towse A, Briggs A, de Pouvourville G, Grueger J, Mohr PE, et al. Performance-Based Risk-Sharing Arrangementsâ€"Good Practices for Design, Implementation, and Evaluation: Report of the ISPOR Good Practices for Performance-Based Risk-Sharing Arrangements Task Force. ;16: 703-719. doi: 10.1016/j.jval.2013.04.011.

33. WHO. The global health expenditure database. . November 17, 2016. Available: http://apps.who.int/nha/database.

34. Gressani D, Saba J, Fetini H, Rutkowski M, Maeda A, Langenbrunner J. Islamic Republic of Iran Health Sector Review, Volume I, Main Report. . June 2007;39970 – IR.

35. Cheraghali A.M., Nikfar S., Behmanesh Y., Rahimi V., Habibipour F., Tirdad R., et al. Evaluation of availability, accessibility and prescribing pattern of medicines in the Islamic Republic of Iran. . 2004;10: 406-415.

36. Beyhaghi H, Basmenji K. Developing A Framework For The Inclusion Of Pharmaceuticals In Health Insurance Benefit Package - A Comparative Study On Iranian Social Security Organization. . 2009.

37. Delgoshaei B., Tourani S., Khalesi N., Dindust P. Pricing and Reimbursement of Pharmaceuticals in Iran and Selected Countries: A Comparative Study. . 2005;22: 55-74.

38. Drug deputy of Iran Food and Drug Organization. The drug sales statistics during 1390 (Amar nameh). . 2012.

39. Education and Research Administration of Social Security of Organization. The Social Security of Organization introduction. 1st ed. Tehran, Iran: Social Security of Organization; 2011.

40. Social Security Organization. Health Services. . Available: http://www.tamin.ir/NSite/FullStory/News/?Serv=3&Id=1007. 2011, Updated:25/09/2011, Accessed:2012, 07/15.

41. Imam Khomeini Relief Foundation. The Summary of 34 years performance statistics. . Available: http://www.emdad.ir/mcontent/amar/amar_gozaresh_saliane/kholase%2091.pdf. 2013: 1, Accessed:2013, 01/28.

42. Iran Food and Drug Organization. Council to Consider and Compilation Drugs. . Available: http://fdo.behdasht.gov.ir/index.aspx?siteid=114&pageid=12425. 2010, Updated:06/06/2010, Accessed:2012, 06/20.

43. Iran Food and Drug Organization. Iran Pharmacopeia. . Available: http://fdo.behdasht.gov.ir/index.aspx?siteid=114&pageid=29763. 2012, Updated:06/24/2012, Accessed:2012, 07/01.

44. Health Department of SSO. Drug reimbursement list. . Available: http://www2.darman.sso.ir/Forms/Public/Druglist.aspx?pagename=hdpDrugList. 2012, Updated:07/10/2012, Accessed:2012, 07/10.

45. Gressani D, Saba J, Fetini H, Rutkowski M, Maeda A, Langenbrunner J. Islamic Republic of Iran Health Sector Review, Volume II: Background Sections. . June 2007;39970 – IR.

46. Food and Drug Organization. The regulation of orphan and emergency drugs. . Available: http://behdasht.gov.ir/index.aspx?siteid=1&pageid=12961&newsview=2902&pro=nobak, http://behdasht gov ir/index aspx?siteid=1&pageid=12961&newsview=2902&pro=nobak. 2009, Updated:27.04.2009, Accessed:2013, 02/02.

47. Abbas Kebriaeezadeh, Nasser Nassiri Koopaei, Akbar Abdollahiasl, Shekoufeh Nikfar and Nafiseh Mohamadi. Trend analysis of the pharmaceutical market in Iran; 1997–2010; policy implications for developing countries. DARU Journal of Pharmaceutical Sciences. 2013;21: 52-60.

48. WHO Representative in Iran. Iran (Islamic Republic of): health profile, . Available: http://www.who.int/countries/irn/en/. 2013, Updated:04/2013, Accessed:2013, 07/15.

49. WHO. Management Sciences for Health; Session 10. Standard Treatment Guidelines. In: Anonymous Drug and Therapeutics Committee Training Course. Arlington, USA: Rational Pharmaceutical Management Plus; 2007. pp. 2.

50. CRNN. Guideline for trastuzumab prescription and an eligibility priority setting for Iranian breast cancer patients., Part 1 (Ultimate guideline). First ed. Tehran, Iran: Cancer Research National Network, Iran Ministry of Health; 2012.

51. Ansaripour A, Uyl-de Groot CA, Steenhoek A, Redekop WK. The Drug Reimbursement Decision-Making System in Iran. Value in Health Regional Issues. 2014;3: 174-181. doi: http://dx.doi.org/10.1016/j.vhri.2014.04.010.

52. CRNN. A guideline for prescribing of trastuzumab and prioritizing Iranian breast cancer patients who are eligible to receive trastuzumab. . 2012.

53. SSO. Drug list. . Available: http://www.darman.tamin.ir/Forms/Public/Druglist.aspx?pagename=hdpDrugList. 2014, Updated:25.02.2014, Accessed:2014, 25.02.2014.

54. SSO. General Statistics Report for Social Security Organization activities during 2013.03.21 - 2013.12.21. . 2014;-.

55. Barrett A, Roques T, Small M, Smith RD. How much will Herceptin really cost. BMJ. 2006;333: 1118-1120. doi: 10.1136/bmj.39008.624051.BE.

56. CRNN. Guideline for trastuzumab prescription and an eligibility priority setting for Iranian breast cancer patients., Part 2 (Clinical guideline). First ed. Tehran, Iran: Cancer Research National Network, Iran Ministry of Health; 2012.

57. Harirchi I, Kolahdoozan S, Karbakhsh M, Chegini N, Mohseni SM, Montazeri A, et al. Twenty years of breast cancer in Iran: downstaging without a formal screening program. Annals of Oncology. 2011;22: 93-97. doi: 10.1093/annonc/mdq303.

58. Iran Social Security Organization. Annual performance statistics report 1392 (2013.12.21 - 2014.03.21). . 2014.

59. Poncet B, Colin C, Bachelot T, Jaisson-Hot I, Derain L, Magaud L, et al. Treatment of metastatic breast cancer: A large observational study on adherence to french prescribing guidelines and financial cost of the anti-HER2 antibody trastuzumab. . 2009;32: 369-374.

60. CBI. The results of the household budget in urban areas of Iran - 2013. . 2014.

61. Raja. Mothers death due to lack of funding. . Available: http://www.rajanews.com/news/89533. 2011, Updated:28/10/2011, Accessed:2015, 05/2015.

62. Tebyan. Payers leave you when the cancer comes . . Available: http://www.tebyan.net/newindex.aspx?pid=246429. 2012, Updated:14/04/2012, Accessed:2015, 05/25.

63. Metcalfe S, Evans J, Priest G. PHARMAC's funding of 9 weeks Herceptin: many assumptions in a high-risk decision. . 2007;120: 2593.

64. Akdag E. Does approvals for new cancer drugs is delayed? . Available: http://www.aksiyon.com.tr/aksiyon/newsDetail_openPrintPage.action?newsId=26549. 2010, Updated:19/04/2010, Accessed:2014, 08/08.

65. Huybrechts M, Hulstaert F, Neyt M, Vrijens F, Ramaekers D. Trastuzumab in Early Stage Breast Cancer. Health Technology Assessment (HTA). . 2006;KCE reports 34C (D/2006/10.273/25).

66. Gradishar Wj, Allred DC, Anderson BO, et al. NCCN clinical practice guidelines in oncology: breast cancer. Version 3.2014. . Available: www.NCCN.org. 2014, Updated:04/01/2014, Accessed:2014, 08/07.

67. Auvinen P, Heikkila P, Huvinen R, et al. Breast cancer in a nationwide diagnostic and treatment recommendation. . Available: http://rintasyoparyhma-yhdistysavain-fi-bin.directo.fi/@Bin/34a62894c45d6b00e05937f857589c57/1407416183/application/pdf/171266/www.terveysportti.fi-rintasyovanvaltakunnallinendiagnostiikka-jahoitosuositus2013.pdf. 2013, Accessed:2014, 06/08.

68. SIGN. Treatment of primary breast cancer. (SIGN publication no. 134). 1st ed. Edinburgh, Scotland: Scottish Intercollegiate Guidelines Network (SIGN).; September 2013.

69. CONITEC. Trastuzumabe para tratamento do câncer de mama inicial. . Available: http://www.femama.org.br/novo/arquivos/0.674513001346439788.pdf. 2012, Updated:July 2012, Accessed:2014, 06/25.

70. IKNL. Breast cancer, Dutch Guideline, version 2.0. . Available: http://www.richtlijnendatabase.nl/. 2012, Updated:13/02/2012, Accessed:2014, 06/2014.

71. Aydıner A, Dincer M, Topuz E. Adjuvant Therapy in Breast Cancer, Abant consensus report. 1st ed. Istanbul, Turkey: Nobel tip kitabevleri; 2010.

72. NZGG. Management of Early Breast Cancer. 1st ed. Wellington, New Zealand: New Zealand Guidelines Group (NZGG), Ministry of Health; 2009.

73. ANBCC. Recommendations for use of Trastuzumab (Herceptin®) for the treatment of HER2-positive breast cancer. 3rd ed. New South Wales, Australia: Australia National Breast Cancer Centre; 2007.

74. NICE. Trastuzumab for the adjuvant treatment of early-stage HER2-positive breast cancer. . Available: http://www.nice.org.uk/guidance/TA107. 2007, Updated:June 2007, Accessed:2014, 06/26.

75. GLOBOCAN 2012. Breast Cancer, Estimated Incidence, Mortality and Prevalence Worldwide in 2012. . Available: http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx. 2016, Accessed:2016, 05/07.

76. Ansaripour A, Uyl-de Groot CA, Foroozanfar M, Rahimimoghadam S, Redekop WK. Which is more important for doctors in a middle-income country, a national guideline or the medical literature? An adherence survey of trastuzumab use for breast cancer in Iran. Journal of Cancer Policy. 2016;8: 8-13. doi: https://doi.org/10.1016/j.jcpo.2016.05.005.

77. Cazap E, Magrath I, Kingham TP, Elzawawy A. Structural Barriers to Diagnosis and Treatment of Cancer in Low- and Middle-Income Countries: The Urgent Need for Scaling Up. . 2016;34: 14-19. doi: 10.1200/JCO.2015.61.9189.

78. Waning B, Kaplan W, King AC, Lawrence DA, Leufkens HG, Fox MP. Global strategies to reduce the price of antiretroviral medicines: evidence from transactional databases. . 2009;87: 485-564.

79. Prashant Yadav. Differential Pricing for Pharmaceuticals - Review of current knowledge, new findings and ideas for action. The U K Department for International Development,. 2010;London.

80. Kaló Z, Alabbadi I, Al Ahdab OG, Alowayesh M, Elmahdawy M, Al-Saggabi A, et al. Implications of external price referencing of pharmaceuticals in Middle East countries. . 2015;15: 993-998. doi: 10.1586/14737167.2015.1048227.

81. Ansaripour A, Franken M, Uyl-de Groot C, Kalo Z, Redekop WK. Is External Reference Pricing A Threat to International Equal Affordability? Value in Health. 2016;19: A759-A760. doi: 10.1016/j.jval.2016.09.2359.

82. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the Economic Evaluation of Health Care Programmes. Fourth ed. New York, United State: Oxford University Press; 2015.

83. Larose DT. Hierarchical and k-Means Clustering. In: Anonymous Discovering Knowledge in Data. : John Wiley & Sons, Inc.; 2004. pp. 147-162.

84. Freitas AA. Data mining and knowledge discovery with evolutionary algorithms: Springer Science & Business Media; 2013.

85. Larose DT. Association Rules. In: Anonymous Discovering Knowledge in Data. : John Wiley & Sons, Inc.; 2004. pp. 180-199.

86. The Official Gazette of the Islamic Republic of Iran. Healthcare services tariffs in private sector. . Available: http://www.rrk.ir/Laws/, Updated:15/07/2016, Accessed:2016, May 20.

87. Iranian Government. Determination of diagnostic and therapeutic services in the public and the private sector2 in 2013-2014 (1392 Persian calendar). Cabinet Decree. 2013;63883.

88. Montserrat Vera-Llonch, Derek Weycker, Andrew Glass, Sue Gao, Rohit Borker, Angie Qin, et al. Healthcare costs in women with metastatic breast cancer receiving chemotherapy as their principal treatment modality. BMC Cancer. 2011;11: 250. doi: https://dx.doi.org/10.1186/1471-2407-11-250.

89. Pivot X, Romieu G, Debled M, Pierga J, Kerbrat P, Bachelot T, et al. 6 months versus 12 months of adjuvant trastuzumab for patients with HER2-positive early breast cancer (PHARE): a randomised phase 3 trial. The Lancet Oncology. 2013;14: 741-748. doi: http://dx.doi.org/10.1016/S1470-2045(13)70225-0.

90. Paik S, Bryant J, Tan-Chiu E, Yothers G, Park C, Wickerham DL, et al. HER2 and Choice of Adjuvant Chemotherapy for Invasive Breast Cancer: National Surgical Adjuvant Breast and Bowel Project Protocol B-15. Journal of the National Cancer Institute. 2000;92: 1991-1998. doi: 10.1093/jnci/92.24.1991.

91. Asadzadeh Vostakolaei F, J. M. Broeders M, Rostami N, A. A. M. vanDijck, J., Feuth T, A. L. M. Kiemeney, L., et al. Age at Diagnosis and Breast Cancer Survival in Iran. International Journal of Breast Cancer. 2012. doi: 10.1155/2012/517976.

92. Jazayeri SB, Saadat S, Ramezani R, Kaviani A. Incidence of primary breast cancer in Iran: Ten-year national cancer registry data report. ;39: 519-527. doi: 10.1016/j.canep.2015.04.016.

93. Parsa M, Aramesh K, Nedjat S, Kandi MJ, Larijani B. Informal Payments for Health Care in Iran: Results of a Qualitative Study. Iranian Journal of Public Health. 2014;44: 79-88. PMID: 26060779.

94. A news report. Physicions' private office closure for three months as a punishment for receiving under-the-table payment. . Available: https://goo.gl/EM91tP. 2016, Updated:11/05/2016, Accessed:2016, June/03.

95. Goldhirsch A, Gelber RD, Piccart-Gebhart M, de Azambuja E, Procter M, Suter TM, et al. 2 years versus 1 year of adjuvant trastuzumab for HER2-positive breast cancer (HERA): an open-label, randomised controlled trial. The Lancet;382: 1021-1028. doi: http://dx.doi.org/10.1016/S0140-6736(13)61094-6.

96. Ansaripour A, Zendehdel K, Tadayon N, Sadeghi F, Uyl-de Groot C, Redekop WK. Use of Data-Mining to Perform a Real World Cost Analysis of Her2-Positive Breast Cancer In Iran. . 2016;19: A355. doi: 10.1016/j.jval.2016.09.052.

97. Vostakolaei FA, Broeders MJM, Rostami N, van Dijck JAAM, Feuth T, Kiemeney LALM, et al. Age at Diagnosis and Breast Cancer Survival in Iran. International Journal of Breast Cancer. 2012;2012: 8.

98. Rezaianzadeh A, Heydari ST, Hosseini H, Haghdoost AA, Barooti E, Lankarani KB. Prevalence of Breast Cancer in a Defined Population of Iran. . 2011;13: 647-650.

99. Haghighat S, Akbari ME, Ghaffari S, Yavari P. Standardized Breast Cancer Mortality Rate Compared to the General Female Population of Iran. . 2012;13: 5525-5528.

100. Gianni L, Dafni U, Gelber RD, Azambuja E, Muehlbauer S, Goldhirsch A, et al. Treatment with trastuzumab for 1 year after adjuvant chemotherapy in patients with HER2-positive early breast cancer: a 4-year follow-up of a randomised controlled trial. . 2011;12: 236-244. doi: http://dx.doi.org/10.1016/S1470-2045(11)70033-X.

101. Untch M, Gelber RD, Jackisch C, Procter M, Baselga J, Bell R, et al. Estimating the magnitude of trastuzumab effects within patient subgroups in the HERA trial. Annals of Oncology. 2008;19: 1090-1096. doi: 10.1093/annonc/mdn005.

102. Piccart-Gebhart M, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I, et al. Trastuzumab after Adjuvant Chemotherapy in HER2-Positive Breast Cancer. N Engl J Med. 2005;353: 1659-1672. doi: 10.1056/NEJMoa052306.

103. Tanis E, van de Velde CJH, Bartelink H, van de Vijver MJ, Putter H, van der Hage JA. Locoregional recurrence after breast-conserving therapy remains an independent prognostic factor even after an event free interval of 10 years in early stage breast cancer. Eur J Cancer. 2012;48: 1751-1756. doi: http://dx.doi.org/10.1016/j.ejca.2012.02.051.

104. Suter TM, Procter M, van Veldhuisen DJ, Muscholl M, Bergh J, Carlomagno C, et al. Trastuzumab-Associated Cardiac Adverse Effects in the Herceptin Adjuvant Trial. Journal of Clinical Oncology. 2007;25: 3859-3865. doi: 10.1200/JCO.2006.09.1611.

105. Talaei M, Sarrafzadegan N, Sadeghi M, Oveisgharan S, Marshall T, Thomas GN, et al. Incidence of Cardiovascular Diseases in an Iranian Population: The Isfahan Cohort Study. . 2013;16: 138-144.

106. Metzger-Filho O, Sun Z, Viale G, Price KN, Crivellari D, Snyder RD, et al. Patterns of Recurrence and Outcome According to Breast Cancer Subtypes in Lymph Node–Negative Disease: Results From International Breast Cancer Study Group Trials VIII and IX. Journal of Clinical Oncology. 2013;31: 3083-3090. doi: 10.1200/JCO.2012.46.1574.

107. National Organization for Civil Registration. Age-specific mortality rate regarding gender in rural and urban areas. . Available: https://www.sabteahval.ir/Upload/Modules/Contents/asset99/fg93.pdf. 2015, Updated:2015, Accessed:2015, 10/07.

108. Dawood S, Broglio K, Buzdar AU, Hortobagyi GN, Giordano SH. Prognosis of Women With Metastatic Breast Cancer by HER2 Status and Trastuzumab Treatment: An Institutional-Based Review. . 2009;28: 92-98. doi: 10.1200/JCO.2008.19.9844.

109. Niwinska A, Murawska M, Pogoda K. Breast cancer brain metastases: differences in survival depending on biological subtype, RPA RTOG prognostic class and systemic treatment after whole-brain radiotherapy (WBRT). Annals of Oncology. 2010;21: 942-948. doi: 10.1093/annonc/mdp407.

110. Lidgren M, Wilking N, Jonsson B, Rehnberg C. Health related quality of life in different states of breast cancer. . 2007;16: 1073-1081. doi: 10.1007/s11136-007-9202-8.

111. Calvert MJ, Freemantle N, Cleland JGF. The impact of chronic heart failure on health-related quality of life data acquired in the baseline phase of the CARE-HF study. . 2005;7: 243-251. doi: 10.1016/j.ejheart.2005.01.012.

112. The Official Gazette of the Islamic Republic of Iran. Healthcare services tariffs in public and private sectors. . Available: http://www.rrk.ir/Laws/. 2017, Accessed:2017, July/03.

113. SSO. Drug list. . Available: http://www.darman.tamin.ir/Forms/Public/Druglist.aspx?pagename=hdpDrugList. 2015, Updated:25.10.2015, Accessed:2015, 25.10.2015.

114. WHO. Choosing interventions that are cost-effective. . Available: http://www.who.int/choice/en/. 2015, Accessed:2015, Oct 20.

115. Briggs A, Fenn P. Confidence intervals or surfaces? Uncertainty on the cost-effectiveness plane. Health Econ. 1998;7: 723-740. doi: 10.1002/(SICI)1099-1050(199812)7:83.0.CO;2-O.

116. Halpern EF, Weinstein MC, Hunink MGM, Gazelle GS. Representing both first- and second-order uncertainties by Monte Carlo simulation for groups of patients. Medical Decision Making. 2000;20: 314-322. doi: 10.1177/0272989X0002000308.

117. CBI. History of exchange rate. . Available: http://www.cbi.ir/nonRefExRates/nonRefRates_fa.aspx. 2016, Updated:18/02/2016, Accessed:2016, 02/18.

118. The World Bank. GDP per capita (current US$). . Available: http://data.worldbank.org/indicator/NY.GDP.PCAP.CD. 2015, Accessed:2015, 10/20.

119. R Core Team (2015). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL: http://www.R-project.org/.

120. Joensuu H, Kellokumpu-Lehtinen P, Bono P, Alanko T, Kataja V, Asola R, et al. Adjuvant Docetaxel or Vinorelbine with or without Trastuzumab for Breast Cancer. N Engl J Med. 2006;354: 809-820. doi: 10.1056/NEJMoa053028.

121. U.S. National Institutes of Health. A Randomized Phase III Study Comparing Trastuzumab Plus Docetaxel (HT) Followed by 5-FU, Epirubicin, and Cyclophosphamide (FEC) to the Same Regimen Followed by Single-Agent Trastuzumab as Adjuvant Treatments for Early Breast Cancer. . Available: https://clinicaltrials.gov/ct2/show/NCT00593697. 2015, Accessed:2016, June 20.

122. Guarneri V, Frassoldati A, Bruzzi P, D'Amico R, Belfiglio M, Molino A, et al. Multicentric, Randomized Phase III Trial of Two Different Adjuvant Chemotherapy Regimens plus Three Versus Twelve Months of Trastuzumab in Patients with HER2-Positive Breast Cancer (Short-HER Trial; NCT00629278). . 2008;8: 453-456. doi: http://dx.doi.org/10.3816/CBC.2008.n.056.

123. Cancer Research UK. A trial comparing 6 months and 12 months of trastuzumab (Herceptin) for early breast cancer (PERSEPHONE). . Available: http://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-comparing-6-months-and-12-months-of-trastuzumab-for-early-breast-cancer. 2015, Accessed:2016, June 20.

124. Aboutorabi A, Hadian M, Ghaderi H, Salehi M, Ghiasipour M. Cost-Effectiveness Analysis of Trastuzumab in the Adjuvant Treatment for Early Breast Cancer. . 2015;7: 98-106.

125. SSO. Price of trastuzumab 150 mg and 440 mg vials in Iran. . Available: http://darman.tamin.ir/Forms/DrugStore/DrugLstLocal.aspx?pagename=hdpDrugLstLocal. 2016, Updated:12/01/2016, Accessed:2016, 01/12.

126. Chen W, Jiang Z, Shao Z, Sun Q, Shen K. An Economic Evaluation of Adjuvant Trastuzumab Therapy in HER2-Positive Early Breast Cancer. . 2009;12: S82-S84. doi: 10.1111/j.1524-4733.2009.00634.x.

127. Kurian AW, Thompson RN, Gaw AF, Arai S, Ortiz R, Garber AM. A Cost-Effectiveness Analysis of Adjuvant Trastuzumab Regimens in Early HER2/neu–Positive Breast Cancer. . 2007;25: 634-641. doi: 10.1200/JCO.2006.06.3081.

128. Garrison LP, Lubeck D, Lalla D, Paton V, Dueck A, Perez EA. Cost-effectiveness analysis of trastuzumab in the adjuvant setting for treatment of HER2-positive breast cancer. Cancer. 2007;110: 489-498. doi: 10.1002/cncr.22806.

129. Van Vlaenderen I, Canon JL, Cocquyt V, Jerusalem G, Machiels JP, Neven P, et al. Trastuzumab treatment of early stage breast cancer is cost-effective from the perspective of the Belgian health care authorities. Acta Clin Belg. 2009;64: 100-112. doi: 10.1179/acb.2009.019.

130. Millar JA, Millward MJ. Cost Effectiveness of Trastuzumab in the Adjuvant Treatment of Early Breast Cancer : A Lifetime Model. Pharmacoeconomics. 2007;25: 429.

131. Buendía JA, Vallejos C, Pichón-Rivière A. An economic evaluation of trastuzumab as adjuvant treatment of early HER2-positive breast cancer patients in Colombia. . 2013;33: 411-417.

132. Cameron D, Piccart-Gebhart M, Gelber RD, Procter M, Goldhirsch A, de Azambuja E, et al. 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. . 2017;389: 1195-1205. doi: 10.1016/S0140-6736(16)32616-2.

133. Leung W, Kvizhinadze G, Nair N, Blakely T. Adjuvant Trastuzumab in HER2-Positive Early Breast Cancer by Age and Hormone Receptor Status: A Cost-Utility Analysis. PLOS Medicine. 2016;13: e1002067.

134. Ansaripour A, Uyl-de Groot C, Redekop WK. Adjuvant trastuzumab therapy for early HER2-positive breast cancer in Iran. A cost-effectiveness and scenario analysis for an optimal treatment strategy. PharmacoEconomics. 2018;36: 91-103. doi: https://doi.org/10.1007/s40273-017-0557-6.

135. van Haalen, H. G. M., Severens JL, Tran-Duy A, Boonen A. How to Select the Right Cost-Effectiveness Model? Pharmacoeconomics. 2014;32: 429-442. doi: 10.1007/s40273-014-0139-9.

136. Welte R, Feenstra T, Jager H, Leidl R. A Decision Chart for Assessing and Improving the Transferability of Economic Evaluation Results Between Countries. Pharmacoeconomics. 2004;22: 857-876. doi: 10.2165/00019053-200422130-00004.

137. The World Bank. Life expectancy at birth, female (years). . Available: http://data.worldbank.org/indicator/SP.DYN.LE00.FE.IN?locations=IR, Accessed:2017, Feb 6.

138. European Health & Life Expectancy Information System. Age-specific life expectancy in European countries. . Available: http://www.eurohex.eu/ehleis/IS/web/app.php/Ehleis/LifeGeographic?Typ=Life&SubTyp=None, EurOhex, Accessed:2016, Feb 6.

139. USA Social Security. Period Life Table, 2013. . Available: https://www.ssa.gov/oact/STATS/table4c6.html, Updated:2016, Accessed:2016, Dec 20.

140. Macedo A, Monteiro I, Andrade S, Cirrincione A, Ray J. Cost-effectiveness of trastuzumab in the treatment of early stages breast cancer patients, in Portugal. Acta Med Port. 2010;23: 475-482.

141. Redekop WK, Orlewska E, Maciejewski P, Rutten FFH, Niessen LW. Costs and effects of secondary prevention with perindopril in stable coronary heart disease in Poland: An analysis of the EUROPA study including 1251 Polish patients. Pharmacoeconomics. 2008;26: 861-877. doi: 10.2165/00019053-200826100-00006.

142. Luengo-Fernandez R, Leal J, Gray A, Sullivan R. Economic burden of cancer across the European Union: a population-based cost analysis. . 2013;14: 1165-1174. doi: 10.1016/S1470-2045(13)70442-X.

143. WHO. Constitution of WHO: principles. . Available: http://www.who.int/about/mission/en/. 1948, Updated:7 April 1948, Accessed:2016, 05/20.

144. Toumi M, Rémuzat C, Vataire A, Urbinati D. External reference pricing of medicinal products: simulation- based considerations for cross country coordination. Final report. . 2014.

145. WHO. WHO Model List of Essential Medicines. 19th list. . Available: who.int/selection_medicines/committees/expert/20/EML_2015_FINAL_amended_AUG2015.pdf?ua=1. 2015, Updated:April 2015.

146. COFPO. Trastuzumab 150 mg price in Spain. . Available: http://www.cofpo.org/index.php/medic-es.html?id=13813. 2016, Updated:09/02/2016, Accessed:2016, 03/02.

147. ANVISA. Trastuzumab 150 mg price in Brazil . . Available: http://portal.anvisa.gov.br/wps/wcm/connect/d3042d804aa6f0c3a1c5b7218f91a449/LISTA+CONFORMIDADE_2015-11-20.pdf?MOD=AJPERES. 2015, Updated:20/11/2015, Accessed:2016, 01/10.

148. Lægemiddelstyrelsen. Trastuzumab 150 mg price in Denmark. . Available: http://www.medicinpriser.dk/Default.aspx?id=15&vnr=573477. 2016, Updated:03/28/2016, Accessed:2016, 01/2016.

149. Γαληνός. Trastuzumab 150 mg price in Greece. . Available: http://www.galinos.gr/web/drugs/main/packages/2187. 2016, Updated:02/15/2016, Accessed:2016, 03/20.

150. CEDD. Trastuzumab 150 mg price in Hungary. . Available: http://cedd.oep.hu/drugs.tib?s=drug-database&mode=country&f=cedddrug1&id=8lkdbdqvvfg2glq8&portallang=en&HU_currentletter=HE&actualcountry=HU&validity=20100302&opage=0, Accessed:2016, 01/10.

151. AIFA. Trastuzumab 150 mg price in Italy. . Available: http://www.agenziafarmaco.gov.it/sites/default/files/111.84470.1172743348645ce4c.pdf. 2007, Updated:09/02/2007, Accessed:2016, 01/10.

152. OMoH. Trastuzumab 150 mg price in Oman. . Available: https://www.moh.gov.om/en/web/dgpadc/resources. 2016, Updated:02/03/2016, Accessed:2016, 03/12.

153. Medycyna Praktyczna. Trastuzumab 150 mg price in Poland. . Available: http://bazalekow.mp.pl/lek/52525,Herceptin-proszek-do-sporzadzania-koncentratu-roztworu-do-infuzji. 2016, Updated:01/5/2016, Accessed:2016, 01/10.

154. Saudi Drug Database. Trastuzumab 150 mg price in Saudia Arabia. . Available: http://nassersite.com/drugdb/view.php?id=2746. 2016, Accessed:2016, 01/10.

155. Tandvårds- och läkemedelsförmånsverket. Trastuzumab 150 mg price in Sweden. . Available: http://www.tlv.se/beslut/sok/lakemedel/. 2016, Accessed:2016, 02/12.

156. ZIN. Trastuzumab 150 mg price in the Netherlands. . Available: http://www.medicijnkosten.nl/. 2016, Updated:10/01/2016, Accessed:2016, 01/10.

157. Central Pharmacy of Tunisia. Trastuzumab 150 mg price in Tunisia . . Available: http://www.phct.com.tn/index.php?option=com_searchproduct&view=searchproduct&layout=result&Itemid=48&lang=en#b. 2015, Updated:28/12/2015, Accessed:2016, 01/10.

158. onlinepharmacyteam. Trastuzumab 150 mg price in the USA. . Available: http://onlinepharmacyteam.com/herceptin_150_mg_1_flacon_online_pharmacy.html. 2016, Accessed:2016, 02/15.

159. Medicare and Medicaid. Trastuzumab price per 10 mg in the USA. . Available: https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/2015ASPFiles.html. 2016.

160. OANDA. Yearly average exchange rate in 2015. . Available: https://www.oanda.com/currency/average. 2016, Updated:26/04/2016, Accessed:2016, 04/26.

161. Slamon D, Clark G, Wong S, Levin W, Ullrich A, McGuire W. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science. 1987;235: 177-182. doi: 10.1126/science.3798106.

162. Slamon D, Godolphin W, Jones L, Holt J, Wong S, Keith D, et al. Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. Science. 1989;244: 707-712. doi: 10.1126/science.2470152.

163. Fonseca M, Araujo GT, Saad ED. Cost-effectiveness of anastrozole, in comparison with tamoxifen, in the adjuvant treatment of early breast cancer in Brazil. Rev Assoc Med Bras. 2009;55. doi: 10.1590/S0104-42302009000400015.

164. The World Bank. PPP conversion factor, GDP (LUC international $) . . Available: http://data.worldbank.org/indicator/PA.NUS.PPP. 2015, Accessed:2015, 12/02.

165. Ramsey FP. A contribution to the theory of taxation. . 1927;37: 47-61.

166. Danzon PM, Towse A. Differential pricing for pharmaceuticals: reconciling access, R&D and patents. . 2003;3: 183-205.

167. The World Bank. Population, total. . Available: http://data.worldbank.org/indicator/SP.POP.TOTL. 2015, Updated:Dec 2015.

168. The World Bank. GDP per capita, PPP (current international $). . Available: http://data.worldbank.org/indicator/NY.GDP.PCAP.PP.CD. 2017, Updated:27 May 2017.

169. The World Bank. Health expenditure, total (% of GDP). . Available: http://data.worldbank.org/indicator/SH.XPD.TOTL.ZS. c2016, Updated:2016.

170. The World Bank. World Bank Country Classification. http://data.worldbank.org/about/country-classifications]. . Available: http://data.worldbank.org/about/country-classifications. 2017, Updated:Jan 2017. Available: http://data.worldbank.org/about/country-classifications.

171. Elek P, Takács E, Merész G, Kaló Z. Implication of external price referencing and parallel trade on pharmaceutical expenditure: indirect evidence from lower-income European countries. Health Policy and Planning. 2016;32: 349-358. doi: http://dx.doi.org/10.1093/heapol/czw133.

172. Balabanova D, McKee M. Understanding informal payments for health care: the example of Bulgaria. Health Policy. 2002;62: 243-273. doi: https://doi.org/10.1016/S0168-8510(02)00035-0.

173. Espin J, Rovira J, Calleja A, Azzopardi-Muscat N, Richardson E, Palm W, et al. How can voluntary cross-border collaboration in public procurement improve access to health technologies in Europe? Policy Brief 21. . 2017.

174. Neumann PJ, Chambers JD, Simon F, Meckley LM. Risk-Sharing Arrangements That Link Payment For Drugs To Health Outcomes Are Proving Hard To Implement. Health Affairs. 2011;30: 2329-2337. doi: 10.1377/hlthaff.2010.1147.

175. Garrison Jr. LP, Towse A, Briggs A, de Pouvourville G, Grueger J, Mohr PE, et al. Performance-Based Risk-Sharing Arrangements—Good Practices for Design, Implementation, and Evaluation: Report of the ISPOR Good Practices for Performance-Based Risk-Sharing Arrangements Task Force. . 2013;16: 703-719. doi: https://doi.org/10.1016/j.jval.2013.04.011.

176. SSO. Medicine price list. . Available: http://darman.sso.ir/. 2016, Updated:15/02/2016, Accessed:2016, 02/15.

177. Kruk ME, Porignon D, Rockers PC, Van Lerberghe W. The contribution of primary care to health and health systems in low- and middle-income countries: A critical review of major primary care initiatives. Social Science & Medicine. 2010;70: 904-911. doi: http://dx.doi.org/10.1016/j.socscimed.2009.11.025.

178. Hill T, Westbrook R. SWOT analysis: It's time for a product recall. Long Range Planning. 1997;30: 46-52. doi: http://dx.doi.org/10.1016/S0024-6301(96)00095-7.

179. FDO. Pharmaceutical pricing in Iran. . Available: http://www.fda.gov.ir/item/1369. 2015, Updated:14/10/2015, Accessed:2016, 02/18.

180. Islamic Parliament of Iran. Law amending some provisions of law relating to medical, pharmaceutical and food and beverage products affairs. Adopted in 1955. . Available: http://www.dastour.ir/Print/?lid=131304. 1988, Accessed:2016, 03/10.

181. [Anonymous]. Directive 2013/50/EU of the European parliament and of the council. . Available: http://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX:32013L0050. 2013, Updated:Oct 22.

182. Jönsson B, Ramsey S, Wilking N. Cost effectiveness in practice and its effect on clinical outcomes. Journal of Cancer Policy. 2014;2: 12-21. doi: https://doi.org/10.1016/j.jcpo.2014.02.001.

183. Mohseninejad L, van Gils C, Uyl-de Groot CA, Buskens E, Feenstra T. Evaluation of Patient Registries Supporting Reimbursement Decisions: The Case of Oxaliplatin for Treatment of Stage III Colon Cancer. . 2015;18: 84-90. doi: http://doi.org/10.1016/j.jval.2014.10.008.

184. Gliklich R, Dreyer N, Leavy M,. Registries for Evaluating Patient Outcomes: A User's Guide. Volume 1. Third ed. Rockville, MD, USA: Agency for Healthcare Research and Quality; 2014.

185. Anbari Z, Mohammadbeigi A, Mohammadsalehi N, Ebrazeh A. Health Expenditure and Catastrophic Costs for Inpatient- and Out-patient Care in Iran. . 2014;5: 1023-1028.

186. Islamic Republic News Agency. Dept of payers to healthcare providers in Khorasan Razavi. . Available: http://www.irna.ir/rkhorasan/fa/News/82360831/, IRNA, Updated:25 Dec 2016, Accessed:2017, June 05.

187. salmatonline. Payres have not paied insurance claims since six month ago. . Available: https://goo.gl/YrlB4a, Updated:June 5, 2017, Accessed:2017, June 5.

188. Bahadori M, Ravangard R, Alimohammadzadeh K, Hosseini SM. Plan and road map for health reform in Iran. BMJ. 2015;351. doi: 10.1136/bmj.h4407.

189. National Institute of Health Research. Objectives and components of the health reform plan. . Available: https://goo.gl/A36UeJ, Accessed:2017, June 5.

190. Heshmati B, Joulaei H. Iran's health-care system in transition. The Lancet. 2016;387: 29-30. doi: 10.1016/S0140-6736(15)01297-0.

191. Moradi-Lakeh M, Vosoogh-Moghaddam A. Health Sector Evolution Plan in Iran; Equity and Sustainability Concerns. . 2015;4: 637-640. doi: 10.15171/ijhpm.2015.160.

192. Lega F, Prenestini A, Spurgeon P. Is Management Essential to Improving the Performance and Sustainability of Health Care Systems and Organizations? A Systematic Review and a Roadmap for Future Studies. Value in Health. 2013;16: S46-S51. doi: https://doi.org/10.1016/j.jval.2012.10.004.

193. Mehrnews Agency. Conflict between ministries of Health and Welfare was pulled to the House floor. . Available: mehrnews.com/news/3868225/, Mehrnews Agency. 2017, Updated:5 Jan 2017, Accessed:2017, June 2017.

194. Independent Commission on Good Governance in Public Services. The Good Governance Standard for Public Services. 1st ed. London: Office for Public Management Ltd; 2004.

195. Carlson J. Paying for Outcomes: Innovative Coverage and Reimbursement Schemes for Pharmaceuticals. . 2009;15: 683-687. doi: 10.18553/jmcp.2009.15.8.683.

196. Adamski J, Godman B, Ofierska-Sujkowska G, OsiÅ„ska B, Herholz H, Wendykowska K, et al. Risk sharing arrangements for pharmaceuticals: potential considerations and recommendations for European payers. . 2010;10: 153-153. doi: 10.1186/1472-6963-10-153.

197. Kindig D, Stoddart G. What Is Population Health? Am J Public Health. 2002;93: 380-383.

198. Iwanczuk T, Zawodnik S, Hermanowski TR, Matusewicz W. PHP271 - Risk-Sharing Schemes In Poland - Analysis And Classification of Rss Proposed In Reimbursement Application Received by Ahtapol In 2013. . 2014;17: A449. doi: http://dx.doi.org/10.1016/j.jval.2014.08.1207.

199. Franken M, le Polain M, Cleemput I, Koopmanschap M. Similarities and differences between five European drug reimbursement systems. Int J Technol Assess Health Care. 2012;28: 349-357. doi: 10.1017/S0266462312000530.

200. Joseph K. Bismarck vs. Beveridge: is there increasing convergence between health financing systems? . 2011.

201. [Anonymous]. Health Care Systems - Four Basic Models. . Available: http://www.pnhp.org/resources/health-care-systems-four-basic-models.