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Pharmacoeconomic evaluation in Egypt and its role in the medicine reimbursement

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Abstract

Aim: The purpose of this research was to assess the validity of pharmacoeconomic evaluation in Egypt three years after the guideline was issued and analyse challenges and opportunities for improvement.

Objectives: To conduct a literature review of pricing, medicine reimbursement, and pharmacoeconomic evaluation. Examine, in conjunction with relevant stakeholders, the progress of the pharmacoeconomic evaluation. To present examples of pharmacoeconomic evaluation deployment. To propose recommendations on how to optimize the pharmacoeconomic implementation.

Methods: A literature review and a qualitative research method that was conducted using a semi-structured interview with stakeholders of the reimbursement process in Egypt. In addition, examples were analysed to determine the impact of pharmacoeconomic methods on medicine reimbursement in Egypt.

Results: The Egyptian Pharmacoeconomic Evaluation Unit was established in 2013, it supports various reimbursement decisions, especially for new technologies. The unit evaluations depended mainly on the available international data. However, fragmentation of the health care system in Egypt is a major obstacle to progress. The guidelines are still non-compulsory for implementation, and accordingly some reimbursement committees do not consider its evaluation in its decision making.

Conclusion and Recommendations: The pharmacoeconomic evaluation has demonstrated a good start in Egypt. To gain the full benefit of pharmacoeconomic evaluation, authorities need to consider reducing the complexity of health care system, setting clear strategies, building capabilities to improve pharmacoeconomic awareness; endorsing risk sharing strategy and building a proper health related information system along with creation of full Health Technology Assessment program. The above-mentioned recommendations could be associated together under the Universal Health Coverage road map that Egypt committed to achieve by 2030.

Keywords: Pharmacoeconomic Evaluation, Cost effectiveness analysis, Reimbursement decision making.

Declaration

I declare that this thesis that I now submit for assessment on the programme of study leading to the degree Master of Science in Pharmacy Administration and Policy Regulation has not been submitted for a degree at this or any other higher education institution. It is entirely my own work and has not been taken from the work of others, save the extent that such work has been cited and acknowledged within the text of my work.

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Signed……Mohamed Khalil…… *Dated…15 March 2018…..*

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List of Abbreviations

CAPA: Central Administration for Pharmaceutical Affairs

CBA: Cost-Benefit Analysis

CCO: Curative Cure Organization

CEA: Cost-Effectiveness Analysis

CUA: Cost-Utility Analysis

DALY: Disability-Adjusted Life Year

FHFs: Family Health Funds

GDP: Gross domestic product (final consumption + gross capital formation + net exports).

HIO: Health Insurance Organization

HTA: Health Technology Assessment

ISPOR: International Society for Pharmacoeconomics and Outcomes Research

MOHP: Ministry of Health and Population

OECD: The Organisation for Economic Co-operation and Development

PTES: Program for Treatment at the Expense of the State

QALY: Quality-Adjusted Life Year

SHI: Social Health Insurance

TDL: Tender Drug List

THIO: Teaching Hospitals and Institutes Organization

UHC: Universal Health Coverage

USA: United States of America

WHO: World Health Organization

1. Introduction

Economics is a social science, which deals with production, distribution and consumption of goods and services. There are different definitions of economics, Samuelson and Nordhaus (1998) defined economics as the study of how societies use scare resources to produce valuable commodities and distribute them among different people.

One branch of economics is health economics, which is concerned with issues related to the production and consumption of health and health care as defined by Vati and Sahib (2013). Under health economics is pharmacoeconomics which focuses on economic comparison between alternative pharmaceutical products and treatment strategies. The Canadian Agency for Drugs and Technologies in Health (2006) used the term "value for money" judgments to refer to such decisions.

The importance of health economics is highlighted by the fact that health care expenditure utilizes a considerable portion of countries Gross domestic product (GDP), WHO (2015) highlighted that the average global total expenditure of health accounted for 8.6% of the global GDP and that total expenditure on health per capita was 1173 USD for the year 2012.

A study on the pharmaceutical spend compared to heath care expenditure was conducted by The Organisation for Economic Co-operation and Development (OECD), and revealed that, the pharmaceutical spend in 2013 accounted for about 20% of total health spending across the 35 OECD countries as highlighted by OECD (2015), and

reached around USD 800 billion. The data highlights the value of pharmacoeconomics to the entire health care system, as opposed to health economics as is stated in the thesis.

However, this direction reduced the incentives of developing new drugs; OECD (2015) noted this impact and encouraged the healthcare policy makers to balance the access of patients to new effective medicines with the limited health care budgets, while providing the right incentives to manufacturers to develop new generations of drugs.

This thesis focused on the pharmacoeconomic aspects of Egypt as a representative of Africa/Middle East/developing countries. The health statistics of Egypt showed some interesting specificities, where pharmaceutical spend was 34.20% percentage of the total health expenditure as reported by Ministry of Health Egypt (2011). This is far higher than the previously mentioned percentage across OECD countries (20%), and in consequence highlighted the value of pharmacoeconomics in relation to health economics/overall economics of Egypt.

In 2013, the Egyptian Drug Authority created a Pharmacoeconomic unit with the aim of understanding the costs compared to the outcomes of pharmaceutical products. The newly created unit started a pharmacoeconomic evaluation program that implemented the first pharmacoeconomic guideline model in the middle-east region in the same year.

Aim of this thesis was:

- To assess the validity of pharmacoeconomic evaluation in Egypt, three years after the guideline were issued and analysed the challenges and opportunities for improvement.

The objectives of this thesis were to:

- Conduct a literature review of medicine pricing, medicine reimbursement, and pharmacoeconomic evaluation in Egypt with comparison to the global picture.
- Review the pharmacoeconomic evaluation program in Egypt with various stakeholders to define how far the program progressed
- Present examples of how the different pharmacoeconomic evaluation models in Egypt impacted on medicine reimbursement.
- Propose recommendations on how to optimize the pharmacoeconomic implementation in Egypt.

2. Review of medicine pricing, medicine reimbursement, and pharmacoeconomic evaluation in Egypt.

2.1 Global health economics overview

There is a link between health care spend and economic growth, Velenyi (2016) summarized this relationship as a directly proportional one, where more efficient and strategic spending could lead to better health outcomes, and in parallel improved population health status could act as an economic growth multiplier.

Comparison of the health care spending to GDP showed an interesting phenomenon as analysed by Drouin, Hediger and Henke (2008) where for almost 50 years, health care spending has grown by 2 percentage points more than GDP growth across 35 countries that membered the Organisation for Economic Cooperation and Development (OECD). With such a trend, most OECD countries would spend a fifth of their GDP on health care by 2050. The above trend obliged policy makers to start acknowledging the value of optimization of health care expenditure.

2.2 Egypt health economics overview

Fantom and Serajuddin (2016) mentioned the classification of The World Bank to Egypt's economy as a low-middle income economy. Egypt's economic indicators show challenges when linked to health care financing. Pande et al. (2013) showed that although total health care expenditure of Egypt is equivalent to the average expenditure of the world's low-middle income economies and that of the countries in the Middle East North Africa region. Nevertheless, the figures from Egypt were the least for governmental expenditure and the uppermost for out-of-pocket spending which is the private expenditure on health.

Nakhimovsky *et al.* (2011) analysed the out-of-pocket trend in Egypt and found that the private expenditure on health was 71.8% for 2008/2009. This was considered a large increase compared to the 60% spending of previous years.

Looking at the total expenditure on health as percentage of GDP in Egypt, the World Health Organisation (WHO) in 2015 showed a negative trend from 5.4% in the year

2000 to 4.9% in 2012, which is contrary to the average percentage of all other WHO regions/income groups. They showed an increase in the total expenditure on health as percentage of GDP for the same period, that resulted in an increase of the global overall average from 2000 (7.7%) to 2012 (8.6%).

The above analysis of Egypt's total health expenditure, out of pocket spend accompanied by around 26.3% of Egyptians living below the poverty line and 13.2% unemployment rate, showed how much the health care system in Egypt is challenged for reaching the Universal Health Coverage (UHC), which is one of the United Nations sustainable development goals, that all UN Member States have agreed to try to achieve universal health coverage by 2030. Because of healthcare constraints facing Egypt, the access to new health technologies has become more challenging than in other countries.

2.3 ***Healthcare systems Categorization:***

Healthcare systems can be categorized into various categories based on the type of health insurance. Anan (2014) summarized such categories into:

- Traditional sickness insurance: Fundamentally a private insurance market approach with state support (e.g., Germany)
- National health insurance: National-level health insurance system (e.g., Canada, Finland, Norway, Spain and Sweden)
- National health services: State provides the healthcare (e.g., Denmark, Greece, Italy, New Zealand, Portugal, Turkey and the United Kingdom)

- Mixed systems: Contain elements of both traditional sickness insurance and national health coverage (e.g., Switzerland and the United States)

In the following sections, when discussing the global overview, countries that cover more than one category will be represented to provide a good overview of various health care systems.

Anan (2014) highlighted that Egypt started as a national health service in the 1950s, but is now considered as a mixed system. However, Egypt's national health is complex by nature and fragmented with more than one financing agent.

The World Bank (2015) highlighted the four key financing players in Egypt's health care viz., Social Health Insurance (SHI), Ministry of Health and Population (MOHP), Program for Treatment at the Expense of the State (PTES), and Family Health Funds (FHFs). Each has its own coverage/health service package. The mentioned agencies were designed to complement each other; nevertheless, such fragmentation brought more complexity into the overall picture with more scattered patient/disease information and less integration between such entities.

2.4 Methodologies used in economic evaluation and pharmacoeconomics

Economic evaluation is considered the core of assessing health technologies. The outcome of such evaluation will highlight the efficiency of various alternatives under assessment, and accordingly could guide policy makers to decide on the available

alternatives. The most important methodologies for economic evaluation are highlighted below, along with their advantages and disadvantages from the policy maker perspective.

2.4.1 Cost-benefit analysis:

Cost-benefit analysis is used to evaluate and compare different projects and products. It measures the benefits and cost of each available project in monetary terms in addition it considers all the periods during which the project will last. The concept of the analysis/decision explained by Svensson, M. and Hultkrantz, L. (2017) that if the net present value of the benefits outweighs the costs the investment is said to increase social welfare. This means that social benefits obtained from the project will be greater than social monetary costs, accordingly project prioritized based on the ratio of benefits to costs.

Cost-Benefit Analysis (CBA) = B/C, where B represent the total monetary benefit and C represents the total monetary cost. The key of this analysis is to get the proper measurement of costs and benefits in monetary terms; one of the difficulties that is considered as disadvantage, is measuring monetary terms especially for some costs and benefits that have no price e.g. measuring the benefits/costs of vaccination against flu.

Another disadvantage of cost-benefit analysis highlighted by Harrington, Heinzerling and Morgenstern (2009) was the fact that criteria of choice at CBA differs from that at policy makers; where CBA directs investment towards equity in terms of risk outcomes, policy makers' direct investment more towards equity in terms of the cost

per life saved. Accordingly, economists developed two approaches to provide the value for a human life, the human capital approach and the approach of the willingness to pay for avoiding risks. Such approaches could support the measurement of benefits and monetary values.

However, difficulties of measurement and linking every aspect to monetary value lead to the development of another two approaches for economic evaluation that will be analysed below.

2.4.2 Cost effectiveness analysis:

Jamison *et al.* (2006) explained Cost Effectiveness Analysis (CEA) as a method for assessing the gains in health relative to the costs of different health interventions, with specificity of directly relating the financial and scientific implications of different interventions. It is limited when the aim of the project is clear, and its only goal is to find the best option between two alternatives. The two alternatives that shall be compared shall have their benefits in the same units (e.g. same unit of morbidity or health status). The analysis still needs to measure the costs in monetary terms.

The analysis compares the ratio of incremental costs to the incremental output as shown in the equation.

Incremental Cost Effectiveness Ratio *(ICER) = (C1 - C2) / (E1 - E2),* where C1= cost of the new treatment, C2= cost of existing treatment, E1=Health outcome of new treatment, & E2= Health outcome of existing treatment (e.g. number of events (strokes), number of cases detected, symptom free days, etc.).

WHO (2014) indicated three situations where policy makers could benefit from ICER, as follows: (i) when the health effect target is specified by policy makers and the aim of the cost effectiveness analysis is to minimize the expenditure needed to achieve that target; (ii) when a budget constraint is specified by policy makers and the aim is to maximize the health benefits while keeping expenditure within budget; and (iii) when policy makers have specified an explicit standard or threshold for what should be considered cost effective.

The CEA is a more practical approach than CBA, where it avoids the measuring of benefits in monetary terms; however the approach is still challenged. The two main challenges summarized by Goeree and Diaby (2013) was for occasionally measuring outcomes that are intermediate in nature with questionable impact on final patient outcomes, and the fact that it is difficult for decision-makers to compare CEA outcomes across diseases and interventions when making health care resource allocation decisions.

2.4.3 Cost utility analysis:

WHO (2003) explained Cost Utility Analysis (CUA) as the analysis used to determine cost in terms of utilities, especially quantity and quality of life. Unlike cost-benefit analysis, cost-utility analysis is used to compare two different drugs or procedures whose benefits may be different. The project is evaluated as a function of the incremental cost for each extra Quality-Adjusted Life Year (QALY) obtained for the patients.

QALY= ∑ Fi qi/(1+d)I, then (ICER) = (C1-C2)/(QALY1 – QALY 2), where C1= cost of the new treatment, C2= cost of existing treatment, QALY1= Quality-adjusted life year of new treatment, & QALY2= Quality-adjusted life year of existing treatment.

Utility could be considered as a health outcome and accordingly one type of CEA. However, some literature, (Jakubiak, and Jakubczyk, 2014; Nas, 2016) still considered a CUA to be unique because QALY usually combines various outcomes or impacts from a disease or intervention into a single health measure. Such speciality could then facilitate decision-maker comparisons across diseases or interventions.

Considering the above, CUA is the most favourable tool for Health Technology Assessment (HTA) for decision-makers, and most economic evaluations are based on measuring QALY. However, literature demonstrates some drawbacks/challenges from evaluating alternatives based on QALY. Whitehead and Ali (2010) highlighted the main challenge of QALY is being too reductionist, which reflect the inability of QALY to capture all benefits of an intervention, example of uncaptured benefits would be the impact of improvement in the health of a woman/man with children on the health of their children.

Another challenge linked to efficiency highlighted by Whitehead and Ali (2010), was the fact that QALY does not consider higher weights to those who contribute more to the society (i.e. more productive individuals, e.g. young adults), contrary to other health measures like Disability-Adjusted Life Year (DALY), which is an indicator of the

relative impact of illnesses and injuries on losses of healthy life years, that gives greater weight to a year lived by a young adult compared with a child or an elderly person.

Lastly, QALY does not consider higher weights to vulnerable populations such as children, those severely ill, and the socioeconomically disadvantaged which is against the concept of equity. Whitehead and Ali (2010) used the term equity-weighted QALY maximization to mention the need of decision-makers to reach distributional equity of health outcomes and target health care to disadvantaged groups, and mentioned that further research is required in this area before using such approach as norm in economic evaluation.

From the overview analysis conducted above on various economic evaluation tools, we can conclude that each analysis has its own limitation, having highest difficulties in measuring the CBA. As for CEA, there are limitations of generalizing CEA across the overall health care resources allocation. Such limitations, keep CUA the option of choice for economic evaluation, using DALY as the health measure. The DALY approach is commonly used for international comparisons of disease burden, and is frequently used by organizations such as the World Bank and WHO.

WHO (2014) mentioned the approach promoted by the organization for choosing interventions that are cost–effective. The report highlighted that interventions where the disability-adjusted life-year (DALY) avoided, costs less than three times the national annual GDP per capita, would be considered as cost-effective. whereas

intervention that costs less than one of the national annual GDP per capita, would be considered as highly cost–effective.

2.5 Medicine pricing:

Pharmaceutical prices are driven by supply and demand; however, market imperfections arise from both the supply and the demand sides. Ruggeri and Nolte (2013) detailed such imperfections in the supply side to be related to patent protection or regulatory approval processes. On the demand side, it includes various factors such as the prescribing physician, pharmacist, patient, and third party payers. In the sub-sections below the research will focus on the supply side and analyse the pricing strategies in some selected developed countries in addition to the pricing strategy in Egypt.

2.5.1 Medicine pricing strategy (example from developed countries):

Pharmaceutical pricing strategies differ from one jurisdiction to another. Ruggeri and Nolte (2013) analysed the approach by six high-income countries to pharmaceutical pricing and highlighted that price negotiation, external reference pricing, price-volume agreement as main strategies for innovative drugs, while having internal reference systems and a fixed portion of the originator price as strategies used mainly for generic drugs.

Health Technology Assessment (HTA) is another important strategy that is used by jurisdictions for deciding initial price and/or reimbursement status of innovative drugs. Compared to other pricing strategies, HTA is superior in getting value for

money in one hand, but on the other hand the HTA process itself is higher in cost. Drummond *et al.* (2010) worked on comparing the value of conducting HTA strategy over an internal reference pricing strategy by comparing 4 drug groups prices in 4 countries in Europe, the conclusion of the study showed that the most efficient approach for drug pricing might be a combination of both policies although the study is limited to only 4 countries/drug groups but this was the only literature that researched this aspect of medicine pricing strategy.

2.5.2 Medicine pricing strategy in Egypt:

In Egypt, the pharmaceutical pricing is mandatory and regulated by the health authorities. It has passed through various stages since it was initially legalised in 1960. Wanis (2014) summarised pricing into three stages over the years, started by cost-plus and mark up regulation, then external reference pricing that was introduced in 2009, and finally external reference pricing combined with mark-up regulation as of legislation in 2012.

The final legislation is detailed in the Ministry decree (499/2012) on the pricing of pharmaceutical drugs, which details the pricing system for innovative drugs and generic drugs. Under the decree, the price of innovative drugs would be set 10% lower than the cheapest consumer price of the drug in the countries in which it is currently available (Appended to the decree is a list of 36 countries that shall be consulted by the Ministry of Health).

The price of generic drugs would be set at a fixed percentage markdown of brand name drugs. The decree establishes three categories of generic drugs based on the certifications obtained by the manufacturers. The first category is products that shall be priced 30% lower than the brand medicine, which includes those drugs made by a facility that is licensed by the Egyptian Ministry of Health and certified by international agencies.

The second category is products that shall be priced 40% lower than the brand medicine, which includes those drugs made by facilities licensed by the Egyptian Ministry of Health and are not certified by other agencies.

The third category is products that shall be priced 60% lower than the brand medicine, which includes drugs owned by companies that have sub-contracted the license to manufacture the drug by a contract manufacturing organisation.

2.6 Global overview of pharmacoeconomic evaluation:

The first Jurisdiction to announce the requirement of economic evaluation for medicine was the Australian authorities in 1991, as mentioned by Drummond (2013). Since then, other jurisdictions followed Australia and required economic analyses in varying degrees. The various pharmacoeconomic guidelines/recommendations from different countries all over the globe is listed in the link: http://www.ispor.org/PEguidelines/index.asp. Analysing the listed jurisdictions indicates that economic evaluation of pharmaceutical medicines is required by at least 2 countries in each continent, with main domination of such regulations in Europe.

Drummond (2013) analysed the application of economic evaluation in drug reimbursement in several jurisdictions, and showed that some jurisdictions are in favour of economic evaluation of drugs but varied in their applications, ranging from countries like Denmark, Italy, Spain where there is consideration for ‘‘value for money’’ but with no requirement from manufacturers to submit economic evaluation, up to jurisdiction like Scotland that require all new drugs to be economically assessed. In between, there are some jurisdictions (like England, Portugal) that focus such evaluations towards drugs that are likely to have a major clinical or economic impact.

In contrast, Drummond (2013) mentioned jurisdictions that are not in favour of economic evaluation of drugs still varied in their applications, ranging from authorities that fully oppose the use of cost or cost effectiveness in denying access to medicine like the United States of America (USA), to countries like France & Germany that require only assessment of “added clinical benefit’’ of new drugs as basis of establishing the price.

However, further analysis, indicated that the economic evaluation in some opposing jurisdictions is still worth exploring. Sorenson *et al.* (2012) mentioned that interest has been shown by the USA private insurance sector in using the most cost effective medicine and in deciding the level of co-payment based on the value for money of drugs. Similarly, in Germany Nasser and Sawicki (2009) highlighted the additional role that the Institute for Quality and Efficiency in Health Care was given to develop

methods for cost benefit evaluation of drugs. This was to define a ceiling price and to further support competition between statutory health insurance providers.

The summary of this global overview showed that economic evaluation is becoming more prevalent due to direct regulations mandated by health authorities who are in favour of economic evaluation during drug submission and due to public/private health insurance reimbursement scheme design schemes.

2.7 Pharmacoeconomic evaluation in Egypt:

Until recently there was little literature on the pharmacoeconomic evaluation deployment in Egypt. Soliman, Hussein and Abdulhalim (2012) investigated the foundation of the pharmacoeconomic evaluation science and the status of pharmacoeconomics education in Egyptian schools of pharmacy. The research concluded that pharmacoeconomics education in Egypt was still in its infancy and highlighted the opportunity for talents to provide structured pharmacoeconomics education to student pharmacists, researchers, and stakeholders. With the aim to help the country establish an integrated scientific community to apply pharmacoeconomic evaluation to healthcare decision making.

In 2013, Egypt issued its first pharmacoeconomic evaluation guidelines; Elsisi *et al.* (2013) highlighted the intention of the guidelines to focus on pricing and/or reimbursement applications of pharmaceuticals. However, the contribution of pharmacoeconomic evaluation in medicine pricing in Egypt is considered nil. This finding could be explained from the existing pricing decree in Egypt (Decree

499/2012), as the decree relies on external reference pricing in addition to mark-up regulation with no reference of pharmacoeconomic evaluations. Such conflict in legislations, kept the contribution of pharmacoeconomic evaluation in medicine pricing minute, while it had maximum contribution in reimbursement applications.

2.8 Medicine Reimbursement process, global perspective:

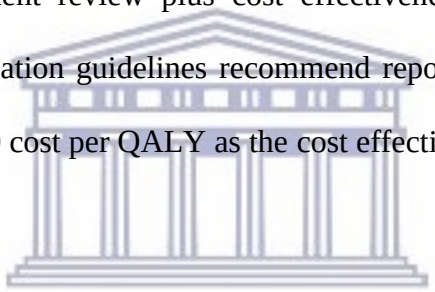
In 2014, Barnieh *et al.* conducted a review of medicine reimbursement process in all OECD countries

General analysis of the 35 formulary systems reviewed by Barnieh, *et al.* (2014) showed that 94% of the formulary systems reviewed have expert committees for the drug reimbursement decision-making process. Thirty-one of those expert committees either made recommendations to an agency (often the Ministry of Health or other government agency) that made the final decision regarding medicine listing or decide directly on the medicine reimbursement.

In addition, the review showed that 69% of the systems were not negotiating price at the reimbursement phase, while 31% of the systems were. Seventy one percent of the expert committees; which make recommendations/decisions, required submission of cost effectiveness. Lastly, 74% of the formulary systems had guidelines on how to prepare economic evaluations.

The research considered England and Germany from the Barnieh *et al.* (2014) review, as they both represent developed countries, and each of them has different health care systems. England represented the "national health services", while Germany represented the "traditional sickness insurance" health care system.

Focusing on England, Barnieh *et al.* (2014) reported that England had an expert committee for drug reimbursement who directly decides on the medicine reimbursement, and negotiate the prices during the reimbursement process. The reimbursement submission includes clinical evidence that could come from a manufacturer or independent review plus cost effectiveness which is mandatory. England's economic evaluation guidelines recommend reporting cost per QALY, as England considers £30,000 cost per QALY as the cost effectiveness threshold.



For Germany, Barnieh *et al.* (2014) reported that Germany had an expert committee for drug reimbursement that made recommendations to the Ministry of Health, who made the final decision regarding medicine listing. No price negotiation is conducted at the reimbursement process in Germany, the reimbursement submission requires clinical evidence that would be come from manufacturer only. While cost-effectiveness was not mandatory, Germany still issued economic evaluation guidelines.

The global overview of the medicine reimbursement showed that there is no single model that developing countries could replicate, and that although pharmacoeconomic evaluation is useful to conduct at medicine reimbursement, each health care system could still decide the setup which would be more appropriate for its specificity.

2.9 Medicine Reimbursement process in Egypt:

The research examined the medicine reimbursement process in Egypt and we have illustrated a summary of the reimbursement process in a flow diagram in Figure 1 below.

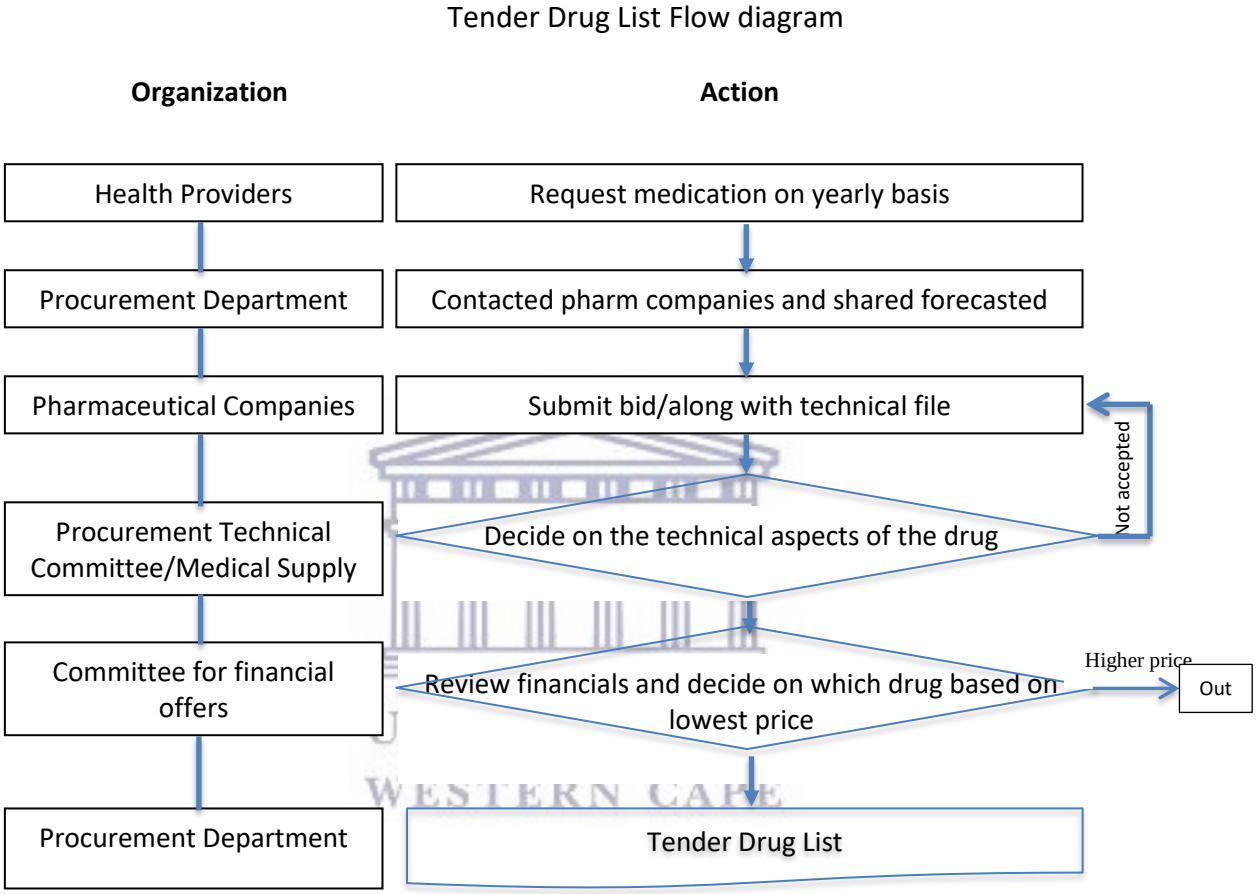


Figure 1 Process flow of Tender Drug List (TDL) for drug reimbursement in Egypt, the flow is similar for the issuance of the 3 TDLs (Main TDL, add-ons List, and TDL of HIO)

As previously highlighted, the healthcare system in Egypt is fragmented with many authorities involved in healthcare management, funding and service providing. With respect to management, the MOHP is the prime authority responsible for healthcare provision. However, because of various decentralized service providers in Egypt twenty seven governorates (states), the decision making process is spread across the

country. The four main financing parties in Egypt health care as SHI, MOHP, PTES, and FHFs.

As for the health service providers, Phamax (2015) mentioned that many parties operate autonomously, but are under the overall overview of MOHP. University hospitals, Health Insurance Organization (HIO), Teaching Hospitals and Institutes Organization (THIO), Curative Cure Organizations (CCO) and private hospitals in addition to the decentralized units, are all under MOHP umbrella. This is the same in all Egyptian governorates (states).

Furthermore, Phamax (2015) highlighted other health providers like many ministries which have their own hospitals such as the Ministry of Interior, the Transport Ministry, the Ministry of Agriculture, the Ministry of Religious Affairs, and the Defence Ministry. Such diversity in health providers confirm the complexity of Egyptian health care system.

Phamax (2015) analysed how the reimbursement process took place within such a fragmented system and clarified that not all the drugs that are granted a marketing authorization are reimbursed by MOHP, only those included in the Tender Drug List (TDL) could be reimbursed in the public-sector hospitals.

The TDL, which is renewed every two years, is published from the Procurement Department of Central Administration for Pharmaceutical Affairs (CAPA), the list is framed based on requests from all health providers, and then the procurement

department contacts pharmaceutical companies and shares forecasted quantities requesting a bid. After bid submission, procurement technical committee (made up of physicians, procurement department academic pharmacists, legal affairs personnel from MOHP, and Head of CAPA) takes the decision on listing of the drug or not based on technical aspects.

The application then goes to the committee for financial offers at the MOHP to review the financial issues and selects the pharmaceutical company which presented the lowest price for each active ingredient (medication) to get reimbursement. International Society for Pharmacoeconomics and Outcomes Research (ISPOR) (2012) summarised the reimbursement decisions to be based on acceptable technical offers and the lowest price provided by the drug manufacturers or wholesalers.

ISPOR (2012) highlighted that in the case of a projected negative reimbursement decision (rejection), the Procurement Technical Committee informs the applicant about the decision. The applicant has the flexibility to apply for re-evaluation before the final reimbursement decision has been issued. The overall duration of application submission to obtaining reimbursement is about 8 months. Public sector entities follow MOHP regulations of reimbursement, but they are independent, while the private sector has its own set of regulations.

There are in total three tender drug lists ISPOR (2012). The first is the main list discussed above; the second is the “add-ons” when all MOHP hospitals and primary care units’ needs are not covered by the main or first tender drug list. The third is the

list issued by the medical supply department at HIO which is complimentary to the procurement committee at MOHP because not all drugs requested by HIO are covered by the Procurement Committee at MOHP. The medical supply department at HIO covers the rest of drugs in this third tender drug list.

The above analysis of the health care status in Egypt shows how complex the public healthcare system is in Egypt. Especially the reimbursement process, where the procedure suffers from multiple payers, with multiple tender drug lists, and some entities wearing a double hat (e.g. entities served as payer and health provider at the same time).

The pharmacoeconomic evaluation; if implemented would fit in the technical part of the reimbursement process, i.e. at the procurement technical committee decision step. The following section will analyse how far the pharmacoeconomic evaluation progressed, and its impact on the drug reimbursement process in Egypt, with an overview of the extent that such evaluations were considered in medicine reimbursement decision making.

2.10 Pharmacoeconomics and Risk sharing concept (tool to facilitate public financing):

Risk sharing is highly linked to pharmacoeconomic evaluation and it is recently being used as a tool to facilitate public financing especially for new technologies and new innovative drugs that are normally challenged by payers, resulting in an unwillingness to cover. As an introduction; the research analysed briefly the pathway of new drug

development, and the recent requirements for a phase 4 trial before discussing the risk sharing concept.

New drug development goes through various stages and clinical studies to assure drug safety and efficacy. Accordingly, an innovating company needs to conduct phase I, II, & III clinical studies starting by unblinded and uncontrolled studies in a few volunteers until reaching relatively large, randomised, controlled and blinded trials. During the progress of the trials the level of confidence in the drug increases and most risks decreases. After successful completion of phase 3 clinical study, the expectation is regulators' approval of the drug application and accordingly product release authorization.

However not all drugs which pass the clinical study phase III & the regulatory gate showed consistent risk/benefit balance. This defect in turn led to market withdrawal as in the example of Zomepirac that was withdrawn from market 1983 due to serious allergic reactions, including five deaths from anaphylaxis (Ninan and Wertheimer, 2012). Accordingly, regulators started to require the conduction of phase 4 trials post product release; that includes large trials or observational studies with the focus on adverse events and associated product safety measures.

Having the possibility of drug withdrawal due to risk/benefit imbalance increased the barrier of public trust towards new innovative drugs especially from payers' side where they preferred to spend money on the confirmed low risk medicine. This situation decreases the probability of utilizing a risky product, however on the other hand hinders

proper innovation accesses and could lead to demotion of innovation incentives for drug developers as mentioned by Adamski *et al.* BMC Health Services Research (2010).

Adamski *et al.* BMC Health Services Research (2010) highlighted the concept of risk sharing approach, where payers and pharmaceutical providers could reach an agreement of a risk sharing mechanism through which the innovation will be sponsored promptly once the product is authorized for release and on the other hand the drug will be reimbursed based on outcome or effectiveness.

To understand the link between the risk sharing concept and pharmacoeconomic evaluation, we need to consider the economic evaluation of new innovative drugs that could be assessed using cost-effectiveness analysis. However, for some innovations, due to lack of data, there could be difficulties in assessing the new drug benefits and in turn difficulty in proper assessment of such health technologies.

One fair mechanism from payers to move forward with the innovation and not to wait for more confidence in the drug could be a risk sharing setup. The setup would include financial benefits in addition to reimbursement link with the new drug outcome.

Porzsolt *et al.* (2009) proposed in addition, a hybrid approach where depending on the phase of innovation, different risk sharing models are proposed between manufacturers, private insurers and public funding. This could be considered as a win-win situation between the pharmaceutical industry and the public financing structure.

The researcher noted that the main benefit of the risk sharing model for the pharmaceutical industry would be the early endorsement of the drug in the health insurance umbrella which would increase the product penetration and access. Such early endorsement would even enrich any sort of market surveillance that is required by the company for building more confidence on the drug.

On the other hand, the researcher noted the main benefit of risk sharing model for the public financing structure would be the reduced pricing scheme during the early innovation phase of the product, in addition to prompt access of the society to the innovative drug which could impact the overall utility of the impacted individuals.

3. Semi Structured interviews

A qualitative research method was applied in the form of a semi-structured interview with a focus group with the aim of capturing more procedural information. In addition, real examples of pharmacoeconomic evaluation intervention were analysed in an attempt to demonstrate the benefits of such intervention in an Egyptian context.

To properly define the thesis focus group, stakeholders from the market access department in a leading multi-national pharmaceutical company with tangible presence in Egypt were contacted and discussed the reimbursement process in Egypt. The discussion supported the creation of the process flow diagram along with communication flow between the main stakeholders.

The figure below (figure 2) illustrate, the role of each stakeholder of the drug reimbursement process in Egypt along with the communication type between the various parties. This was an important start of the research as it guided the selection of interview focus group and gave a good overview of stakeholders' interactions with the reimbursement process.

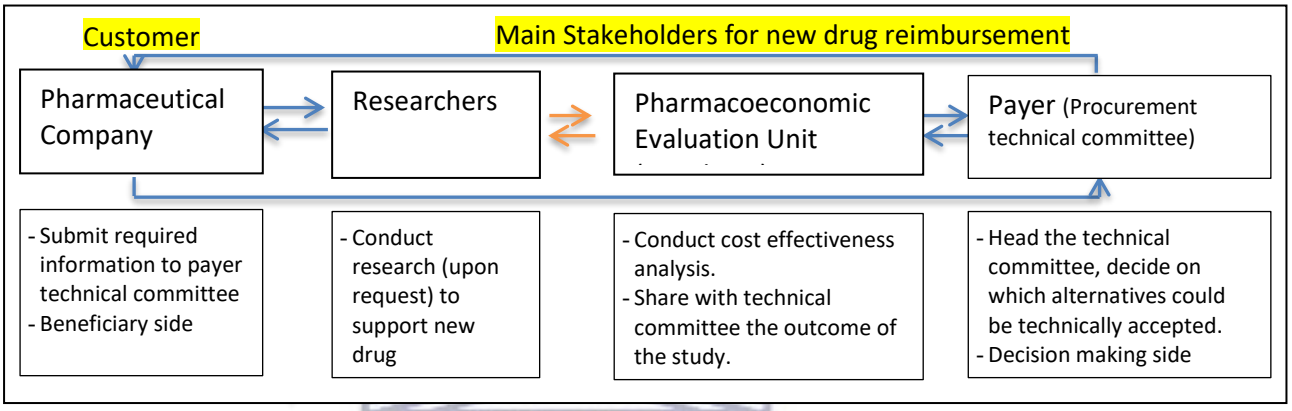


Figure 2 mapping of main various stakeholders for new drug reimbursement in Egypt with the role of each party along with communication type between the various parties.

Primary Communication
Secondary Communication

Accordingly, the research focused on contacting personnel representing Regulators, Payers, and Researchers to conduct the qualitative semi-structured interview as detailed below.

Key person working in the Pharmacoeconomic Unit in Egypt represented the regulator side in this study (referred to in this thesis as, the regulator). A member of the procurement technical committee was representing the payer side/decision making party in this study (referred to in this thesis as, the payer). An academic in pharmacy with pharmacoeconomic evaluation research experience represented the researcher side in this study (referred to in this thesis as, the researcher).

The guiding questions in the interview were mostly the same during the interview of the three representatives. Questions considered the journey pharmacoeconomic evaluation program took, from initial stakeholders' expectations till the outcome evaluation. This was followed by questions on the main challenges faced during the implementation of the program, and finally, proposals for program improvement. The detailed questions were attached to this thesis as in appendix 1.

4. Findings and Analysis

4.1 Semi-structured interview (Qualitative research) findings:

The three stakeholders agreed on the expected aim of the Pharmacoeconomic evaluation unit to be the guidance of reimbursement decision making via a science based approach, and changing the previous cost based mind-set and the consultancy nature of such economic evaluations.

However, the stakeholders did not rate the outcome of the program the same, ranging from a very satisfied Researcher, satisfied Regulator to a dissatisfied Payer. The Payer highlighted his dissatisfaction because some technical committees did not include pharmacoeconomic evaluation in their decision criteria and still rely only on the clinical drug effect approach, which will encourage reimbursement based on cost based approach.

The three stakeholders agreed that cost effectiveness is an important parameter in the reimbursement decision, provided that the Technical Committee considered pharmacoeconomic evaluation. However, this was not the only parameter; other

parameters include budget and disease prevalence. The three stakeholders agreed that there is no existing model that includes various parameters in one equation, accordingly decision makers dealt with applications in a case by case scenario. The Researcher highlighted another parameter that impacts on the decision making, which is the political perspective.

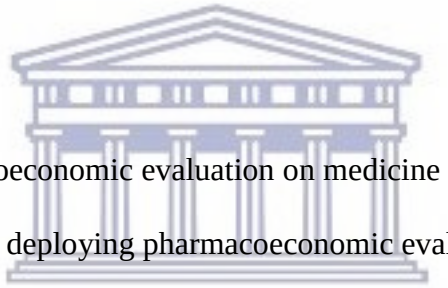
Examples of pharmacoeconomic evaluation unit assessments confirmed the above discussion, where some assessments focused on budget impact as the priority parameter. This was specific for rare diseases where the societal willingness to pay is highly uncertain and demand for the treatment of these diseases is low.

As reported by Pharmacoeconomic Unit (2015) for Enzyme Replacement Therapy for treating paediatrics with Type 1 Gaucher disease. The pharmacoeconomic assessment focussed on the budget impact instead of conducting normal cost effectiveness study, which is useful information for the medicine reimbursement decision. However, the Pharmacoeconomic unit did not define a process on when to consider budget analysis during the unit technical appraisals; accordingly, this process is more on an ad hoc basis.

Upon discussing the expected role of pharmacoeconomic evaluation in the context of UHC, the Regulator suggested medicine reimbursement (medicine inclusion) as the main role of pharmacoeconomic evaluation. However, the Payer suggested that the role of pharmacoeconomic evaluation should be extended to support pricing decisions in addition to medicine inclusion. Currently pricing decision is part of medicine

marketing authorization. For the Researcher, suggested the same role as regulator, but also highlighted risk sharing as another key role of pharmacoeconomic evaluation.

Examples from pharmacoeconomic evaluation unit assessments showed that risk sharing decision was proposed for 15% of the assessments conducted by the pharmacoeconomic evaluation unit. However, such risk sharing decisions were more focused on the medicine cost only, rather than considering the full risk sharing concept. An example of this is reported by Pharmacoeconomic Unit (2014) for treatment of previously untreated Multiple Myeloma patients by Bortezomib Plus Dexamethasone.



For the impact of pharmacoeconomic evaluation on medicine access, the Regulator highlighted the fact that by deploying pharmacoeconomic evaluation, the medication access has been increased due to better budget allocation. Furthermore, the regulator referred to internal data that after 2 years of the program implementation, pharmacoeconomic evaluation lead to cost saving of 80 million Egyptian Pound (EGP). These savings were directed to other disease medication.

The Payer highlighted that the patient access was increased by deploying the pharmacoeconomic evaluation but not to a large extent, and highlighted that the main improvement in patient access was due to inclusion of target medicines used in cancer treatment. This was due to its high cost effectiveness compared to ordinary cancer treatments which were not previously considered for reimbursement based on its high relative costs. The Researcher had no input on the impact of pharmacoeconomic

evaluation on medication access and referred to the Regulator input for more accurate data.

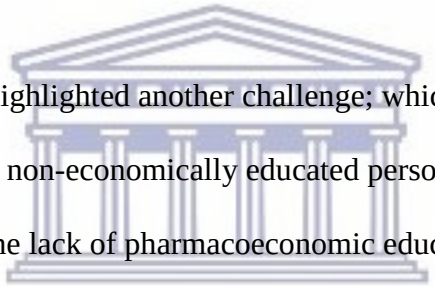
Examples from pharmacoeconomic evaluation unit assessments supported the Payer's view in more than one case, an example reported by Pharmacoeconomic Unit (2016) for Prevention of Chemotherapy-Induced Nausea and Vomiting. The study concludes that (serotonin 5-HT3 receptor antagonist) palonosetron vial (354.20 EGP) is more cost effective than ondansetron vials (94.99 EGP), with incremental cost-effectiveness ratio (ICER) for palonosetron versus ondansetron as 2973.33 EGP/QALY.

Upon discussing the availability of data between alternatives, the Regulator highlighted the possibility of the lack of data between alternatives (comparators) to analyse. The Regulator referred to the use of indirect comparison in such cases, comparing each comparator to a placebo. However, the Regulator highlighted that in some cases such indirect comparison could not be conducted if the literature does not contain comparable studies between comparators and the placebo.

The regulator mentioned "filgrastim vs lenograstim for treatment of neutropenia" as an example of such difficulty, where Pharmacoeconomic unit could not decide on cost effectiveness due to lake of data. This was not the only example of such difficulty in analysis. The Pharmacoeconomic Unit listed studies with gaps in analysis due to unavailability of data and posted in their website under the topic "Research Gaps": http://www.eda.mohealth.gov.eg/Articles.aspx?id=165.

The Researcher highlighted the same point (as per regulator comment) and emphasized that the main debate with pharmaceutical companies would come from challenging such simulation/indirect comparison. The Payer highlighted the problem of a lack of local data making indirect comparison difficult.

With regards to challenges faced upon analysing cost effectiveness, the Regulator referred to the previous point of indirect comparison in addition to the challenge of ignoring pharmacoeconomic evaluation by some technical committees. The Payer was in full alignment with the Regulator feedback with regards to this.



However, the Researcher highlighted another challenge; which was presenting pharmacoeconomic data to non-economically educated personnel who has the decision-making power. The lack of pharmacoeconomic education was emphasized by Soliman *et al* (2012) who reported that only 7 pharmacy schools in Egypt out of 24 offered pharmacoeconomics education in their curriculum.

In addition, the Researcher highlighted another challenge upon analysing cost effectiveness, which is the QALY calculation. To date all QALYs are calculated from international data which is not fully representative of the quality of life in Egypt or even in the emerging markets.

Finally, the stakeholders commented on the future of pharmacoeconomic evaluation in Egypt. The regulator emphasized building capacity and increasing the awareness of other technical staff in order to increase the political will of endorsing the program.

The same point was highlighted by the Payer. The Payer mentioned that changing the legislation of drug reimbursement in order to include mandatory pharmacoeconomic evaluation would take years, as this requires stakeholder buy-in from various sectors in the country including Parliament, Ministry of Finance, and Ministry of Health.

The payer also emphasized that an improvement in the information management throughout the full health care system is required. This was the same point of concern form the Researcher who mentioned that is key to the start of a better health care system in Egypt.

4.2 Examples of Pharmaeconomic evaluation conducted in Egypt:

Since 2013, which is when the Pharmacoeconomic evaluation unit in Egypt commenced, the unit has assessed various technologies for its cost effectiveness. Some studies were not completed due to difficulties in incremental effectiveness calculation, as highlighted above, whereas others were completed successfully. The Pharmacoeconomic evaluation unit issued for each evaluation, a technical report which include - on general - objectives of the study, detailed cost effectiveness, and conclusion of the evaluation under the heading of "Technology appraisal assessment".

The Pharmacoeconomic evaluation unit to date completed more than thirty technology appraisal assessments and published these assessments on the Pharmacoeconomic unit website: http://www.eda.mohealth.gov.eg/Articles.aspx?id=167. Analysis of the completed technology appraisal assessments demonstrated that 52% of the studies were

concluded as “cost-effective”, while 27% were “not cost-effective” of the technology under assessment. Fifteen percentage of the studies proposed “risk sharing”, and 6% of the studies focused on budget impact.

Below are examples of technology appraisal assessments proposed by the Egyptian Pharmacoeconomic unit. This would cover the various conclusions taken by the unit.

4.2.1 Insulin Detemir versus Insulin Glargine in the treatment of Diabetes Mellitus Type 2:

The study conducted by the Pharmacoeconomic Unit on November 2016, showed that although cost of insulin detemir (79.41 EGP), was less than insulin glargine alternative (90 EGP); choosing detemir would be not cost effective. The Pharmacoeconomic Unit (2016c) detailed the assessment and defined the willingness to pay threshold as (3xGDP/capita per QALY i.e. 70,000 EGP/QALY) and showed that using Insulin detemir will cost 411,968 EGP/QALY which is higher than willingness to pay threshold.

4..2.2 Deferasirox versus Deferiprone in the Treatment of High Levels of Iron in the Blood in B-Thalassemia:

The study conducted by Pharmacoeconomic Unit on September 2016, showed that although cost of deferasirox (1033 EGP/pack), was more than the alternative deferiprone (550 EGP/pack), choosing deferasirox would be cost effective. The Pharmacoeconomic Unit (2016b) detailed the assessment and defined the willingness to pay threshold as (3xGDP/capita per QALY, i.e. 70,000 EGP/QALY) and showed

that using deferasirox will cost 58,827 EGP/QALY which is lower than willingness to pay threshold.

4.2.3 "Bortezomib + Dexamethasone" versus "Vincristine + Adriamycin + Dexamethasone" in previously untreated Multiple Myeloma:

The study conducted by the Pharmacoeconomic Unit on June 2014, demonstrated that bortezomib plus dexamethasone significantly improved post-induction and post-transplantation compared with vincristine plus adriamycin plus dexamethasone and resulted in a trend for longer progression free survival from the myeloma.

The Pharmacoeconomic Unit (2014) highlighted that bortezomib plus dexamethasone should be considered as the standard for care in this setting. However, it did not recommend endorsing the new technology (bortezomib plus dexamethasone), but proposed negotiation with the pharmaceutical company on the price or conducting risk sharing agreement. This decision was based on the fact that bortezomib + dexamethasone would cost 942, 291 EGP/QALY which is above the willingness to pay threshold, which is 3xGDP/capita per QALY, i.e. 70,000 EGP/QALY.

It should be noted the decision by the Pharmacoeconomic Unit in this case, was not completely dismissed as "not cost effective" but proposed the use of other strategies to endorse the new technology. The reason for this recommendation could be linked to the high effectiveness of the new technology.

5. Recommendations:

Egypt recently started the deployment of a pharmacoeconomic evaluation concept to support drug reimbursement decision making. This pharmacoeconomic evaluation is not yet mandatory, and accordingly not fully considered by Egyptian Health authorities in setting the medicine reimbursement policies and decisions. Egypt is considered the first country in the region to utilize this science and the experience of this could be useful for other countries in the region for their possible implementation.

The lack of availability of localized clinical data hinders the proper completion of some pharmacoeconomic studies in Egypt. In addition, the pharmacoeconomic education especially for individuals making the medicine reimbursement decision has not yet reached the proper maturity level in the country. Both issues are considered big challenges for the pharmacoeconomic evaluation progress so far.

Pharmacoeconomic evaluation has been progressing in a challenging health care environment in Egypt, and showed good start. However, the analysis of the progress of the process revealed various areas of improvements within the health care system before reaping the full benefits of the implementation of the pharmacoeconomic evaluation program.

The main improvement required in the public health care system of Egypt is the reduction of the complexity of the system, as previously mentioned The World Bank (2015) highlighted four key financing players in Egypt's health care viz, Social Health Insurance, Ministry of Health and Population, Program for Treatment at the Expense

of the State, and Family Health Funds. Each has its own coverage/health service package.

The reduction of complexity could be achieved by unifying payers, using only one list of drugs for local tenders, and separating payers from providers. In addition, the MOHP needs to develop a clear vision, formulate and implement clear strategies towards health care. Instead of the existing initiatives that are not necessarily related or synchronized with each other and are changed from time to time due to the changing political climate.

The second improvement area to consider is building capabilities within the MOHP personnel and other related stakeholders to improve pharmacoeconomic excellence within technical staff that would assure competent evaluations. In addition, to improve awareness to create a culture within the health care stakeholders, this would direct legislation towards more empowered pharmacoeconomics.

The third improvement area to consider is the encouragement of innovation to penetrate the Egyptian market; this could be facilitated by the establishment of risk sharing strategy that is appealing to new innovators towards the Egyptian market. Such a strategy should not only focus on financials and pricing but would also consider the risk sharing model.

The fourth improvement area to consider is setting up guidance on how to localize international QALY data, to improve the precision of the pharmacoeconomic

evaluation outcomes, and subsequently benefit pharmacoeconomic evaluation deployment.

The fifth improvement area is to consider adopting ISPOR guidelines on budget impact analysis into a local procedure. This would keep consistent systematic approach on how to economically evaluate new technologies, and when to conduct budget impact analysis, which would reduce the case by case scenarios.

Lastly, building a proper health related information system with the aim of creating an epidemiology profile for Egypt along with detailed local clinical data. Such local information is crucial for getting more valuable pharmacoeconomic evaluations and in turn reaching a factual based decision making mechanism in the health care system. In addition to the above, MOHP should work on creating a full HTA program that would consider societal perspective parameters. All those improvements could be linked under the road map of UHC that Egypt committed to be achieved by 2030.

6. Conclusion:

Thesis objectives:

The thesis objectives were met, where, a literature review was conducted on medicine pricing, medicine reimbursement, and pharmacoeconomic evaluation in Egypt with reference to other global perspectives.

In addition, a review of the pharmacoeconomic evaluation program in Egypt was conducted with various stakeholders to define how far the program progressed via

semi-structured interviews. This was followed by examples of how the pharmacoeconomic evaluation impacted medicine reimbursement. Finally, recommendations were presented based on the findings in an attempt to further progress the pharmacoeconomic implementation in Egypt.

Payers fragmentation and lack of independency between payers/service providers are considered the major obstacles existing in Egypt health care system that hinder improvements required to reach the UHC, Egypt committed to achiever by 2030.

New research on Egypt pharmacoeconomic evaluation, needs to include pharmaceutical companies and patient feedback on the process as they are considered the direct beneficiaries/main customers of the drug reimbursement process.

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Appendices

Appendix 1: Semi Structured Interview Questions

Appendix 1

Semi Structured Interview Questions

Questions
1- Can you specify, what was the excepted outcome from Pharmacoeconomic evaluation unit?
2- After 3 years from the guidelines issuance, you can score the outcome vs what was expected as? (5 scale choices) - strongly satisfied with outcome - satisfied with outcome - neutral - Dissatisfied with outcome - strongly dissatisfied with outcome
3- Did you find that CE is the most important parameter in reimbursement decision making?
4- If answer of 3 was no, what is the most important parameter the? - Budget - Social aspects - Affordability - Other (specify)
5- Moving towards Universal Health Coverage as part of WHO roadmap, How do you see the Pharmaeconomic evaluation supporting the decision for: - Inclusion - Pricing - Budget allocation - Others (Specify)
6- What was the effect of deploying pharmacoeconomic evaluation on patients' medication access?
7- Did you face difficulty in choosing of comparator for a drug that requires pharmacoeconomic evaluation, if yes Which procedure are you following to evaluate the Pharmaeconomic?
8- What are the main challenges you faced upon analyzing the cost effectiveness of drug?
9- Considering cost effectiveness threshold, which is better to consider DALY or QALY?
10- What are the next steps for the future pharmacoeconomics in Egypt?